REVIEW ARTICLE

Clostridium Difficile Infection

Guideline-Based Diagnosis and Treatment

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SUMMARY

<u>Background:</u> *Clostridium difficile (C. difficile)* is the pathogen that most commonly causes nosocomial and antibiotic-associated diarrheal disease. Optimized algorithms for diagnosis, treatment, and hygiene can help lower the incidence, morbidity, and mortality of *C. difficile* infection (CDI).

<u>Methods:</u> This review is based on pertinent articles that were retrieved by a selective search in PubMed for recommendations on diagnosis and treatment (up to March 2014), with particular attention to the current epidemiological situation in Germany.

<u>Results:</u> The incidence of CDI in Germany is 5 to 20 cases per 100 000 persons per year. In recent years, a steady increase in severe, reportable cases of CDI has been observed, and the highly virulent epidemic strain Ribotype 027 has spread across nearly the entire country. For therapeutic and hygiene management, it is important that the diagnosis be made as early as possible with a sensitive screening test, followed by a confirmatory test for the toxigenic infection. Special disinfection measures are needed because of the formation of spores. The treatment of CDI is evidence-based; depending on the severity of the infection, it is treated orally with metronidazole, or else with vancomycin or fidaxomicin. Fulminant infections and recurrences call for specifically adapted treatment modalities. Treatment with fecal bacteria (stool transplantation) is performed in gastroenterological centers that have experience with this form of treatment after multiple failures of drug treatment for recurrent infection. For critically ill patients, treatment is administered by an interdisciplinary team and consists of early surgical intervention in combination with drug treatment. A therapeutic algorithm developed on the basis of current guidelines and recommendations enables risk-adapted, individualized treatment.

<u>Conclusion:</u> The growing clinical and epidemiological significance of CDI compels a robust implementation of multimodal diagnostic, therapeutic, and hygienic standards. In the years to come, anti-toxin antibodies, toxoid vaccines, and focused bacterial therapy will be developed as new treatment strategies for CDI.

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Clostridium difficile is the most common pathogen in nosocomial and antibiotics-associated diarrheal diseases (1–3). It is also responsible for diarrheal diseases in patients with no risk factors (community-acquired *Clostridium difficile* infection) (4, 5). The frequency of *Clostridium difficile* infection (CDI) and its increased morbidity, which is associated with prolonged duration of inpatient treatment and a considerable rise in the use of hygiene management, lead to a significant increase in hospital treatment costs (approx. €7200 per treated case) (6, 7). This paper aims to summarize current diagnosis and treatment guidelines and to comment on the current epidemiological situation in Germany (endemic spreading of hypervirulent strains and increase in particularly severe CDI) (1, 8–10). This should be of help in making optimized diagnosis, treatment, and hygiene management comprehensive and in reducing disease burden in the long term.

Pathogen and etiopathogenesis

C. difficile was described as a Gram-positive, spore-forming, anaerobic bacillus in the intestinal flora of healthy neonates as early as 1935 (11). The correlation between toxin-producing CDI and pseudomembranous antibiotic-associated colitis was first described in 1977 and confirmed in animal experiments (12). Only toxigenic strains with a pathogenicity locus (PaLoc) cause disease (toxin A = enterotoxin, toxin B = cytotoxin); nontoxigenic strains are apathogenic. Hypervirulent strains, such as ribotype 027, carry characteristic mutations in the toxin repressor gene tcdC (13) which can be used in molecular diagnosis (14). They also express the binary toxin, which damages human cells by inhibiting actin polymerization (14, 15).

C. difficile infection occurs via the fecal-oral route, as a result of ingestion of spores that are resistant to their environment. During gastrointestinal passage, bile acids and other substances stimulate the germination of vegetative growth forms; these produce toxins, depending on the surrounding microflora (microbiota) (16). The main risk factors for CDI are disrupted intestinal flora following antibiotic treatment and absence of antibody response to toxins, particularly in the elderly (immunosenescence) (4, 17).

