Clostridium difficile infection : epidemiology, complications and recurrences

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Chapter 8

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

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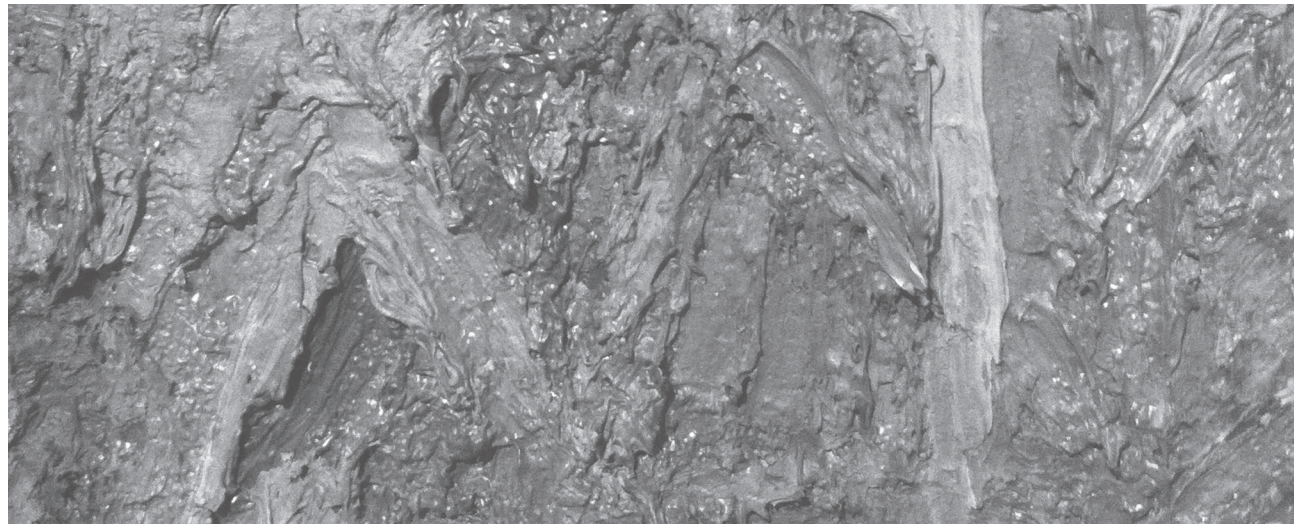

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Abstract

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 adminstered. 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*, treatment, guideline

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 to 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 =
   e. radiological signs of distension of the colon and
   f. signs of a severe systemic inflammatory response

Signs of severe colitis:

- fever (core body temperature $> 38.5\ ^{o}C$)
- 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 $> 15 \cdot 10^{9}/l$)
- 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 high age (≥ 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 three 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 stool 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) + 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 bid, 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 under '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.

Since treatment of CDI can be complicated by these many problems, the CDI Guidance Document Executive Committee decided that there was a need for this evidence-based guideline.

Objective

The objective of this guideline 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 guideline by 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 according to The Canadian Task Force on the Periodic Health Examination was used (table 1).

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

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 plus microbiological evidence of toxin-producing *C. difficile* in stool and absence of another cause is necessary. Compatible clinical 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

Table 1 Strength of recommendation and quality of evidence according to The Canadian Task Force on the Periodic Health Examination

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 ≥ 1 properly randomized, controlled trial
II:	evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from ≥ 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

5 to 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. We refer to the ESCMID guideline on diagnosis of CDI, which is currently being prepared, for information on microbiological evidence for CDI. The above-mentioned criteria are largely in line with the recommendations by 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 antiperistaltic and immunosuppressive medication. It is unknown what the weight of these prognostic factors is in comparison to 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 · 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 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 for severe disease.

Factors associated with unfavourable outcome that are no direct markers of severe colitis include high age, comorbidity, a decreased antibody response, gastric acid suppressants and need to prolong inciting antibiotic therapy. High 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 H2-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 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 feature [6,11].

Markers of severe colitis

Markers that could reasonably be assumed to correlate positively with 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 time in the disease course to be a predictor of outcome.

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 leukocytosis (leukocyte count > 15 · 10^9/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 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, pseudo-polyps and plaques, with severity of disease is unclear.

