Clostridium difficile infection : epidemiology, complications and recurrences

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Chapter 9

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

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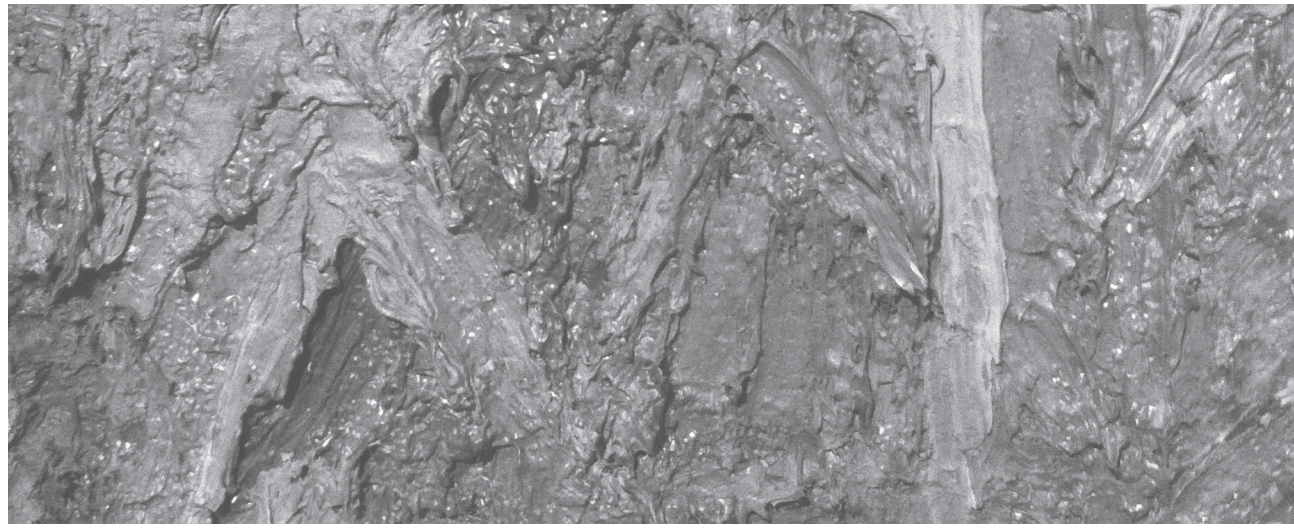

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Abstract

In 2009 the first European Society of Clinical Microbiology and Infection (ESCMID) treatment guidance document for *Clostridium difficile* infection (CDI) was published. The guideline has been applied widely in clinical practice. In this document an update and review on the comparative effectiveness of the currently available treatment modalities of CDI is given, thereby providing evidence-based recommendations on this issue. A computerized literature search was carried out to investigate randomized and non-randomized trials investigating the effect of an intervention on the clinical outcome of CDI. 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 ESCMID and an international team of experts from 11 European countries supported the process. To improve clinical guidance in the treatment of CDI, recommendations are specified for various patient groups, e.g. initial non-severe disease, severe CDI, first recurrence or risk for recurrent disease, multiple recurrences and treatment of CDI when oral administration is not possible. Treatment options that are reviewed include: antibiotics, toxin-binding resins and polymers, immunotherapy, probiotics, and faecal or bacterial intestinal transplantation. Except for very mild CDI that is clearly induced by antibiotic usage antibiotic treatment is advised. The main antibiotics that are recommended are metronidazole, vancomycin and fidaxomicin. Faecal transplantation is strongly recommended for multiple recurrent CDI. In case of perforation of the colon and/or systemic inflammation and deteriorating clinical condition despite antibiotic therapy, total abdominal colectomy or diverting loop ileostomy combined with colonic lavage is recommended.

Introduction

The previous European Society of Clinical Microbiology and Infection (ESCMID) guidance document, which has been applied widely in clinical practice, dates from 2009 [1]. Meanwhile, new treatments for *Clostridium difficile* infection (CDI) have been developed and limitations of the currently recommended treatment options of CDI are considered. As the current ESCMID treatment guidance document is already implemented in clinical practice, an update of this widely applied guidance document is essential to further improve uniformity of national hospital infection treatment policies for CDI in Europe. In particular, after the recent development of new alternative drugs for the treatment of CDI (e.g. fidaxomicin) in the USA and Europe, there has been an increasing need for an update on the comparative effectiveness of the currently available antibiotic agents in the treatment of CDI, thereby providing evidence-based recommendations on this issue.

The objectives of this document are to:

1. Provide an overview of currently available CDI treatment options
2. Develop an evidence-based update of treatment recommendations

Update methodology

Studies on CDI treatment were found with a computerized literature search of PUBMED and Google Scholar 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 analysed. Furthermore, systematic reviews from the most recent Cochrane analysis [2] and the up-dated guidelines of the Infectious Diseases Society of America, the Australasian Society for Infectious Diseases, the American College of Gastroenterology, and the Health Protection Agency/Public Health England guidance document (http://www.hpa.org.uk) were evaluated [3–5]. Recommendations were based on a systematic assessment of the quality of evidence. 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 [6,7].

Draft versions of the guideline were written by the executive committee (consisting of: S. Debast, M. Bauer and E. Kuijper) and criticized by the Executive Committee and advisors. After this, consensus was reached, resulting in the final version. The methods to evaluate the quality of evidence and to reach group consensus recommendations were based on the method described by Ullmann et al. [8].

Definition of the strength of recommendation is given in Table 1. The quality of the published evidence is defined in Table 2a. Grouping quality of evidence into three levels only may lead to diverse types of published evidence being assigned specifically to a level II. To increase transparency in the evaluation of the evidence an index (Table 2b) to the level II recommendations was added where appropriate.

The guideline followed the Appraisal of Guidelines Research and Evaluation Collaboration (AGREE) self-assessment tool [9].

Tabel 1 Definition of the Strength of Recommendation Grade (SoR) ESCMID

Strength	Definition
A	**Strongly** supports a recommendation for use
B	**Moderately** supports a recommendation for use
C	**Marginally** supports a recommendation for use
D	**Supports** a recommendation against use

Definitions

Diagnosis

The diagnosis of CDI is based on (1) a combination of signs and symptoms, confirmed by microbiological evidence of *C. difficile* toxin and toxin-producing *C. difficile* in stools, in the absence of another cause, or (ii) colonoscopic or histopathological findings demonstrating pseudomembranous colitis [1,3,10–12]. There are many different approaches that can be used in the laboratory diagnosis of CDI; however, the best standard laboratory test for diagnosis has not been established. Diagnostic tests for CDI include: (i) detection of *C. difficile* products: cell culture cytoxicity assay (CCA), glutamate dehydrogenase (GDH) and Toxins A and/or B, (ii) toxigenic culture of *C. difficile*, and (iii) nucleic acid amplification tests (NAAT): 16S RNA, toxin genes, GDH genes. Preferably a two- or three-stage algorithm is performed to diagnose CDI, in which a positive first test is confirmed with one or two confirmatory tests or a reference method [3,4,12,13]. Faeces samples could be investigated with an enzyme immunoassay detecting GDH, an enzyme immunoassay detecting toxins A and B, or NAAT detecting Toxin B (TcdB). Samples with a negative test result can be reported as negative. Faeces samples with a positive first test result should be re-tested with a method to detect free faeces toxins, or with a method to detect GDH or toxin genes, dependent on the assay applied as first screening test. If free faeces toxins are absent but *C. difficle* TcdB gene or GDH are present, CDI cannot be differentiated from asymptomatic colonization. Recently, a large study was presented in which several diagnostic

Tabel 2a Definition of the Quality of Evidence (QoE) Level ESCMID. Adapted from ref [8].

Quality of Evidence Level	Definition
I	Evidence from at least 1 properly designed randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Tabel 2b Definition of the Quality of Evidence (QoE) Index ESCMID. Adapted from ref [8].

Quality of Evidence Index	Definition
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence i.e. results from different patients‘ cohorts, or similar immune-status situation
h	Comparator group is a historical control
u	Uncontrolled trial
a	Abstract published at an international meeting

algorithms were evaluated to optimize the laboratory diagnosis of CDI [14]. The investigators concluded that two-stage algorithms improve diagnosis of CDI. Two commonly recommended methods in the laboratory diagnosis of CDI are the use of GDH detection in stools as a means of screening for CDI, confirmed by NAAT such as PCR to detect toxigenic strains of *C. difficile* [4,12]. Furthermore, patients with a positive stool toxin had *C. difficile* disease with an increased risk of mortality compared with patients with only a positive toxigenic culture, thereby implying that stool toxin testing should be included in a testing algorithm to optimize *C. difficile* diagnostic testing [15]. Diarrhoea is defined as loose stools, i.e. taking the shape of the receptacle or corresponding to Bristol stool chart types 5– 7, plus a stool frequency of three stools in 24 or fewer consecutive hours or more frequently than is normal for the individual (definition World Health Organization, http://www.who.int/topics/diarrhoea) [1,3,16–18].

Clinical pictures compatible with CDI are summarized in Table 3.

Tabel 3 Clinical pictures compatible with *Clostridium difficile* infection (CDI). Adapted from refs [1,3,11,19,20]

Sign/symptom	Definition
Diarrhoea	Loose stools, i.e. taking the shape of the receptacle or corresponding to Bristol stool chart types 5 to 7 and a stool frequency perceived as too high by the patient
Ileus	Signs of severely disturbed bowel passage such as vomiting and absence of stool and radiological signs of bowel distension
Toxic megacolon	Radiological signs of distension of the colon and signs of a severe systemic inflammatory response

Definition of *Clostridium difficile* infection. An episode of CDI is defined as: A clinical picture compatible with CDI and microbiological evidence of free toxins and the presence of *C. difficile* in stool without reasonable evidence of another cause of diarrhoea. or Pseudomembranous colitis as diagnosed during endoscopy, after colectomy or on autopsy [3,11,19].

Treatment response

Definition of treatment response. 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. 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 [21–23]. After clinical response, it may take weeks for stool consistency and frequency to become entirely normal [23,24].

Recurrences

Definition of recurrent *Clostridium difficile* infection. Recurrence is present when CDI re-occurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment [4,11].

It is not feasible to distinguish recurrence due to relapse (renewed symptoms from already present CDI) from recurrence due to reinfection in daily practice [20,25–28].

Severity of disease

Definition of severe *Clostridium difficile* infection. Severe CDI is defined 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 [1,4,29].

Clostridium difficile infection without signs of severe colitis in patients with greater age (≥65 years), serious comorbidity, Intensive Care Unit (ICU) admission, or immunodeficiency may also be considered at increased risk of severe CDI [30,31].