Figure 1: Endoscopic, surgical, and radiological images of severe *Clostridium difficile* infection (CDI).

a) Typical endoscopic image of pseudo-membranous colitis.

b) Intraoperative view of a 70-year-old male patient with acute abdomen due to fulminant CDI affecting the colon transversum. Surgery took the form of lavage, without resection of the colon. Together with concomitant conservative therapy, surgical treatment achieved complete recovery.

c) Severe *C. difficile*–associated pancolitis in a 71-year-old male dialysis patient. Individual pseudomembranes can no longer be distinguished in this severe case (image source: Dr. Christoph Lübbert, Leipzig).

d) CT of the same patient (coronary reconstruction) shows severe wall thickening of the entire colon area.

(Figures 1a, 1b, and 1d from [32]: Weis S. et al.: Clostridium-difficile-Infektionen (CDI) im Wandel der Zeit–ein Thema nur für den Internisten? Zentralbl Chir 2014; 139: 460–8; reproduced with the kind permission of Thieme publishers, Stuttgart, Germany)
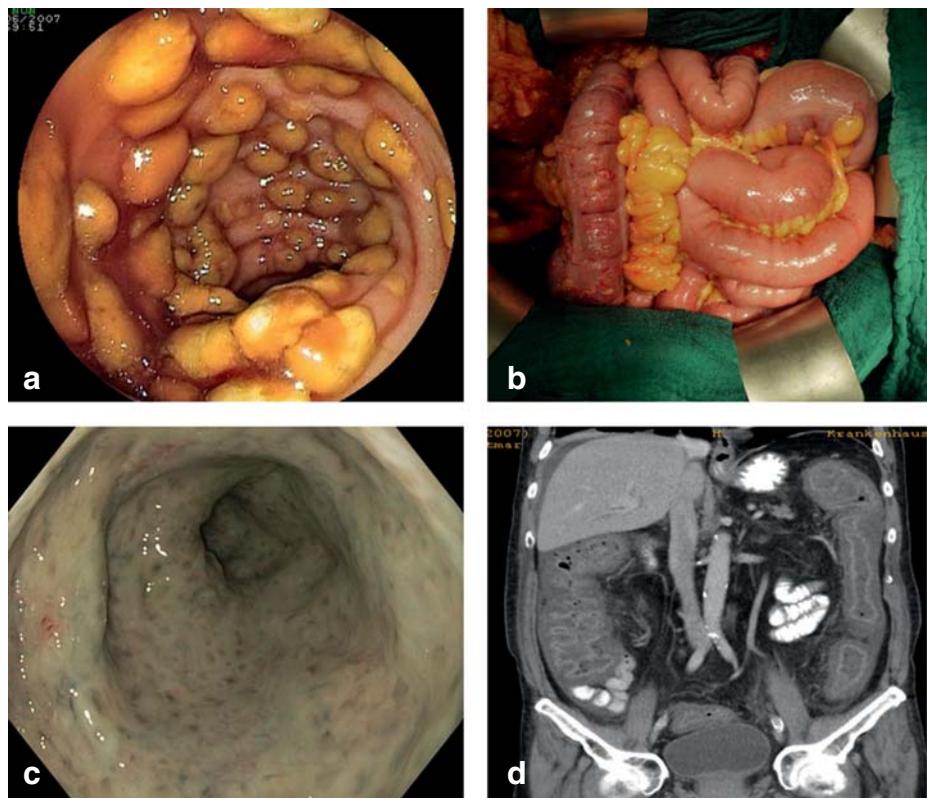
Epidemiology

The frequency of CDI is increasing worldwide (2). Data from Saxony, the only German state in which general reporting is mandatory, shows an incidence of between 5 and 20 cases per 100 000 population (17). In contrast, in some regions of North America incidence is up to 100 cases per 100 000 population (18). It is striking that the number of cases of particularly severe CDI requiring intensive care and accompanied by toxic megacolon, ileus, and perforation is increasing in Germany (mandatory reporting according to Article 6, paragraph 1, point 5a of the German Protection Against Infection Act [IfSG]) (19–21). At the same time, the highly virulent epidemic strain ribotype 027 has taken hold in many German regions (21). This is a worrying new development, although ribotype 027 is not the only strain that gives rise to the risk of severe infections. In many German states ribotype 027 is already detected more frequently than the endemic strain ribotype 001 (20). Ribotype 027 also plays a particular role in infections in homes for the elderly and care homes (22).