Prognostic markers other than disease severity
- high 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, there is treatment failure. It is only reasonable to evaluate treatment response after at least three days, assuming that the patient is not worsening on treatment. Treatment with metronidazole, in particular, may only result in a clinical response after three to five 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 on treatment of CDI, both initial (tables 2 [6, 18-32], 3 [17, 33-36] and 4 [9,11,13,15,37-48]) and recurrent episodes (tables 5 [33,49-52] and 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 of 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.

Stopping the inciting antibiotic without antibiotic treatment

It is unknown what the rate of spontaneous resolution is in patients with mild CDI. In one study [40], 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 stopping 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 only stop the inciting antibiotic 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 versus 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 over metronidazole in cases of severe CDI. Two trials investigating the efficacy of the toxin-binding polymer, tolevamer [34,35], also showed superiority of oral vancomycin over metronidazole in severe cases. A recent Cochrane systematic review [70] has examined the available literature on antibiotic treatment options of 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 versus 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 6-8 hourly) 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 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/ anthelminthic nitazoxanide, which has been shown to be statistically similar to metronidazole in a small prospective randomized trial [28], but whose non-inferiority to vancomycin

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 1978 [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 1983 [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 1985 [20]	vancomycin 125 mg qid, 7 days	21	86	33
	bacitracin 20000 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 1986 [21]	vancomycin 500 mg qid, 10 days	15	100	20
	bacitracin 25000 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 1989 [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 1990 [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 1992 [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 ('at least 1 month'). Differences not statistically significant.			
Wiström 1994 [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. 3 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 1996 [26]	vancomycin 500 mg tid, 10 days	31	94	17
	metronidazole 500 mg tid, 10 days	31	94	17
	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 versus teicoplanin ($p = 0.042$).			
Wullt 2004 [27[	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 2006 [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 2006 [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 2007 [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.			

Table 2 Continued.

Trial	Treatment	Number of patients	Cure [%]	Relapse [%]
Louie 2009 [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 2009 [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 2009 [32]	vancomycin 125 mg qid , 10 days	284	90	24
	fidaxomicin 200 mg bid, 10 days	265	92	13
	Unpublished trial			

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 [%]
Probiotics:				
McFarland 1994 [33]	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:				
Louie 2006 [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 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.			
Louie 2007 [34]	tolevamer 3g 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 2008 [35]	tolevamer 3g 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.			
Immunotherapy:				
Lowy 2009 [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 for treatment of initial CDI.

Trial	Treatment	Number of patients	Cure [%]	Relapse [%]
Antibiotics:				
Bartlett 1980 [37]	vancomycin	79	96	14
Silva 1981 [38]	vancomycin	16	100	13
Cherry 1983 [39]	metronidazole	13	100	15
Bartlett 1984 [40]	vancomycin	189	97	24
de Lalla 1989 [41]	vancomycin 500 mg qid, 10 days	23	100	13
	teicoplanin 200 mg bid, 10 days	22	100	0
Olson 1994 [42]	metronidazole	632	98	6
	vancomycin	122	99	10
Kyne 2001 [15]	metronidazole	44	?	50
Fernandez 2004 [11]	metronidazole	99	62	?
Musher 2005 [43]	metronidazole	207	78	28
Pépin 2005 [9]	metronidazole	1123	84	29
	vancomycin	112	?	28
Louie 2005 [44]	difimicin varying dose	45	91	5
Musher 2007 [45]	nitazoxanide 500 mg bid, 10 days Patients first failed metronidazole.	35	74	27
Al Nassir 2008 [16]	metronidazole** Ten patients switched to vancomycin.	34	>90	12
	vancomcyin	18	>90	11
Herpers 2009 [46]	tigecycline varying duration Severe CDI. Follow-up at least 3 months.	4	100	0
Toxin-binding resins and polymers:				
Mogg 1982 [47]	colestipol 10 g qid, 5 days Originally set up as a randomized placebo-controlled trial. Placebo group was merged with historical control, however. Only 6 patients had toxin-positive stool..	12	25	-
Passive immunotherapy with immune whey:				
van Dissel 2001 [48]	metronidazole or vancomycin followed by immune whey protein concentrate, 14 days 56% of patients had recurrent CDI; mean follow-up 333 days.	16	100	0
Numan 2007 [13]	metronidazole or vancomycin followed by immune whey protein concentrate, 14 days 109 episodes; 101 patients; 40% of patients had recurrent CDI.	109	100	10

Table 5 Randomized controlled studies of treatment of recurrent CDI.