An overview of characteristics in patients with CDI that are assumed to correlate with the severity of colitis is given in Table 4 [32–39]. We must stress that the prognostic value of these markers is uncertain.

Tabel 4 Clinical signs and symptoms that could reasonably be assumed to correlate positively with severity of colitis or a complicated course of disease in the absence of another explanation for these findings

Category	Signs/symptoms
Physical examination	- Fever (core body temperature > 38.5 °C) - Rigours (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 leucocytosis (leukocyte count > $15 \cdot 10^9$/l) - Marked left shift (band neutrophils > 20% of leukocytes) - Rise in serum creatinine (>50% above the baseline) - Elevated serum lactate - Markedly reduced serum albumin (< 30 g/l)
Colonoscopy or sigmoidoscopy	- Pseudomembranous colitis There is insufficient knowledge on 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.
Other	- High age (≥ 65) - Serious comorbidity and/or immunodeficiency - ICU admission

Clinical prediction markers

Evidence. Clinical studies indicate superiority of specific treatment strategies depending on the severity of disease. In addition, alternative treatment options have been developed, that may be more effective in preventing recurrence of disease. Unfortunately some of the novel treatment strategies can be very expensive, and may only be cost-effective for a certain group of patients depending on the stage and severity of disease. This emphasizes the importance for better identification of clinical markers, preferably early in the course of disease, which might predict the benefit from specific treatment regimens to decrease CDI-related complications, mortality or recurrences. Surprisingly little prospective and validated research has been performed on clinical predictors of outcome [40]. Furthermore, for some complications of CDI, such as ICU admission or death, it is difficult to determine to what extent the complication can be attributed to CDI as opposed to the presenting acute illness(es) or comorbidities.

A wide variety of risk factors for severe or recurrent CDI have been suggested in literature, which makes it difficult to set a rigid clinical prediction rule [1,25,41–46]. Recently, a systematic review was performed to derive and validate clinical rules to predict recurrences, complications and mortality [46]. Most studies were found to have a high risk of bias because of small sample sizes and much heterogeneity in the variables used, except for leucocytosis, serum albumin and age [46]. Bauer et al. used a database of two randomized controlled trials, which contained information for a large patient group (1105 patients) with CDI, to investigate the prognostic value of three markers for severe CDI. They found that both leucocytosis and renal failure are useful predictors of a complicated course of CDI, if measured on the day of diagnosis [45].

A recent meta-analysis of two pivotal randomized controlled trials comparing fidaxomicin and vancomycin revealed previous vancomycin or metronidazole treatment in the 24 h before randomization, low eosinophil count (<0.1 9 109/L) and low albumin level to be independent predictors of persistent diarrhoea or death in the first 12 days [40]. Recently Miller et al. [36] analysed the same two clinical therapeutic trials to derive and validate a categorization system to discriminate among CDI patients and correlate the grouping with treatment response. They concluded that a combination of five clinical and laboratory variables measured at the time of CDI diagnosis, combined into a scoring system, were able to accurately predict treatment response to CDI therapy with fidaxomicin and vancomycin. These variables include: age, treatment with systemic antibiotics, leucocyte count, albumin and temperature (ATLAS).

C. Strain type has been suggested as an additional cause of excess morbidity, disease severity and higher recurrence rates of CDI. In a Canadian study [47], PCR ribotype 027 was correlated with more severe disease and fatal outcome among

patients at almost all ages. Some studies on the other hand suggested that PCR ribotype 027 strains might only be associated with worse outcome in settings where 027 strains are epidemic, and not in an endemic situation [38,48]. However, these findings are questioned by others [49]. Recently, a large study by Walker et al. clearly showed that strain types varied in the overall impact on mortality and biomarkers (predominantly those associated with inflammatory pathways) [50]. Besides *C. difficile* PCR ribotype 027, other strains are also associated with outbreaks and severe *C. difficile* infection, e.g. PCR ribotype 078 [51]. Despite increased virulence of specific strain types, the value of the PCR ribotype as a prediction marker for disease severity may be limited, as the ribotype involved in an infection is commonly not known upon diagnosis. However, in an epidemic situation the PCR ribotype may be taken into account in deciding on the choice of empirical treatment regimens [21,39].

The level of host immune response to *C. difficile* exposure has been shown to be an important determinant of the severity and duration of clinical manifestations [52–57]. Anti-toxin antibody levels have been demonstrated to be higher in healthy adult controls compared with healthy children, and levels were found to fall with increasing age. In addition, anti-toxin antibodies increased after resolution of diarrhoea, which coincided with decreased incidence of CDI recurrence [57]. Inability to mount an adequate humoral immune response (e.g. during use of rituximab) may therefore be an important additional prediction marker for severe and/or recurrent CDI [25,57–62]. Unfortunately, in most cases this information is not available at presentation/diagnosis; also, as the strength of evidence for immunodeficiency as an independent predictor for severe and/ or recurrent CDI is still limited, we did not include this risk factor as a separate prediction marker.

The results from individual studies, reviews and meta-analyses on prognostic markers for CDI were evaluated to reach a group consensus on a selection of markers that may be useful in clinical practice to distinguish patients with increased risk for severe or life-threatening CDI and recurrences. For detailed recommendations we refer to Tables 5 and 6.

Recommendations. *Clostridium difficile* infection is judged to be severe when one or more of the clinical markers of severe colitis mentioned in Table 4 is present, and/or when one or more unfavourable prognostic factors (Table 5) is present:

1. Marked leucocytosis (leucocyte count >15 9 109/L)
2. Decreased blood albumin (<30 g/L)
3. Rise in serum creatinine level (≥133 lM or ≥1.5 times the premorbid level)

Clostridium difficile infection without signs of severe colitis in older patients (≥65 years), serious comorbidity, ICU admission, or immunodeficiency may also be regarded as increased risks of developing severe CDI.

Table 5 Consensus recommendation: prediction markers for severe *Clostridium difficile* infection (CDI) and/or complicated course of disease

Marker	SoR	QoE	Reference(s)	Comment(s)
Age (≥ 65 years)	A	IIr	[32,41,46]	Large cohort study on CDI mortality at 30 d, and review of studies of factors associated with CDI outcome. [41] Systematic review of studies describing the derivation or validation of Clinical Prediction Rules for unfavorable outcomes of CDI [46]
Marked leukocytosis (leukocyte count > $15 \cdot 10^9$/l)	A	IIrht	[32,37,39,45,46,63,64]	Systematic review [46] Cohort study: severity score on malignancy, white blood cell count, blood albumin, and creatinine [37] Retrospective cohort study on risk factors for severe CDI: death < 30d, ICU, colectomy or intestinal perforation. [32]
Decreased blood albumin (< 3.0 mg/dL)	A	IIr	[32,37,40,46,65]	Systematic review [46]
Rise in serum creatinin (>50% above the baseline)	B	IIht	[32,37,41,45]	Depending on the timing of measurement around CDI diagnosis [45]
Comorbidity (severe underlying disease and/or immunodeficiency)	B	IIht	[37,41,63,66]	Comorbidity: wide variety of risk factors described/investigated. Cancer, cognitive impairment, cardiovascular, respiratory and kidney disease. [41] Chronic pulmonary disease, chronic renal disease and diabetes mellitus. [66] History of malignancy.[47] Prior operative therapy, inflammatory bowel disease and intravenous immunoglobulin treatment [36]

Table 6 Consensus recommendation: prediction markers for recurrent *Clostridium difficile* infection (CDI)

Marker	SoR	QoE	Reference(s) *Not complete*	Comment(s)
Age (> 65 years)	A	IIrh	[42,43,46,67]	Meta-analysis: [43] Systematic review: [46] Prospective validation study of risk factor: [42]
Continued use of (non-CDI) antibiotics after diagnosis of CDI and/or after CDI treatment	A	IIrh	[42,43]	Meta-analysis: [43] Prospective validation study of risk factor: [42]
Comorbidity (severe underlying disease) and/or renal failure	A	IIh	[42,45,68]	Prospective validation study of risk factor: comorbidity conditions rated by Horn's index (underlying disease severity) [42]
A history of previous CDI (> 1 recurrences)	A	IIt	[26,40,69–71]	Data from randomized controlled trials: [26,70] Meta-analysis of pivotal randomized controlled trials [40].
Concomitant use of antacid medications (PPI)	B	IIrh	[43,72]	Meta-analyses on recurrent CDI:[43], Meta-analysis on CDI: [72]
Initial disease severity	B	IIth	[42,67]	Prospective validation study of risk factor [42] Longterm population based cohort study [67]

Treatment of *Clostridium difficile* infection

Once CDI is diagnosed in a patient, immediate implementation of appropriate infection control measures is mandatory to prevent further spread within the hospital. These include early diagnosis of CDI, surveillance, education of staff, appropriate use of isolation precautions, hand hygiene, protective clothing, environmental cleaning and cleaning of medical equipment, good antibiotic stewardship, and specific measures during outbreaks. Measures for the prevention and control of CDI ('bundle approach') have been described in an ESCMID guideline by Vonberg et al. [73].
Additional treatment measures include [1,3,4,72,74]:

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

In general it is difficult to compare studies on the treatment of CDI because of the use of variable diagnostic criteria, patient selection and subgroup definitions, stringency of searches for potential enteropathogens, severity of CDI, comorbidities, exposures to causative or concomitant antibiotics, and follow up. Moreover, studies have employed different definitions of clinical and/or microbiological cure and recurrence [2,75]. The variability in definitions and criteria of randomized controlled trials of antibiotic therapy for CDI is illustrated in Table 7. In 13/17 randomized controlled trials of antibiotic treatment of initial CDI, recurrences and duration of follow up were defined. Follow up varied from 3 to 6 weeks after treatment for CDI. In 6/17 randomized controlled trials definitions for severity of disease were given. In most of the studies very severe and/or life-threatening CDI was excluded.

A Cochrane analysis published in 2011 reviewed 15 studies on the antibiotic treatment for CDI in adults [2]. The risk of bias was rated high in 12 of the 15 included studies. The authors concluded that a specific recommendation for the antibiotic treatment of CDI could not be made. Nevertheless, and in spite of the observed limitations, it is apparent that a clear and up-to-date guideline on the treatment of CDI is urgently needed for clinical practice. For this purpose the strength of a recommendation and the quality of evidence are assigned in two separate evaluations in this guideline, hence allowing an assessment of the strength of a recommendation independent of the level of supportive evidence (Tables 1 and 2).
To improve clinical guidance in the treatment of CDI, treatment recommendations are specified for various patient groups:

A. Initial CDI: non-severe disease
B. Severe CDI

C. C: First recurrence or (risk of) recurrent CDI
D. D: Multiple recurrent CDI
E. Treatment of CDI when oral administration is not possible

The following treatment options are considered:

1. Oral and non-oral antibiotics
2. Toxin-binding resins and polymers
3. Immunotherapy
4. Probiotics

Faecal or bacterial intestinal transplantation

A. Initial *Clostridium difficile* infection: non-severe disease

Oral antibiotic therapy for non-severe disease

Evidence. The antibiotics commonly used to treat CDI are oral metronidazole or oral vancomycin.