Risk factors

The main risk of acquiring CDI exists in the four weeks following antibiotic treatment (accounting for 40% to 60% of cases) (23–26). A distinction can be made here between antibiotics with high colitogenic potential (clindamycin, quinolone, cephalosporin, amoxicillin/ clavulanic acid) and those with low colitogenic potential (e.g. tetracyclines). Other risk factors are age (over 65), comorbidities, hospitalization in the last three months (18, 26), and residence in a home for the elderly or care home (27). Protein pump inhibitor (PPI) treatment also increases the risk of CDI (28, 29), but enteral feeding does not play a significant role (18, 30). The possible risk groups include immunosuppressed or immunodeficient patients and those with chronic inflammatory intestinal diseases (29, 31–33).

Clinical symptoms

It is important to distinguish between asymptomatic colonization and symptomatic CDI. Symptoms range from simple irritation of the mucosa, watery to soft diarrhea with a sweetish, foul odor (18) to the full clinical picture of pseudomembranous colitis with typical endoscopic findings, preferentially in the region of the sigma and rectum *(Figure 1)*. CDI affecting the right colon alone is rarer (32). Stool frequency can exceed 10 times per day, so in older patients signs of exsiccosis requiring treatment can occur swiftly. If symptoms are prolonged, hypoalbuminemia and protein-losing enteropathy can occur (34). Subfebrile temperatures are common (26). On physical examination, the colon is distended in the lower left abdomen in particular. There

TABLE 1

Microbiological diagnostic tests for *Clostridium difficile* and their value

Test	Indication
Glutamate dehydrogenase (GDH) EIA (TAT <2 hours)	Initial screening test with high sensitivity and high negative predictive value; GDH-positive samples must undergo a confirmation test for the toxigenic infection.
Toxin A and B EIA (TAT <2 hours)	Confirmation test for toxigenic infection in GDH-positive samples (2-step algorithm); good correlation with severe infections, limited sensitivity; NAAT (3-step algorithm) recommended if no toxin detected.
Cytotoxin neutralization assay (CTNA) (TAT <24 hours)	Standard test for evidence of toxins in stool; CTNA is rarely used for routine diagnosis, however, due to its longer TAT and low potential for standardization and automation.
NAAT of toxin genes (TAT <4 hours)	Confirmation test for toxigenic infection. NAAT (e.g. PCR) not recommended as screening test, as asymptomatic *C. difficile* carriers not requiring treatment or isolation may also be detected.
Anaerobic toxigenic culture (TAT >3 days)	Diagnostic gold standard as confirmation test for toxigenic infection; of limited use in early diagnosis of CDI due to long TAT; culture is required for ribotype testing and antibiotic resistance testing in critically ill patients and in outbreaks.

TAT, turn-around time; EIA, enzyme immunoassay; NAAT, nucleic acid amplification test (e.g. polymerase chain reaction [PCR])

is usually only slight local pain on palpation (18, 32). Prognostically unfavorable signs of complicated CDI with ileus, toxic megacolon, perforation, or sepsis (less than 5% of cases) include absence of colonic peristalsis, sudden-onset constipation, extreme leukocytosis, and high fever (18, 26, 32). This requires further diagnostic measures such as contrast CT of the abdomen; an experienced visceral surgeon should be consulted for this (32).

Mortality resulting from CDI depends on the severity of symptoms, underlying diseases, and age. It ranges from 3% to 14% (18, 26). Relapses occur in approximately 20% of cases following completion of initial treatment, typically within the first 2 to 6 weeks in patients with risk factors (29, 35–37).

Diagnosis

The international CDI diagnosis guidelines (1, 8–10) allow evidence-based, rapid detection of toxigenic CDI from stool samples (38–40). Multistep diagnostic procedures are recommended (14), combining a sensitive screening test with a confirmation test for the toxigenic infection *(Table 1)*. Only symptomatic patients should be tested. Repeat stool samples are not usually required. Rapid antigen tests and nucleic acid amplification tests (NAATs) are particularly important in routine diagnosis thanks to their short turnaround time (TAT), which ranges from 15 minutes to 3 hours. The toxigenic culture, i.e. the anaerobic culture in special media, combined with evidence of the toxin in the culture supernatant, is the diagnostic gold standard. Anaerobic culture is required for further special tests such as antibiotic resistance testing and ribotype testing. Cultures are not well suited to acute diagnosis, as they have a long turnaround time (more than 72 hours).