Trial	Treatment	Number of patients	Failure* [%]
Probiotics:			
McFarland 1994 [33]	vancomycin or metronidazole + *Saccharomyces boulardii* $2{\cdot}10^{10}$ 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 2000 [49]	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

Table 5 Continued.

Trial	Treatment	Number of patients	Failure* [%]
	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.		
Wullt 2003 [50]	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..		
Lawrence 2005 [51]	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:			
Mattila 2008 [52]	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 6 Observational studies for treatment of recurrent CDI.

Trial	Treatment	Number of patients	Failure* [%]	Mean follow-up
Antibiotics:				
Buggy 1987 [53]	vancomycin 125 mg qid + rifampicin 600 mg bid, 7 days	7	0	12 m
McFarland 2002 [7]	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
Johnson 2007 [54]	vancomycin, 14 days, followed by rifaximin varying dose, 14 days	8	13	233 d
Garey 2008 [55]	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	-
Probiotics:				
Gorbach 1987 [56]	metronidazole or bacitracin, 10 days, followed by *Lactobacillus* GG 10^{10} CFU/day, 7–10 days	5	20	-
Biller 1995 [57]	*Lactobacillus* GG $6{\cdot}10^{8}$ CFU/day, 14 days	4	0	11 m
Faecal or bacterial instillation:				
Bowden 1981 [58]	faecal enema	16	19	-
Tvede 1989 [59]	faecal or bacterial enema	6	0	-
Lund-Tønnesen 1998 [60]	faecal instillation through coloscope or gastrostoma	18	17	-

Table 6 Continued.

Trial	Treatment	Number of patients	Failure* [%]	Mean follow-up
Aas 2003 [61]	faecal instillation through nasogastric tube, median 3 courses	16	6	90 d
Jorup-Rönström 2006 [62]	faecal enema	5	0	-
Nieuwdorp 2008 [63]	vancomycin 500 mg qid, followed by faecal instillation by nasoduodenal tube or colonoscopy	7	29	150 d
Borody§	faecal enema	61	10	-
Lund-Tønnesen §	faecal instillation through nasojejunal tube	20	17	-
Moore§	faecal enema	65	3	-
Aas§	faecal instillation through nasogastric tube	9	0	-
Macconnachie 2009 [64]	faecal instillation through nasogastric tube	15	27	-
Immunotherapy:				
Leung 1991 [65]	iv gammaglobulin 400 mg/kg every 3 weeks, 4 – 6 months	5	0	5 m
Beales 2002 [66]	iv gammaglobulin 400 mg/kg day 1 and 21	4	0	7.5 m
	iv gammaglobulin, varying dose	5	40	2.8 m
Wilcox 2004 [67]	iv gammaglobulin 300 to 500 mg/kg, 1 to 6 doses	5	40	86 d
McPherson 2006 [68]	iv gammaglobulin 150 to 400 mg/kg	14	71	6.6 m

* Non-response or relapse
§ As reported by Bakken [69]
d = days; m = months

could not be shown in another trial due to lack of power [31]. As yet, there is also insufficient evidence for 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].

Duration of antibiotic therapy

The duration of antibiotics has been ten days in most studies. Occasionally, shorter duration (e.g. seven days) has been studied. We feel that there is insufficient evidence for 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 with 125 to 750 mg per day from varying starting doses) and vancomycin pulse strategies (125 to 500 mg of vancomycin every 2 to 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 suffer from major drawbacks such as small numbers, non-randomized allocation of antibiotics to which the probiotics were added and lack of homogeneity between study groups. This is also the conclusion reached by a recent Cochrane systematic review [74]. Therefore, there is insufficient evidence to recommend the addition of probiotics to antibiotics. In addition, several reports 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 mesenterial 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]. Furthermore, 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 other means 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 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 in a relatively early stage of the disease, i.e. before lactate exceeds 5.0 mmol/l [80].

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 stop 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 [81]. There is no evidence that switching to 'low-risk' antibiotics when the antibiotic treatment that triggered the episode of CDI cannot be stopped or its spectrum be 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 stopped, antibiotic treatment for CDI should be initiated. Furthermore, there is no proof that stopping gastric acid suppressants is effective, either.

In all other cases 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 high 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 (C-III)
  normal saline every 4 – 12 h
  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 from colectomy in patients with advanced disease is high, it is recommended to operate in 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, where one should attempt to operate before the threshold of 5.0 mmol/l [80].

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)
  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 (C-III)
  normal saline every 4 – 12 h
  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 [82].

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