Oral metronidazole has been shown to be effective in inducing a clinical response and has the advantage of low cost and is assumed to be associated with reduced vancomycin-resistant enterococci (VRE) selection risk. In a pooled intention-to-treat analysis (treating exclusions, deaths and relapses as treatment failures) of three randomized controlled trials comparing symptomatic cure between metronidazole and vancomycin [77,84,88], no statistically significant differences were found [2,75]. Symptomatic cure was achieved in 79% of patients who received vancomycin compared with 71% of patients who received metronidazole (three studies; 335 patients; RR 0.91; 95% CI 0.81–1.03, p 0.14) [2]. However, a recently presented pooled analysis of data from two phase three randomized controlled trials on the use of tolevamer, comparing resolution of diarrhoea and abdominal pain (clinical success) for vancomycin versus metronidazole, showed that overall metronidazole was inferior to vancomycin [92]. Vancomycin significantly improved clinical success (81.1% vs 72.7%; OR 1.681; 95% CI 1.114–2.537; p 0.0134). In addition a retrospective analysis of case records of hospitalized patients with CDI showed that the symptomatic response time was significantly ($p < 0.01$) shorter in patients treated with vancomycin (3.0 days, $n = 22$) compared with those given metronidazole (4.6 days, $n = 28$) [23]. Oral metronidazole is usually recommended for treatment of non-severe disease, whereas oral vancomycin is generally preferred for treatment of severe infections [1,3–5].

Decreased clinical effectiveness of metronidazole treatment for specific ribotypes causing CDI, e.g. PCR ribotype 027, has been described [93]. Although changes in antibiotic resistance and ribotype prevalence have been reported, in vitro studies

Table 7 Randomized controlled trials of antibiotic treatment of initial *Clostridium difficile* infection (CDI): definitions and criteria of recurrences, follow-up and severity of disease

Trial	Recurrences prior to study	Relapse/recurrences and follow-up	Severity of CDI	Severe CDI excluded/included
[76]	Previous PMC excluded	Recurrences not defined and follow-up not specified	Not defined	Not specified
[77]	Not described	Reappearance of diarrhoea <21 d	Not defined	Not specified
[78]	Not described	Reappearance of diarrhoea <5 wk	Not defined	Not specified
[79]	Not described	Reappearance of diarrhoea after therapy Follow-up: length not clear	Not defined	Not specified
[80]	Not described	"Recurrence of disease": not further specified Follow-up not defined	No definition but judged by physician	Severe/moderate CDI included, mild CDI excluded
[81]	Not described	Not described No follow-up period	Not defined	Not specified
[82]	Not described	Reappearance of diarrhoea and other symptoms ≥1 m Follow-up not further specified	Not defined	Not specified
[83]	Treatment for CDI <6 wk excluded.	Cure followed by return of inclusion criteria CDI <4 wk	Not defined	Not specified
[84]	Not described	Reappearance of diarrhoea and other symptoms <25-30 d	Severity estimated by: number/shape stool, CRP, WBC, ESR	Severe and mild CDI included. Results for PMC specified
[85]	CDI ≤6 m excluded	Reappearance diarrhoea during 28-33 d	Not defined	Not specified. Severe "medical conditions" excluded
[86]	Not specified Excluded oral vanco/metro treatment <7d prior to study (<= 2 doses included)	Reappearance of symptoms < 31 days after start of treatment and after at least 1 negative CD toxin test before retreatment	Not defined	Toxic megacolon excluded
[87]	Previous CDI excluded	Recurrence of diarrhoea during 30 d	Not defined	Not specified. Ileus and toxic megacolon excluded
[88]	Prior failure of treatment for CDI with study-drugs excluded	Recurrence of CD toxin positive diarrhoea within 21 d	Severe CDI defined as severity assessment score ≥ 2 (points). Based on: age (1), Temp (1), Alb (1), WBC (1), endoscopic PMC (2), ICU (2)	Severe and mild CDI included: results specified Life-threatening abdominal complications excluded
[89]	>1 recurrence or relapse within 3 months prior to study excluded	Recurrence of CD toxin positive diarrhoea <6 wk	Severity CDI based on: stools/day, vomiting, ileus, severe abdominal tenderness, WBC, toxic megacolon, life-threatening CDI	Mild to moderately severe CDI included: results not specified Very severe CDI excluded
[90]	>1 recurrence <3 m prior to study excluded Results specified for CDI <90 d before study.	Return of symptoms (toxin positive diarrhoea) <31 d after onset of treatment, or clinical response after empiric re-treatment	Severe CDI defined as severity assessment score ≥ 2 (points). Based on: age (1), stools/day (1), Temp (1), Alb (1), WBC (1)	Severe and mild CDI included: results specified Unstable vital signs or ICU excluded.
[70]	>1 CDI <3 m prior to study excluded. Results specified for patients with/without CDI < 3 m before study.	Reappearance of CD toxin positive diarrhoea <4 wk and need for retreatment for CDI	Mild, moderate and severe CDI: based on bowel movements/day, WBC	Mild, moderate and severe disease included: results specified. Life-threatening or fulminant CDI and toxic megacolon excluded
[91]	>1 CDI <3 m prior to study excluded Results specified for patients with CDI < 3 m before study.	Return of CD toxin positive diarrhoea < 30 d and need for retreatment for CDI	Severe and not-severe CDI based on ESCMID criteria: WBC, Creatinine, Temp.	Severe and not-severe disease included: results specified for severity. Life-threatening or fulminant CDI and toxic megacolon excluded

Alb, serum albumin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; PMC, pseudomembranous colitis; WBC, white blood cell count.

indicate that MICs of metronidazole and vancomycin for endemic *C. difficile* have remained relatively low over the years. Brazier et al. concluded that the MICs of metronidazole and vancomycin were not indicative of clinical failure, but MICs for epidemic ribotypes (027, 106 and 001) were several dilutions higher [94]. Indeed there is increasing evidence of the emergence of reduced susceptibility to metronidazole in some *C. difficile* strains, with evidence for clonal spread [95]. Notably, MIC methodology is crucial to the detection of reduced susceptibility to metronidazole; E-tests in particular underestimate the MIC [95,96]. There is also evidence of inferior microbiological efficacy of metronidazole in comparison with vancomycin [21,22]. Although poor gut concentrations of metronidazole alongside reduced susceptibility to metronidazole could explain reduced treatment efficacy, treatment failures have not been associated with decreased susceptibility [95,97,98]. A case–control study found no significant differences in clinical outcome for CDI cases from which strains with reduced susceptibility to metronidazole were recovered versus matched (metronidazole-susceptible) controls [99]. Response to metronidazole was generally poor (slow and prone to recurrence) and the frail elderly patients had a 21% 30-day mortality. However, much larger study groups are needed to determine the clinical significance of CD isolates with reduced susceptibility to metronidazole [99].

Orally administered vancomycin is poorly absorbed from the gastrointestinal tract, and therefore luminal drug levels are high and orders of magnitude are greater than the susceptibility breakpoint concentration for all strains of *C. difficile* tested so far, thereby resulting in a more rapid suppression of *C. difficile* to undetectable levels during therapy and faster resolution of diarrhoea [22,23]. Metronidazole, on the other hand, is well absorbed from the gastrointestinal tract. Mean antibiotic concentrations reported in faeces of patients receiving oral metronidazole range from <0.25 to 9.5 mg/L, and drug concentrations in faeces decrease to undetectable levels as mucosal inflammation improves and diarrhoea resolves [100]. Increased MIC for metronidazole could therefore have implications on clinical cure or recurrences in CDI. Although there are no published reports in which treatment failure has been linked to antimicrobial metronidazole resistance in *C. difficil*e, the pharmacokinetic properties of vancomycin are considered superior to those of metronidazole in severe *C. difficile* disease [88].

There is concern that use of vancomycin may be more likely to promote colonization and transmission of VRE by selection pressure. However, both oral metronidazole and oral vancomycin have been associated with the promotion of persistent overgrowth of VRE in stool samples obtained from colonized patients during CDI treatment, thereby increasing the risk of transmission [101]. In a small study of VRE-colonized patients with CDI, who experienced frequent faecal incontinence, skin and environmental VRE contamination was common during and after resolution of diarrhoea. It was concluded that the frequency of VRE contamination of skin or the environment was similar between patients treated with metronidazole (n = 17) and those given vancomycin (n = 17), although the study clearly had only limited power to examine this issue [102]. In a large retrospective analysis, increased vancomycin use during an outbreak of CDI was not associated with an increase in VRE colonization during a follow-up period of 2 years after the outbreak period [103]. The authors concluded that restriction of vancomycin use during CDI outbreaks because of the fear of increasing VRE colonization might not be warranted. However, the interpretation of the data was complicated by an outbreak of VRE (VanA) cases that was observed after approximately 20 months of increasing preferential use of vancomycin. As the rate of VanA cases subsequently decreased very quickly, the investigators concluded that this temporary increase reflected a localized clonal outbreak unrelated to the CDI therapy at that time [103].

Although vancomycin and metronidazole are effective in the treatment of CDI, they are both broader-spectrum agents that cause significant disruption of the commensal colonic microbiota. A disruption in the commensal microbiota may predispose to recurrent CDI and intestinal colonization by health- care-associated pathogens such as VRE and Candida species. Fidaxomicin appears to cause less disruption of the anaerobic colonization microbiota, and has activity against many VRE strains [104] so it is suggested that the risk of colonization with and transmission of VRE associated with fidaxomicin treatment may be lower compared with vancomycin therapy. A recent study concluded that fidaxomicin was indeed less likely than vancomycin to promote acquisition of VRE and Candida species during CDI treatment. However, selection of pre-existing subpopulations of VRE with elevated fidaxomicin MICs was more common during fidaxomicin therapy [105].

Similar cure rates have been demonstrated for oral vancomycin and oral teicoplanin [82,84]. For bacteriological cure, oral teicoplanin may even be more effective than vancomycin [2,82]. Both glycopeptides are active in vitro against *C. difficile* isolates [106]. Since 2013 teicoplanin does have a licensed indication for CDI and is available for oral administration. Teicoplanin is not available in the USA. For the purpose of this treatment guideline only oral vancomycin is included in the treatment recommendations.