A macroscopic finding of pseudomembranous colitis is in many cases so characteristic that CDI can also be diagnosed via endoscopy or colonoscopy, though with limited sensitivity (e1, e2) *(Figure 1)*.

Hygiene management

C. difficile spores cannot be deactivated using conventional alcohol-based disinfectants (e2, e3). CDI therefore requires isolation precautions (single rooms/cohort isolation with individual sanitation), lab coats and gloves, and sporicidal disinfection (see lists compiled by the Association for Applied Hygiene [VAH, Verbund fur Angewandte Hygiene e.V.] at www.vah-online.de) (32, e2, e3). During outbreaks and following contamination of the hands, washing with soap and water (mechanical removal of spores) is recommended. In addition to specific hygiene measures, antibiotic stewardship also contributes substantially to reducing CDI (24).

Conservative therapy

Evidence of toxigenic CDI requires rapid, risk-adapted treatment *(Table 2)*. This usually leads to clinical improvement within 48 to 72 hours (1). If possible, the antibiotic treatment that has led to toxigenic CDI should be interrupted or switched to a less colitogenic drug such as tetracycline or tigecycline. Continued systemic antibiotic treatment increases the probability of a relapse (10). Naturally, sufficient rehydration therapy should also be administered. Motility inhibitors should be avoided and protein pump inhibitor (PPI) treatment should be discontinued if possible (28, 29).

Oral metronidazole, vancomycin, or fidaxomicin treatment is an evidence-based recommendation

TABLE 2

Clostridium difficile infection treatment recommendations by clinical presentation (according to [1, 8–10])

Clinical classification	Therapy	Duration	Level of evidence	Grade of recommendation
Simple	Metronidazole, 3 × 500 mg orally	10 days	I	A
	Vancomycin, 4 × 125 (to 250) mg orally	10 days	I	A
	Interruption of antibiotic treatment that triggered infection, clinical observation, no specific treatment		II	C
Severe	Vancomycin, 4 × 125 (to 250) mg orally	10 days	I	A
	Fidaxomicin, 2 × 200 mg orally	10 days	I	B
Severe, complicated	If possible, vancomycin, 4 × 125 to 500 mg orally (rationale for dose escalation purely empirical)	10 days	I	A
	(plus) metronidazole, 3 × 500 mg IV	10 days	II	A
	(plus) vancomycin retention enemas 4 × daily, intracolonically 500 mg (in 100 mL saline)	10 days	III	B
	(plus) tigecyclin 2 × 50 mg IV	10 days	III	C
First recurrence	Vancomycin, 4 × 125 (to 250) mg orally	10 days	I	B
	Fidaxomicin, 2 × 200 mg orally	10 days	I	B
Multiple recurrences	Vancomycin, 4 × 125 (to 250) mg orally (10 days) followed by pulse schedule for at least 3 weeks (125 to 500 mg orally every 2 to 3 days)	5 weeks	II	B
	Vancomycin, 4 × 125 (to 250) mg orally (10 days) followed by tapering schedule (approx. 5 weeks)	7 weeks	II	B
	Fidaxomicin, 2 × 200 mg orally	10 days	II	B
	Rescue therapy: stool transplantation (possibly colonoscopic) in an experienced center following preliminary vancomycin treatment, 4 × 500 mg orally (4 days)	<1 week	I	A

(e4–e7). Only metronidazole can also be administered intravenously in exceptional cases, as a result of its pharmacokinetics. There is little data based on experience with other orally administered antibiotics such as bacitracin, nitazoxanide, fusidic acid, rifaxamin, and teicoplanin (authorized since 2013) (e8). Toxin-binding drugs such as tolevamer were inferior to standard treatment in clinical trials (e9).

There is little experience with immunotherapy using intravenously administered immunoglobulin drugs (e10). There is good data from animal experiments, however, on active and passive vaccination (e10, e11). Current research on vaccination is at the stage of Phase III clinical trials. One innovative treatment is reconstitution of protective intestinal flora via the application of vital bacteria; this is known as bacteriotherapy. The use of conventional probiotics remains controversial, as most studies into this are of poor quality. This means that no overall recommendation can be provided. In contrast, numerous observational studies and one randomized controlled trial have shown complex bacteriotherapies such as microbiome transfer to be effective (e12–e37).
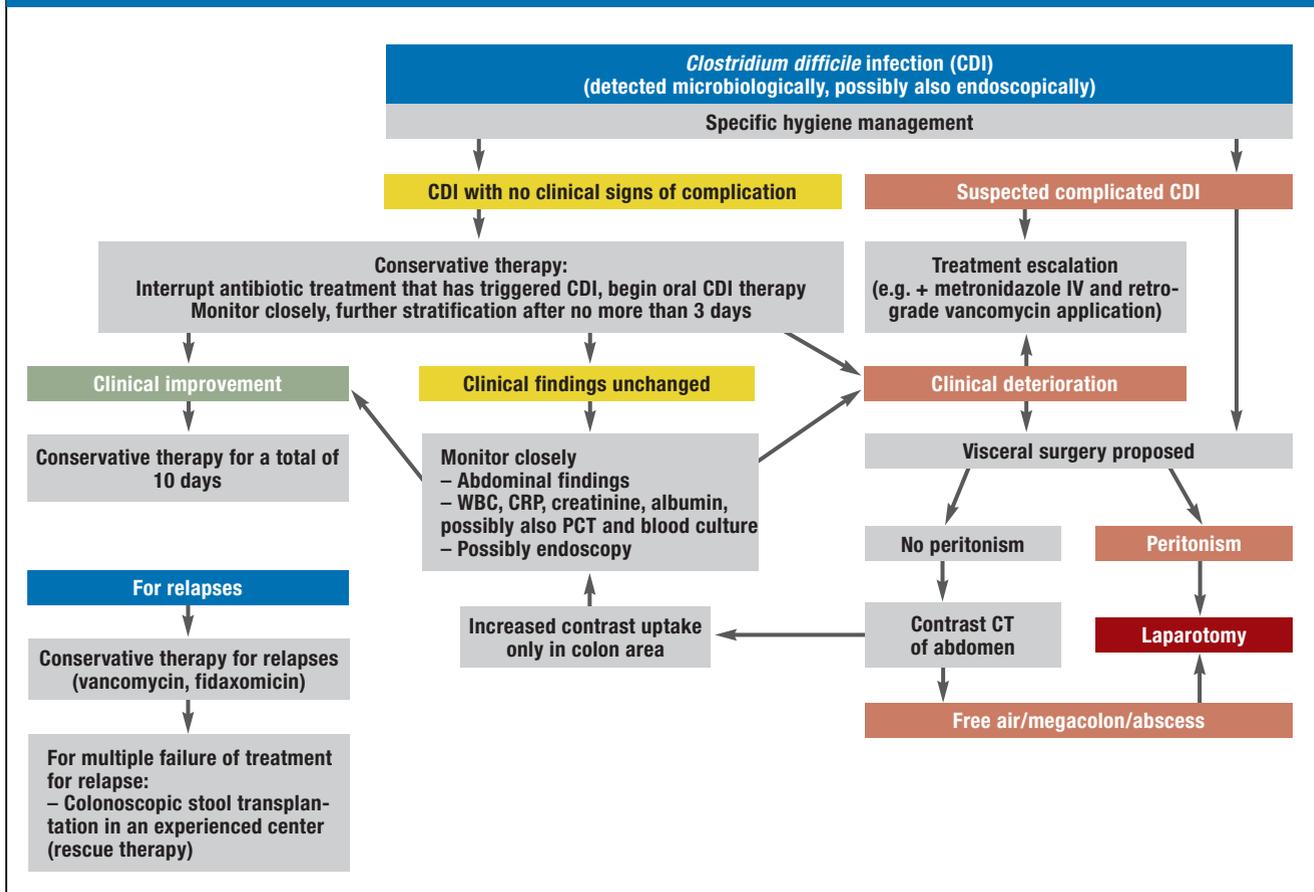
Risk-adapted treatment stratification
International treatment guidelines (1, 8–10) distinguish between simple, severe, and complicated infections and relapses *(Table 2, Figure 2)*. The criteria given for a diagnosis of severe infection are leukocytosis (>15 000/µL), hypoalbuminemia (<30 g/L), and increased creatinine levels (>1.5 mg/dL; alternatively, an increase by more than 1.5 times initial creatinine level). If there are additional risk factors, such as age over 65, immunosuppression, serious concomitant underlying illnesses, dialysis, or history of CDI, patients can be treated as for severe CDI. There is no need to modify therapy for initial treatment of specific highly virulent genotypes (9).