Tables 8 and 9 report the evidence for oral treatment of initial CDI from randomized trials and observational studies with comments on methodology.

Although oral metronidazole absorption is very high and potentially can lead to more systemic side-effects, adverse effects of oral metronidazole are commonly mild to moderate in severity. The most common adverse reactions reported involve the gastrointestinal tract [107]. Rarely, particularly in association with long duration therapy, metronidazole has been linked to more severe safety issues, e.g. peripheral and optic neuropathy [108] and interactions with warfarins [109].

Tabel 8 Randomized controlled trials of oral antibiotic treatment of initial *Clostridium difficile* infection (CDI). Initial cure rate, and sustained response rates as a percentage of all patients and relapse rate as a percentage of initially cured patients.

Trial	Treatment	Number of patients	Cure [%]	Recurrence [%]	Sustained response [%]
[76]	vancomycin 125 mg qid, 5 days	9	78	0	78
	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.				
[77]	vancomycin 500 mg qid, 10 days	32	100	19	81
	metronidazole 250 mg qid, 10 days	32	97	6	91
	Only data of patients with toxin-positive stools or pseudomembranous colitis shown. Per-protocol analysis. Follow-up 21 days. Differences not statistically significant.				
[78]	vancomycin 125 mg qid, 7 days	21	86	33	58
	bacitracin 20000 U qid, 7 days	21	76	42	44
	Double-blind. 25% drop-out during follow-up of bacitracin group. Follow-up 5 weeks. Differences not statistically significant.				
[79]	vancomycin 500 mg qid, 10 days	15	100	20	80
	bacitracin 25000 U qid, 10 days	15	80	42	46
	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.				
[80]	vancomycin 125 mg qid, mean 10.6 days	24	100	21	79
	vancomycin 500 mg qid, mean 10.1 days	22	100	18	82
	Variable duration of therapy. 18% dropout rate. Per-protocol analysis. Unclear length of follow-up. Differences not statistically significant.				
[81]	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.				

Tabel 8 Continued.

Trial	Treatment	Number of patients	Cure [%]	Recurrence [%]	Sustained response [%]
[82]	vancomycin 500 mg qid, 10 days	20	100	20	80
	teicoplanin 100 mg bid, 10 days	26	96	8	88
	No description of allocation of treatment. Per-protocol analysis. Unclear length of follow-up ('at least 1 month'). Differences not statistically significant.				
[83]	teicoplanin 100 mg qid, 3 days, followed by 100 mg bid, 4 days	24	96	35	62
	teicoplanin 100 mg bid, 7 days	23	70	50	35
	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. 3 patients with improvement in bid group; 1 in qid group. Follow-up 5 weeks. $p = 0.08$ for comparison of cure rates.				
[84]	vancomycin 500 mg tid, 10 days	31	94	17	78
	metronidazole 500 mg tid, 10 days	28	96	7	89
	teicoplanin 400 mg bid, 10 days	29	93	30	65
	fusidic acid 500 mg tid, 10 days				
	Follow-up 30 days. Only statistically significant difference was relapse rate of fusidic acid versus teicoplanin ($p = 0.042$).				
[85]	metronidazole 400 mg tid, 7 days	55	93	30	65
	fusidic acid 250 mg tid, 7 days	59	83	30	58
	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.				
[86]	metronidazole 250 mg qid, 10 days	34	82	30	57
	nitazoxanide 500 mg bid, 7 days	40	90	26	67
	nitazoxanide 500 mg bid, 10 days	36	89	16	75
	No definition of relapse. Double-blind. 23% drop-out during treatment. Per-protocol analysis. Follow-up 31 days. Differences not statistically significant.				
[87]	metronidazole 500 mg tid, 10 days	20	65	38	40
	metronidazole 500 mg tid + rifampicin 300 mg bid, 10 days	19	63	42	37
	Intention-to-treat analysis. Follow-up 40 days. Differences not statistically significant.				

Tabel 8 Continued.

Trial	Treatment	Number of patients	Cure [%]	Recurrence [%]	Sustained response [%]
[88]	vancomycin 125 mg qid, 10 days	71	97	7	90
	metronidazole 250 mg qid, 10 days	79	84	14	72
	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. Intention-to-treat analysis with dropouts regarded as failures resulted in a statistically significant difference between overall cure rates (initial cure minus relapse; 57 out of 90 versus 64 out of 82; risk ratio 0.91). Other comparisons were not significant anymore in the intention-to-treat analysis.				
[89]	fidaxomicin 50 mg bid, 10 days	14	71	8	65
	fidaxomicin 100 mg bid, 10 days	15	80	0	80
	fidaxomicin 200 mg bid, 10 days	16	94	6	88
	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.				
[90]	vancomycin 125 mg qid, 10 days	27	74	7	69
	nitazoxanide 500 mg bid, 10 days	22	77	5	73
	CDI = stool EIA for toxin A or B positive AND (temperature > 38.3 ºC OR abdominal pain OR leukocytosis). Patients with > 1 episode in preceding 6 months were excluded. 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.				
[70]	vancomycin 125 mg qid, 10 days	309	86	25	65
	fidaxomicin 200 mg bid, 10 days	287	88	15	75
	Placebo-controlled. Industry-sponsored. Very severe CDI and more than one previous episode excluded. Designed as non-inferiority trial. 4 weeks follow-up for recurrences after completion of study drug. Cure = < 4 times daily passage of unformed stools AND no necessity for additional treatment. Fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027. Modified intention-to-treat (patients who received at least one dose of the study drug) and per-protocol analyses were similar.				
[91]	vancomycin 125 mg qid, 10 days	257	87	27	64
	fidaxomicin 200 mg bid, 10 days	252	88	13	77
	Methods identical to the trial by Louie [32]. Contrary to that trial, this trial did show fewer recurrences in both PCR ribotype 027 and non-027 patients, although the difference was not significant for the former subgroup.				

Tabel 9 Observational studies of oral antibiotic treatment of initial *Clostridium difficile* infection (CDI). Initial cure rate and sustained response as a percentage of all patients and relapse rate as a percentage of initially cured patients

Trial	Treatment	Number of patients	Cure [%]	Recurrence [%]	Sustained response [%]
Antibiotics:					
[113]	vancomycin	79	96	14	83
[114]	vancomycin	16	100	13	87
[115]	metronidazole	13	100	15	85
[116]	vancomycin	189	97	24	74
[106]	vancomycin 500 mg qid, 10 days	23	100	13	87
	teicoplanin 200 mg bid, 10 days	22	100	0	100
[117]	metronidazole	632	98	6	92
	vancomycin	122	99	10	89
[57]	metronidazole	44	?	50	-
[118]	metronidazole	99	62	?	-
[119]	metronidazole	207	78	28	56
[68]	metronidazole	1123	84	29	60
	vancomycin	112	?	28	-
[120]	fidaxomicin varying dose	45	91	5	86
[121]	nitazoxanide 500 mg bid, 10 days	35	74	27	54
	Patients first failed metronidazole.				
[101]	metronidazole*	34	>90	12	>79
	*Ten patients switched to vancomycin.				
	vancomcyin	18	>90	11	>80
[122]	tigecycline varying duration	4	100	0	100
	Severe CDI. Follow-up at least 3 months.				
[123]	rifaximin 400 mg tid	8	100	10	90
	2 weeks follow-up.				

Oral vancomycin has been shown to be poorly absorbed in most patients, usually producing minimal or subtherapeutic serum concentrations. However, bowel inflammation may enhance absorption of oral vancomycin, particularly in those with renal failure, thereby increasing the risk for systemic side-effects [110]. A recently performed safety analysis of fidaxomicin in comparison with oral vancomycin revealed no differences in serious adverse events between these agents [111]. Fidaxomicin is minimally absorbed. While no specific concerns related to hypersensitivity reactions were identified during the drug development, hypersensitivity reactions associated with fidaxomicin use have been reported to the FDA in the post-marketing phase. The fidaxomicin labeling was revised to include information about the possibility of hypersensitivity reactions [112].

To evaluate the clinical outcomes of the main antimicrobial agents used in the treatment of CDI, we compared dosages, cure rate, recurrence rate, stated time to response and adverse events of treatment with vancomycin, metronidazole and fidaxomicin. Only randomized controlled trials of antibiotic treatment of initial CDI were included. Results are summarized in Table 10.

Recommendations. In case of non-severe CDI (no signs of severe colitis) in non-epidemic situations and with CDI clearly induced by the use of antibiotics, it may be acceptable to stop the inducing antibiotic and observe the clinical response for 48 h, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. Metronidazole is recommended as oral antibiotic treatment of initial CDI in mild/moderate disease. For detailed recommendations on oral antibiotic treatment of initial non-severe CDI refer to Table 11.

Alternative treatment regimens treatment for non-severe disease

Evidence. Tables 12 and 13 report the evidence from randomized trials and observational studies on the non-antibiotic treatment of initial CDI, with comments on methodology. The majority of these alternative treatment strategies are combined with antibiotic treatment. Currently there are no randomized controlled trials on the use of human intravenous gammaglobulins (IVIG). Passive immunizations with IVIG have been reported to be successful in small case series, but the grade of evidence and strength of recommendation of IVIG are too weak to allow recommendations on the use of IVIG in CDI [4,130]. Hypogammaglobulinaemia, e.g. following solid organ transplants, may predispose to CDI. For this subgroup of patients, IVIG may be beneficial, but more studies are needed before this can be recommended definitively [4]. A recent systematic review on the use of probiotics suggests that probiotics are associated with a reduction in antibiotic-associated diarrhoea [131]. A recent meta-analysis on probiotic prophylaxis for CDI, concluded that moderate-quality evidence suggests a beneficial effect of probiotic prophylaxis in CDI without an increase in clinically important adverse events [132]. However, a Cochrane analysis concluded

Table 10 Results of randomized controlled trials of oral antibiotic treatment of initial Clostridium difficile infection (CDI) with vancomycin/teicoplanin, metronidazole and fidaxomicin: comparison of dosages, cure rate, recurrence rate, stated time to response or adverse effects due to treatment

	Trial	Number of patients	Dosages and duration of therapy	Time to initial response (mean)	Cure rate [%]	Recurrence rate [%] and definition	Adverse events [%]
Vancomycin	[76]	9	125 mg qid 5 days	-	78	0 Recurrence not defined, follow-up period not specified	-
	[77]	32	500 mg qid 10 days	3.2 days	100	19 Reappearance of diarrhoea < 21 d after therapy	3 Drug intolerance
	[78]	21	125 mg qid 7 days	-	86	33 Reappearance of diarrhoea < 5 wk after therapy	-
	[79]	15	500 mg qid 10 days	-	100	20 Reappearance of diarrhoea after therapy Follow-up: length not clear	-
	[80]	24	125 mg qid mean 11 days	4 days	100	21	0
		22	500 mg qid mean 10 days	4 days	100	18 Recurrence of disease not further specified Follow-up not defined	0

Table 10 Continued

	Trial	Number of patients	Dosages and duration of therapy	Time to initial response (mean)	Cure rate [%]	Recurrence rate [%] and definition	Adverse events [%]
	[81]	10	500 mg bid 10 days	3.8 days	100	? Not described No follow-up period	0
	[82]	20	500 mg qid 10 days	3.6 days	100	4 Reappearance of diarrhoea and other symptoms ≥ 1 m after therapy. Follow-up not further specified	0
	[84]	31	500 mg tid 10 days	3.1 days	94	17 Reappearance of diarrhoea and other symptoms < 25-30 d after therapy	0
	[88]	71	125 mg qid 10 days	-	97	7 Recurrence of CD toxin positive diarrhoea within 21 d after start of therapy	1 (nausea)
	[90]	27	125 qid 10 days	Median: 96 hr (estimated from Graph)	74	7 Return of symptoms (toxin positive diarrhoea) < 31 d after onset of treatment, or clinical response after empiric re-treatment for CDI	0
	[70]	30	125 mg qid 10 days	Median: 78 hr	86	25 Reappearance of CD toxin positive diarrhoea < 4 wk after treatment and need for retreatment for CDI	Possibly or definitely related: 9 Serious events related to laboratory test results: 1.2
	[91]	257	125 mg qid 10 days	Median: 60 hr (estimated from Graph)	87	27 Return of CD toxin positive diarrhoea < 30 d after treatment and need for retreatment for CDI	Any treatment-emergent adverse event related to study drug: 13.8
Teicoplanin	[82]	26	100 mg bid 10 days	3.4 days	96	2 Reappearance of diarrhoea and other symptoms ≥ 1 m after therapy. Follow-up not further specified	0
	[84]	28	400 mg bid 10 days	2.8 days	96	7 Reappearance of diarrhoea and other symptoms < 25-30 d after therapy	0
	[83]	24	100 mg qid, 3 days, followed by 100 mg bid, 4 days 100 mg bid 7 days		96	35	7-8 % vomiting, nausea, exanthema, arthralgia, pruritus, hallucinations. No abnormal laboratory results
		23			70	50	
Metronidazole	[77]	32	250 mg qid 10 days	3.1 days	97	6 Reappearance of diarrhoea < 21 d after therapy	3
	[84]	31	500 mg tid 10 days	3.2 days	94	17 Reappearance of diarrhoea and other symptoms < 25-30 d after therapy	10 GI discomfort
	[85]	55	400 mg tid 7 days	Within 5 days	93	30 Reappearance diarrhoea during 28-33 d after treatment	14.5 GI, exanthema, taste

Table 10 Continued

	Trial	Number of patients	Dosages and duration of therapy	Time to initial response (mean)	Cure rate [%]	Recurrence rate [%] and definition	Adverse events [%]
	[86]	34	250 mg bid 10 days	Median: 3 days (estimated from Graph)	82	30 Reappearance of symptoms < 31 days after start of treatment and after at least 1 negative CD toxin test before retreatment	related to study drug:0 serious adverse events not related to study drug:18.2 intolerance or allergy:0
	[87]	20	500 mg tid 10 days	6.6 days	65	38 Recurrence of diarrhoea < 30 d after treatment	40 (not specified if related to study drug: rash, nausea vomiting)
	[88]	79	250 mg qid 10 days	Not specified	84	14 Recurrence of CD toxin positive diarrhoea < 21 d after start of therapy	1.3 (nausea)
Fidaxomicin	[89]	14 15 16	50 mg bid 10 days 100 mg bid 10 days 200 mg bid 10 days	Median 6.3 Median 4.8 Median 3.6	71 80 94	8 0 6 Recurrence of CD toxin positive diarrhoea <6 wk after treatment	20% but not related to study drug.
	[70]	287	200 mg bid 10 days	Not reported	88	15 Reappearance of CD toxin positive diarrhoea <4 wk and need for retreatment for CDI	Possibly or definitely related: 9.7 Serious events related to laboratory test results: 4.7
	[91]	252	200 mg bid 10 days	Not reported	88	13 Return of CD toxin positive diarrhoea < 30 d and need for retreatment for CDI	Any treatment-emergent adverse event related to study drug: 11.7

Table 11 Recommendations on oral antibiotic treatment of initial Clostridium difficile infection (CDI): mild/moderate disease

Treatment	SoR	QoE	Reference(s)	Comment(s)
Stop inducing antibiotic(s) and observe the clinical response for 48 hrs	C	II	[116,117]	Rate of spontaneous resolution unknown in mild CDI. Studies performed before increased incidence of hypervirulent strains.
Metronidazole 500 mg tid 10 - 14 days	A	I	[77,84–88]	No statistally significant difference in cure rate between metronidazole and vancomycin or teicoplanin. Statistically significant difference in sustained clinical cure between metronidazole and vancomycin in favour of vancomycin in one study [2,62] (and pooled results of two unpublished randomized controlled trials)
Vancomycin 125 mg qid 10 days or Teicoplanin 100 mg bid 10 days	B	I	[70,76,78,80,82,84,88,90,91]	Teicoplanin significantly better than vancomycin for bacteriologic cure and borderline superior in terms of symptomatic cure [2]
Vancomycin 500 mg qid 10 days or Teicoplanin 400 mg bid 10 days	C	I	[77,79–82,84]	Vancomycin: Equal cure rate 500 mg compared to 125 qid [54] BI Teicoplanin: one dose finding study: 50 mg qid superior to 100 mg bid. [57] No significant differences in cure-rate or recurrence-rate between studies using 400 mg bid and 100 mg bid respectively: [56,58]
Fidaxomicin 200 mg bid 10 days	B	I	[70,89,91]	Industry sponsored studies. Fewer recurrences as compared to vancomycin. [65]

Table 12 Randomized controlled trials of non-antibiotic treatment of initial Clostridium difficile infection (CDI). Initial cure rate and sustained response as a percentage of all patients and relapse rate as a percentage of initially cured patients

Trial	Treatment	Number of patients	Cure [%]	Recurrence [%]	Sustained response [%]
Probiotics:					
[126]	vancomycin or metronidazole + *Saccharomyces boulardii* $2{\cdot}10^{10}$ 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. p = 0.86 for comparison of relapse rates.				
Toxin-binding resins and polymers:					
[24]	tolevamer 1 g tid, 14 days + placebo	94	60	16	50
	tolevamer 2 g tid, 14 days + placebo	91	79	7	74
	vancomycin 125 mg qid, 10 days + placebo	94	91	19	74
	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 2g non-inferior in comparison with vancomycin (Chow-test p = 0.03). Non-inferiority of tolevamer 1g compared with vancomycin could not be demonstrated. p = 0.05 for comparison of relapse rates of tolevamer 2g with vancomycin. Relapse rates of tolevamer 1g and vancomycin not statistically different. Follow-up 6 – 8 weeks.				
[124]	tolevamer 3g tid, 14 days	266	47	3	46
	vancomycin 125 mg qid, 10 days	134	81	23	62
	metronidazole 375 mg qid, 10 days	143	72	27	53
	Unpublished trial.				
[125]	tolevamer 3g tid, 14 days	268	42	6	40
	vancomycin 125 mg qid, 10 days	125	81	18	66
	metronidazole 375 mg qid, 10 days	135	73	19	59
	Unpublished trial.				
Immunotherapy:					
[71]	single dose of 10 mg/kg CDA1 and CDB1 (iv. administered human monoclonal antibodies against TcdA and TcdB) with standard antimicrobial therapy	101	93	7	87
	placebo with standard antimicrobial therapy	99	87	25	65
	Industry-sponsored and -analyzed. Patients must have diarrhea and receive vancomycin or metronidazole at time of enrollement. Diarrhea = >2 unformed stools on 2 consecutive days or >6 unformed stools on 1 dat. Recurrence = new episode of diarrhea with new positive stool toxin test after resolution of initial diarrhea. Analysis for recurrence only performed in those who were cured, received >7 days of antimicrobial therapy and did not receive IVIG (93 vs. 82). Dropout rate 9 vs. 13%, mainly due to deaths not related to CDI. Vancomycin: 30 vs. 22%. Follow-up 12 weeks. p < 0.001 for comparison of relapse rates. Intention-to-treat analysis. Primary endpoint was changed during the study before unblinding. Orginal endpoint: resolution of illness. Subgroup analysis: similar results, although difference much smaller in inpatients than outpatients. Length of hospitalisation did not differ.				

Table 13 Observational studies of non-antibiotic treatment of initial Clostridium difficile infection (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 [%]	Recurrence [%]
Toxin-binding resins and polymers:				
[127]	colestipol 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 6 patients had toxin-positive stool..			
Passive immunotherapy with immune whey:				
[128]	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.			
[129]	metronidazole or vancomycin followed by immune whey protein concentrate, 14 days	109	100	10
	109 episodes; 101 patients; 40% of patients had recurrent CDI.			

that there was insufficient evidence to recommend probiotics, in general, as an adjunct to antibiotics in the treatment of *C. difficile* diarrhoea [133]. Although no cases of translocation of microorganisms have been reported in clinical trials with probiotics for antibiotic-associated diarrhoea or CDI, probiotics should be used with caution. Several studies of invasive disease have been reported, resulting from the use of probiotics such as *Saccharomyces boulardii* in debilitated or immunocompromised patients [134,135]. Moreover, probiotics were associated with increased mortality, partly due to non-occlusive mesenteric ischaemia, in a randomized controlled trial in acute pancreatitis [136].

Recommendations. There is insufficient evidence to support administration of probiotics, toxin-binding resins and polymers, or monoclonal antibodies. For detailed recommendations refer to Table 14.

B: Severe *Clostridium difficile* Infection

Oral antibiotic therapy

Evidence. In 6/17 randomized controlled trials, severity of disease was defined. Definitions varied among the studies. Only in 4/6 of these trials were treatment results specified for severity of disease (Table 15).

Recommendations. Based on its pharmacokinetic properties vancomycin is considered superior to metronidazole in severe *C. difficile* disease [22,88]. The use of high doses of vancomycin (500 mg orally four times daily) was included in the Infectious Diseases Society of America/Society for Healthcare

Epidemiology of America treatment guidelines [3] for management of severe complicated CDI as defined by the treating physician. However, there is insufficient evidence to the use of doses >125 mg four times daily in the absence of ileus [80].

Fidaxomicin was not inferior to vancomycin for initial cure of CDI, but there are no data available on the efficacy of this drug in severe life-threatening disease [70,91]. For detailed recommendations on oral antibiotic treatment of severe CDI refer to Table 16.

Surgery for complicated *Clostridium difficile* infection

Evidence. Patients with fulminant CDI who fail to respond and who progress to systemic toxicity, peritonitis, or toxic colonic dilatation and bowel perforation require surgical intervention [4]. Mortality rates of emergency surgery in complicated CDI remain high, ranging from 19% to 71% depending on the clinical condition of the patient at the time of surgery [138]. However, recently as systematic review of the existing literature was performed to assess the effect on mortality of colectomy for the treatment of fulminant CDI. The authors concluded that colectomy is associated with

Table 14 Recommendations on alternative treatment regimens for initial Clostridium difficile infection (CDI)

Type of intervention	Treatment	SoR	QoE	Reference(s)	Comment(s)
Probiotics	Vancomycin or metronidazole + *Saccharomyces boulardii*	D	I	[126,137]	Comparison of relapse rates: in subgroup analysis efficacy in recurrent CDI, but *not* in initial CDI. Evidence-based review: [137].
Toxin binding resins and polymers	Tolevamer 3 g tid	D	I	[24]	Industry sponsored studie. Non-inferiority trial: tolevamer vs vancomycin.
Immunotherapy	Human monoclonal antibodies against TcdA and TcdB with standard antimicrobial therapy (metronidazole and vancomycin)	C	I	[48]	Industry sponsored study. Fewer recurrences. Subgroup analysis: BI/NAP1/027 strain, patients with >1 recurrence and hospitalization.
	Passive immunotherapy with immune whey after standard oral antimicrobial therapy	C	II	[129]	Observational study: 101 CDI patients (40% recurrent CDI). Results suggest reduction in recurrence rate.

Table 15 Randomized controlled trials of oral antibiotic treatment of initial Clostridium difficile infection (CDI) in which severity of disease is defined and outcome of treatment is specified for severity of diseases

Study	Treatment	CDI severity: Moderate/ Mild (M), Severe (S) Number of patients (%)	Initial cure Number of patients (%)	Relapse Number of patients (% of patients with initial cure)	Sustained response rate* Number of patients (% of all patients)
[88]	vancomycin	M 40/71 (56)	39/40 (98)	2/39 (5)	37/40 (93)
	125 mg qid, 10 days	S 31/71 (44)	30/31 (97)	3/30 (10)	27/31 (87)
	metronidazole	M 41/79 (52)	37/41 (90)	3/37 (8)	34/41 (83)
	250 mg qid, 10 days	S 38/79 (48)	29/38 (76)	6/29 (21)	23/38 (61)
		Intention to treat analysis:	Intention to treat analysis:	Intention to treat analysis:	Intention to treat analysis:
	vancomycin	M 44/82 (49)	39/44 (89)	2/39 (5)	37/44 (84)
	125 mg qid, 10 days	S 38/82 (46)	30/38 (79)	3/30 (10)	27/38 (71)
	metronidazole	M 46/90 (51)	37/46 (80)	3/37 (8)	34/46 (74)
	250 mg qid, 10 days	S 44/90 (49)	29/44 (66)	6/29 (21)	23/44 (52)
[90]	vancomycin	M 17/27 (63)	13/17 (76)	1/13 (8)	12/17 (71)
	125 mg qid, 10 days	S 10/27 (37)	7/10 (70)	1/7 (14)	6/10 (60)
	nitazoxanide	M 12/22 (55)	9/12 (75)	0/9 (0)	9/12 (75)
	500 mg bid, 10 days	S 10/22 (45)	8/10 (80)	1/8 (13)	7/10 (70)
[70]	vancomycin	M 186/309 (60)	156/186 (85)	38/156 (24)	118/186 (63)
	125 mg qid, 10 days	S 123/309 (40)	109/123 (89)	29/109 (27)	80/123 (65)
	fidaxomicin	M 175/287 (61)	161/175 (92)	27/161 (17)	134/175 (77)
	200 mg bid, 10 days	S 112/287 (39)	92/112 (82)	12/92 (13)	80/112 (71)
[91]	vancomycin	M 196/257 (76)	180/196 (92)	46/180 (26)	134/196 (68)
	125 mg qid, 10 days	S 61/257 (24)	43/61 (71)	14/43 (33)	29/61 (48)
	fidaxomicin	M 189/252 (75)	173/189 (92)	24/173 (14)	149/189 (79)
	200 mg bid, 10 days	S 63/252 (25)	48/63 (76)	4/48 (8)	44/63 (70)

*Sustained response rate: clinical cure and no recurrences during follow up

Table 16 Recommendations on oral antibiotic treatment of initial Clostridium difficile infection (CDI): severe disease

Treatment	SoR	QoE	Reference(s)	Comment(s)
Vancomycin, 125 mg four times daily for 10 days	A	I	[70, 88, 90, 91]	Cure rate higher as compared with metronidazole in severe CDI [88][a]
Vancomycin 500 mg four times daily for 10 days	B	III (I*)	[80]	Randomized controlled trial on dose effectiveness: no significant differences in measurable responses of high-dose compared to low-dose regimens. However: results not stratified for severity of illness [80][a].
Fidaxomicin 200 mg twice daily for 10 days	B	I	[70,89,91]	Evidence limited to two Phase III studies [70,91]. Fewer recurrences compared with vancomycin 125 mg four times daily in severe disease (except for PCR ribotype 027). No data on the efficacy in severe life-threatening disease and/or toxic megacolon: excluded from both studies.
Metronidazole, 500 mg three times daily for 10 days	D	I	[88]	Cure rate lower as compared with vancomycin in severe CDI [88]. Intention to treat analysis not reported. Extremely severe CDI excluded[a]. Differences in symptomatic cure of metronidazole versus vancomycin not statistically significant in a pooled analysis [2]. ICU admission and hypoalbuminaemia (= disease severity) predictors of metronidazole failure [119].

aTwo studies reported in abstract form confirm the superiority of vancomycin over metronidazole for treatment of (severe) CDI [92,124,125].

a lower mortality than continued medical treatment when this is no longer improving the patient [139]. Several studies suggest that earlier colectomy (time from presentation to surgery) is associated with improved survival [140]. Independent risk factors for mortality in patients who underwent colectomy that have been found among multiple studies include: the development of shock (need for vasopressors), increased serum lactate (≥5 mM), mental status changes, end organ failure, renal failure and the need for preoperative intubation and ventilation [29,35,138,141,142]. The more negative prognostic signs a patient has, the earlier surgical consultation and operative management should be considered. The established operative management of severe, complicated CDI has been subtotal colectomy with end-ileostomy [140]. However, recently an alternative surgical treatment with creation of a diverting loop ileostomy, followed by colonic lavage, has been shown to reduce morbidity and mortality, while preserving the colon. The surgical approach involves the laparoscopic creation of a diverting loop ileostomy. The colon is then lavaged in an ante-grade fashion through the ileostomy with a high volume of polyethylene glycol 3350 or balanced electrolyte solution and the effluent is collected via a rectal drainage tube. A catheter is placed in the efferent limb of the ileostomy to deliver vancomycin flushes in an antegrade fashion in the postoperative period. In addition, patients receive intravenous metronidazole for 10 days [143]. A multicentre randomized controlled trial is currently being conducted to provide level I evidence for possible implementation of this new treatment into standard practice [http://clinicaltrials.gov/show/ NCT01441271].

Recommendations. Total abdominal colectomy should be performed to treat CDI in case of

- Perforation of the colon
- Systemic inflammation and deteriorating clinical condition despite maximal antibiotic therapy; this includes the clinical diagnoses of toxic megacolon, acute abdomen and severe ileus. Colectomy should preferably be performed before colitis becomes very severe. Serum lactate may, inter alia, serve as a marker for severity (operate before lactate exceeds 5.0 mM).

A future alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with antibiotic treatment (intracolonic antegrade vancomycin and intravenous metronidazole).

C: First Recurrence or (Risk of) recurrent *Clostridium difficile* infection

Oral antibiotic therapy

Evidence. In 3/17 randomized controlled trials of antibiotic treatment of initial CDI, results were specified for CDI before the study (Table 17).

Recommendations. The incidence of a second recurrence after treatment of a first recurrence with oral metronidazole or vancomycin is similar. Fewer secondary recurrences with oral fidaxomicin as compared with vancomycin after treatment of a first recurrence are reported [70,91,144]. However, the evidence on fidaxomicin for this specific subgroup of CDI patients is limited to two phase III studies and based on a retrospective subset analysis of data and a limited number of patients (number of patients in the modified intention-to-treat analysis: fidaxomicin n = 79 and vancomycin n = 80) [144]. There are no prospective randomized controlled trials performed with metronidazole, vancomycin or fidaxomicin in this specific patient group. In addition, fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027 in one of the randomized controlled trials [70]. Therefore, based on the evidence currently available, the Strength of Recommendation for treating a first recurrence of CDI with oral vancomycin or oral fidaxomicin is considered equal (B-I), unless disease has progressed from non-severe to severe.

For detailed recommendations on oral antibiotic treatment of mild/moderate initial CDI with risk for recurrent CDI or a first recurrence refer to Table 18.

D: Multiple recurrent *Clostridium difficile* infection

Antibiotic and non-antibiotic treatment strategies

Evidence. Tables 19 and 20 report the evidence from randomized trials and observational studies with comments on methodology.

Recommendations. In non-severe second (or later) recurrences of CDI oral vancomycin or fidaxomicin is recommended. Vancomycin and fidaxomicin are equally effective in resolving CDI symptoms, but fidaxomicin has been shown to be associated with a lower likelihood of CDI recurrence after a first recurrence [104,144]. However, there are no prospective randomized controlled trials investigating the efficacy of fidaxomicin in patients with multiple recurrences of CDI. Vancomycin is preferably administered using a tapered and/or pulsed regimen.

Recently the first randomized controlled trial on faecal enteric instillation has been published: faecal transplantation following antibiotic treatment with an oral glycopeptide is reported to be highly effective in treating multiple recurrent CDI [145]. For detailed recommendations on treatment regimens of multiple recurrent CDI refer to Tables 21 and 22.

Table 17 Randomized controlled trials of antibiotic treatment of initial *Clostridium difficile* infection (CDI) in which relapses are defined and outcome of treatment is specified for CDI before study

		CDI before study, No. of patients	Initial cure No. of patients	Relapse No. of patients	Sustained response rate[a]
Study	Treatment	(%)	(%)	(% with initial cure)	No. of patients (%)
[90]	Vancomycin, 125 mg four times daily, 10 days Nitazoxanide, 500 mg twice daily, 10 days	5/27 (19)	4/5 (80)	1/4 (25)	3/5 (60)
		2/22 (9)	2/2 (100)	1/2 (50)	1/2 (50)
[70]	Vancomycin, 125 mg four times daily, 10 days	54/309 (17)	48/54 (89)	15/48 (31)	33/54 (61)
	Fidaxomicin 200 mg twice daily, 10 days	48/287 (17)	42/48 (88)	9/42 (21)	33/42 (78)
[91]	Vancomycin 125 mg four times daily, 10 days	36/257 (14)	32/36 (89)	11/32 (34)	21/36 (58)
	Fidaxomicin 200 mg twice daily, 10 days analysed in: [144]	40/252 (16)	37/40 (93)	7/37 (19)	30/40 (75)

aSustained response rate: clinical cure and no recurrences during follow up.

Table 18 Recommendations on oral antibiotic treatment of mild/moderate initial CDI with risk for recurrent Clostridium difficile infection (CDI) or first recurrence

Treatment	SoR	QoE	Reference(s)	Comment(s)
Metronidazole 500 mg tid 10 – 14 days	B	I	[27,88]	Recurrence rate: metronidazole not inferior to vancomycin or teicoplanin for treatment of mild or severe primary CDI [2,82,88] or after a first recurrence [27]. Vancomycin significantly more effective in bacteriological cure than metronidazole in recurrent CDI [69]
Vancomycin 125 mg qid 10 days	B	I	[70,82,90,91]	No statistally significant difference in recurrence rate between vancomycin and teicoplanin [2,82,84]
Vancomycin 500 mg qid 10 days	C	III	[80]	One randomized controlled trial on dose effectiveness in primary CDI: no significant differences in responses of high-dose compared to low-dose regimens vancomycin. However results not stratified for recurrent CDI [80]
Fidaxomicin 200 mg bid 10 days	B	I	[70,89,91]	Industry sponsored studies. Fewer secondary recurrences as compared to vancomycin after treatment of a first recurrence.

Table 19 Randomized controlled studies of treatment of recurrent Clostridium difficile infection (CDI)

Trial	Treatment	Number of patients	Failure* [%]
Faecal or bacterial instillation:			
[145]	vancomycin 500 mg qid, 14 days	13	69
	vancomycin 500 mg qid 14 days + bowel lavage	13	77
	vancomycin 500 mg qid , 4 days + bowel lavage + nasoduodenal infusion donor feces 3/16 patients with failure after first donor feces infusion received second infusion from a different donor: 2/3 resolved. Treatment with donor feces was superior to either of the vancomycin regimens (both P<0.001). Open label. No definition of diarrhoea. Study terminated by use of Haybittle-Peto rule at unplanned interim analysis. Fecotherapy group was older, had more co-morbidities, had higher creatinine, had more infections with PCR ribotype 027. Other characteristics were comparable.	16	19
Probiotics			
[126]	vancomycin or metronidazole + *Saccharomyces boulardii* $2{\cdot}10^{10}$ CFU/ day, 4 weeks	26	35
	vancomycin or metronidazole + placebo 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.	34	65

Table 19 Continued.

Trial	Treatment	Number of patients	Failure* [%]
[146]	vancomycin 500 mg qid, 10 days, followed by *Saccharomyces boulardii* $2{\cdot}10^{10}$ 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 *Saccharomyces boulardii* $2{\cdot}10^{10}$ CFU/ day, 4 weeks	45	51
	vancomycin 125 mg qid, 10 days, followed by placebo	38	45
	metronidazole 1g/day, 10 days, followed by *Saccharomyces boulardii* $2{\cdot}10^{10}$ CFU/ day, 4 weeks	27	48
	metronidazole 1g/ 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 in this group was 22%. No further statistically significant differences.		
[147]	metronidazole 400 mg tid, 10 days + *Lactobacillus plantarum* 299v $5{\cdot}10^{10}$ CFU/ day, 38 days	12	42
	metronidazole 400 mg tid, 10 days + placebo	9	67
	Double-blind. 28% drop-out. Follow-up 70 days. Difference not statistically significant..		
[148]	vancomycin or metronidazole followed by *Lactobacillus* GG $6{\cdot}10^{11}$ 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:			
[149]	colostral 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.		

* Non-response or relapse

Table 20 Observational studies for treatment of recurrent Clostridium difficile infection (CDI)

Trial	Treatment	Number of patients	Failure* [%]	Mean follow-up
Antibiotics:				
[150]	Vancomycin taper, 21 days, followed by vancomycin pulse, 21 days	22	0	6 m
[151]	vancomycin 125 mg qid + rifampicin 600 mg bid, 7 days	7	0	12 m
[69]	vancomycin 1 – 2 g/day	14	71	59 d
	vancomycin <1 g/day	48	54	59 d
	vancomycin ≥2 g/day	21	43	59 d
	vancomycin taper	29	31	80 d
	vancomycin pulse	7	14	80 d
	metronidazole <1 g/day	29	45	59 d
	metronidazole 1.5 g/day	5	40	59 d
	metronidazole 2 g/day	2	0	59 d
[152]	vancomycin, 14 days, followed by rifaximin varying dose, 14 days	8	13	233 d
[153]	rifaximin 400 mg tid, 14 days, followed by rifaximin 200 mg tid, 14 days	5	0	310 d
	rifaximin 400 mg tid, 36 days	1	100	-
[154]	rifaximin 400 mg tid, 14 days	25	36	56 d
	Severe CDI excluded. Patients unresponsive to metronidazole 500 mg tid, 5 days. Cure = negative stool PCR for TcdB. All patients had resolution of diarrhea, but no definition or description of how this was measured are given.			

Table 20 Observational studies for treatment of recurrent Clostridium difficile infection (CDI)

Trial	Treatment	Number of patients	Failure* [%]	Mean follow-up
Probiotics:				
[155]	metronidazole or bacitracin, 10 days, followed by *Lactobacillus* GG 10^{10} CFU/day, 7–10 days	5	20	-
[156]	*Lactobacillus* GG $6{\cdot}10^{8}$ CFU/day, 14 days	4	0	11 m
Faecal or bacterial instillation:				
[157]	faecal enema faecal enema n=15, enteric tube n=1	16	19	(5d-3y)
[158]	faecal or bacterial enema 2 faecal and 4 bacterial mixture	6	0	6 m
[159]	rectal tube	7	0	2 y
[160]	faecal instillation through colonoscope or gastrostoma	18	17	-
[161]	lower gastrointestinal tract	6	0	(9-50 m)
[162]	nasogastric tube, median 3 courses 2 patients died: not CDI related, 15/16 cure after firts FT, 1 relapse	16	6	90 d
[163]	faecal enema	5	0	-
Louie 2008, abstract derived from [164]	Rectal catheter	45	4	(≤1 y)
[165]	Colonoscopy, enema Complete resolution of symptoms in 8/16 and marked reduction in 7/16.	16	6	6 wk
[166]	vancomycin 500 mg qid, followed by faecal instillation by nasoduodenal tube or colonoscopy	7	29 0 after repeated infusion	150 d
[167]	Nasogastric tube	12	17	90 d
Borody 2008, abstract derived from [164]	Faecal enema CDI in refractory IBD	6	0	8 wk
[168]	nasogastric tube	15	27	median 4 m
[169]	Colonoscopy	37	8	12 m
[170]	Colonoscopy 1/19 non-responders after 1st FT; all cured after 2nd FT	19	5	27 m
[171]	Enema	7	0	9 m
[172]	Colonoscopy	13	15	5 m
[173]	Colonoscopy	12	0	(3 wk-8 yr)
[174]	gastroscopy or colonoscopy	40	27	80 d
[175]	Colonoscopy	26	8	11 m
[176]	Colonoscopy 7/77 treatment failures within 90 days after treatment (early recurrence). 8/77 recurrence > 90 days after treatment (late recurrence).	77	19	17 m
[177]	faecal enema 5/27 patients had two FT: 2/5 failures	27	7	427 d
[178]	faecal instillation through coloscope Patients with (14) and without (29) IBD. 6/43 patients had two FT: 2/6 failures	43	14	2 m
[179]	Colonoscopy Initial failures were all PCR-ribotype 027.	70	11	1 y
Immunotherapy:				
[180]	iv gammaglobulin 400 mg/kg every 3 weeks, 4 – 6 months	5	0	5 m
[181]	iv gammaglobulin 400 mg/kg day 1 and 21	4	0	7.5 m
	iv gammaglobulin, varying dose	5	40	2.8 m
[56]	iv gammaglobulin 300 to 500 mg/kg, 1 to 6 doses	5	40	86 d
[182]	iv gammaglobulin 150 to 400 mg/kg once	14	71	6.6 m
[183]	iv gammaglobulin 200 to 300 mg/kg once	18	33 (died or colectomy)	-
[184]	iv gammaglobulin 75 to 400 mg/kg, 1 to 5 days	21	57 (died)	-

* Non-response or relapse
§ As reported by Bakken [131]
d = days; m = months

Table 21 Recommendations on oral antibiotic treatment of multiple recurrent *Clostridium difficile* infection (CDI) (> 1 relapse)

Treatment	SoR	QoE	Reference(s)	Comment(s)
Metronidazole 500 mg tid 10 – 14 days	D	IIrt	[69,75]	Retrospective case cohort of two placebo/antibiotic trials: [126,146]. Trend for lower recurrence frequency for high-dose vancomycin and low-dose metronidazole [69]. Systematic review: [75].
Vancomycin 500 mg qid 10-14 days	C	IIrt	[69,75]	Retrospective case cohort of two placebo/antibiotic trials: [126,146]. Trend for lower recurrence frequency for high-dose vancomycin and low-dose metronidazole [69]. Systematic review: [75].
Vancomycin 125 mg qid for 10 days, followed by pulse regimen (125–500 mg/day every 2–3 days) for at least 3 weeks.	B	IIt	[69,150]	Retrospective case cohort of two placebo/antibiotic trials [69]: [126,146]. Observational study: [150]. Expert opinion [3].
Vancomycin 125 mg qid for 10 days, followed by taper regimen: gradually decreasing the dose to 125 mg per day.	B	IIt	[69,150]	Retrospective case cohort of two placebo/antibiotic trials [69]: [126,146]. Observational study: [150]. Expert opinion [3].
Fidaxomicin 200 mg bid for 10-14 days	B	IIrt	[75,144]	Evidence limited to two Phase III studies [70,91]. Retrospective subset analysis: fewer recurrences as compared to vancomycin treatment after first recurrence [144]. Systematic review: [75]. Efficacy after multiple recurrences was not investigated [144].

Table 22 Recommendations on non-antibiotic treatment of recurrent *Clostridium difficile* infection (CDI) (> 1 relapse)

Type of intervention	Treatment	SoR	QoE	Reference(s)	Comment(s)
Fecal or bacterial instillation	Vancomycin 500 mg qid , 4 days + bowel lavage + nasoduodenal infusion donor feces	A	I	[145]	Also many observational studies and meta-analyses. [164,186,189–191].
Probiotics	vancomycin or metronidazole + *Saccharomyces boulardii*	D	I	[126]	Comparison of relapse rates: in subgroup analysis efficacy in recurrent CDI, but not in initial CDI. Evidence-based review: [137].
	Vancomycin or metronidazole + *Lactobacillus spp.*	D	I	[147,148]	Evidence-based review: [137].
Passive Immunotherapy with immune whey	Colostral immune whey	D	I	[149]	Study interrupted early.

E: Treatment of *Clostridium difficile* infection when oral administration is not possible

Evidence. Metronidazole remains the only parenteral antibiotic therapy supported by case series [192]. Intravenous metronidazole (500 mg intravenous three times daily) may be added to oral vancomycin, if the patient has ileus or significant abdominal distension [4,44]. However, there are no randomized controlled trials available to guide this recommendation.

It is still 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 remain unanswered [193,194]. Prospective clinical trials with other antibiotics, like tigecycline, have not yet been performed to support general use [122,195].

Recommendations. When oral treatment is not possible, parenteral metronidazole is recommended, preferably combined with intracolonic or nasogastric administration of vancomycin. Parenteral tigecycline as salvage therapy is only recommended with marginal strength. For detailed recommendations refer to Table 23.

Summary of definitions

Episode of CDI. A clinical picture compatible with CDI and microbiological evidence of free toxins and the presence of *C. difficile* in stool, without reasonable evidence of another cause of diarrhoea.
or
Pseudomembranous colitis diagnosed during endoscopy, after colectomy or on autopsy.

Clinical pictures compatible with CDI.

Diarrhoea: loose stools, i.e. taking the shape of the receptacle or corresponding to Bristol stool chart types 5–7, plus a stool frequency of three stools in 24 or fewer consecutive hours, or more frequently than is normal for the individual.

Ileus: signs of severely disturbed bowel function such as vomiting and absence of stool with radiological signs of bowel distension.

Toxic megacolon: radiological signs of distension of the colon (>6 cm in transverse width of colon) and signs of a severe systemic inflammatory response.

Severe CDI. Severe or life-threatening CDI is defined as an episode of CDI with (one or more specific signs and symptoms of) severe colitis or a complicated course of

Table 23 Recommendations on non-oral antibiotic treatment of initial Clostridium difficile infection (CDI): mild and severe disease

Patient subgroup	Treatment	SoR	QoE	Reference(s)	Comment(s)
Non-severe disease	Metronidazole iv 500 mg tid iv 10-14 days	A	IIu	[192]	Retrospective uncontrolled study [192]
Severe disease and/ or complicated or refractory CDI	Metronidazole 500 mg tid iv 10-14 days + vancomycin retention enema 500 mg in 100 ml normal saline qid intracolonic	A	IIru	[192-194]	Retrospective uncontrolled study. [192] Systematic review [193-194] Expert opinion [3]
		B	III		
	Metronidazole 500 mg tid iv 10-14 days + vancomycin 500 mg qid oral/ nasogastric tube	A	IIru	[192-194]	Retrospective uncontrolled study. [192] Systematic review [193-194] Expert opinion [3]
		B	III		
	Tigecycline iv	C	III	[122]	Observational study/case report [122]

disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death.

One or more of the following unfavourable prognostic factors can be present without evidence of another cause:

- Marked leucocytosis (leucocyte count >15 9 10 /L)
- Decreased blood albumin (<30 g/L)
- Rise in serum creatinine level (≥133 IM or ≥1.5 times the premorbid level)

Recurrent CDI. Recurrence is present when CDI re-occurs
<8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment.

Treatment response. Treatment response is present when after therapy 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.

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. After clinical response, it may take weeks for stool consistency and frequency to become entirely normal.

Summary of treatment recommendations

Strength of Evidence (SoE: I to III) and Strength of Recommendation (SoR: A to D) are shown in brackets. For grading definitions we refer to Tables 1 and 2.

A: Initial *Clostridium difficile* infection: non-severe disease

Non-antibiotic treatment

In non-epidemic situations and with (non-severe) CDI clearly induced by the use of antibiotics, it may be acceptable to stop the inducing antibiotic and observe the clinical response for 48 h, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. (C-II).

Oral antibiotic treatment

Metronidazole orally 500 mg three times daily for 10 days (A-I)
Vancomycin orally 125 mg four times daily for 10 days (B-I) Fidaxomicin orally 200 mg twice daily for 10 days (B-I)

B: Severe *Clostridium difficile* infection

Oral antibiotic treatment

Vancomycin orally 125 mg four times daily for 10 days (A-I)
Fidaxomicin orally 200 mg twice daily for 10 days (B-I)

Notes:

- It can be considered to increase the vancomycin dosage to 500 mg four times daily for 10 days (B-III)
- There is no evidence that supports the use of fidaxomicin in life-threatening CDI (D-III)

The use of oral metronidazole in severe CDI or life-threatening disease is strongly discouraged (D-I).

Surgical treatment

Total abdominal colectomy with ileostomy should be per- formed in case of:

- Perforation of the colon
- Systemic inflammation and deteriorating clinical condition not responding to antibiotic therapy; including toxic mega- colon, an acute abdomen and severe ileus.

Surgical treatment should preferably be performed before colitis becomes very severe. Serum lactate may, inter alia, serve as a marker for severity (operate before lactate exceeds 5.0 mM).

A future alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with antibiotic treat- ment (intracolonic antegrade vancomycin and intravenous metronidazole).

C: First recurrence or (risk of) recurrent *Clostridium difficile* infection

Oral antibiotic treatment

Fidaxomicin orally 200 mg twice daily for 10 days (B-I) Vancomycin orally 125 mg four times daily for 10 days (B-I) Metronidazole orally 500 mg three times daily for 10 days (C-I)

Note: Fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027 ribotypes.

D: Multiple recurrent *Clostridium difficile* infection

Oral antibiotic treatment

Fidaxomicin orally 200 mg twice daily for 10 days (B-II) Vancomycin orally 125 mg four times daily for 10 days followed by pulse strategy (B-II)
or
Vancomycin orally 125 mg four times daily for 10 days followed by taper strategy (B-II)

Non-antibiotic treatment in combination with oral antibiotic treatment

For multiple recurrent CDI unresponsive to repeated antibiotic treatment, faecal transplantation in combination with oral antibiotic treatment is strongly recommended (A-I).

E: Treatment of *Clostridium difficile* infection when oral administration is not possible

Antibiotic treatment

Non-severe CDI: intravenous metronidazole 500 mg three times daily for 10 days (A-II).

Severe CDI: intravenous metronidazole 500 mg three times daily for 10 days (A-II) combined with vancomycin retention enema 500 mg in 100 mL normal saline four times daily intracolonic, or combined with vancomycin 500 mg four times daily by oral/nasogastric tube for 10 days (B-III).

A schematic overview of currently available therapeutic regimens for CDI, including the quality of evidence (QoE: I to III) and strength of recommendations (SoR: A to D) are shown in Fig. 1.

Authorship

Four draft versions of this guideline document were written by three authors (SD, MB, EK) and critiqued by the Expert Panel. A consensus was reached, resulting in the final version.

Transparency Declaration

Authors: The authors declare that they have no conflicts of interest.
Expert Panel: All members of the expert group completed a Conflict of Interest Disclosure Form (COI).

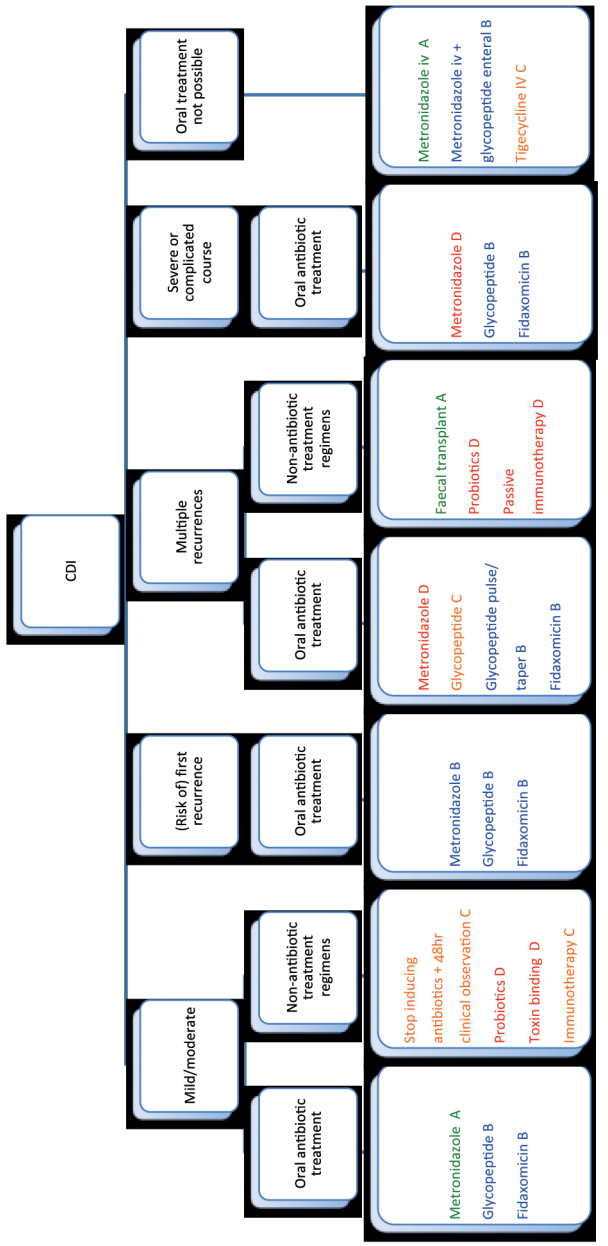

Figure 1 Schematic overview of therapeutic regimens for *Clostridium difficile* infection (CDI). [1]Severe CDI or complicated course: surgical therapy not included in this overview; [2]It can be considered to increase the oral dosage of vancomycin to 500 mg four times daily for 10 days (B-III); [3]There is no evidence that supports the use of fidaxomicin in life-threatening CDI (D-III); Strength of Recommendation (SoR) A = green (Strongly supports a recommendation for use); SoR B = blue (Moderately supports a recommendation for use); SoR C = grey (Marginally supports a recommendation for use); SoR D=red (Recommendation against use).

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