Oral metronidazole is the first-line drug for simple CDI but should not be used for severe CDI. This is because in such cases the response to treatment is lower (73% versus 81%) (e38, e39).

For initial treatment of severe CDI, oral vancomycin is the first-line drug; alternatively, oral fidaxomicin can be used (e39–e44). Treatment response was similar in pooled data from studies that compared these two options (88% versus 86%) (e43, e44). The lower relapse

FIGURE 2

Clostridium difficile infection (CDI)
(detected microbiologically, possibly also endoscopically)

Specific hygiene management

CDI with no clinical signs of complication

Suspected complicated CDI

Conservative therapy:
Interrupt antibiotic treatment that has triggered CDI, begin oral CDI therapy
Monitor closely, further stratification after no more than 3 days

Treatment escalation
(e.g. + metronidazole IV and retro-
grade vancomycin application)

Clinical improvement

Clinical findings unchanged

Clinical deterioration

Conservative therapy for a total of
10 days

Monitor closely
– Abdominal findings
– WBC, CRP, creatinine, albumin,
possibly also PCT and blood culture
– Possibly endoscopy

Visceral surgery proposed

No peritonism

Peritonism

For relapses

Increased contrast uptake
only in colon area

Contrast CT
of abdomen

Laparotomy

Conservative therapy for relapses
(vancomycin, fidaxomicin)

For multiple failure of treatment
for relapse:
– Colonoscopic stool transplan-
tation in an experienced center
(rescue therapy)

Free air/megacolon/abscess

Treatment pathway for patients in whom CDI is detected
WBC, white blood count; CRP, c-reactive protein; CT, computed tomography; PCT, procalcitonin

rate for fidaxomicin should be taken into account, particularly for patients with multiple risk factors, when treatment options are considered (e43, e44). To date there are no studies on patient groups who benefit particularly from fidaxomicin treatment (e45). Discussion of initial therapy is dominated to a great extent by cost considerations. Although fidaxomicin reduces relapses and therefore the subsequent cost of treating relapses, regular prescription of it would lead to an increase in total treatment costs (e46, e47). This is particularly true for areas in which ribotype 027 is endemic, because relapse prevention is limited for ribotype 027 infections (e46, e47).

Complicated CDI is life-threatening and requires interdisciplinary treatment by intensive care physicians and surgeons *(Figure 2)*. A particular challenge is posed by patients in whom gastrointestinal passage, and therefore the main route of application of the appropriate medication, is disrupted (toxic megacolon, ileus). For these patients, metronidazole should be administered intravenously together with intravenous tige-

cycline, although the therapeutic benefit of the latter has so far only been investigated in case series (e48, e49). As far as possible, efforts should be made to continue oral vancomycin treatment in parallel even when intestinal passage is compromised, e.g. via a nasogastric tube. As an alternative, retrograde application (colonoscopy, retention enema) is possible.

A first relapse of CDI should be treated using oral vancomycin or oral fidaxomicin. This means that there is little difference between treatment recommendations for a first relapse and those for initial treatment of severe CDI.

Multiple relapses usually occur within the first 14 days following the end of treatment in patients who are particularly predisposed to CDI. Each new treatment cycle swiftly leads to an improvement in clinical findings, but it is rarely possible to ensure long-term treatment success using conventional treatment cycles (10 to 14 days). Therefore, for vancomycin, after conventional induction therapy, maintenance therapy in the form of intermittent pulse therapy or according to a

TABLE 3

Review of the literature on stool transplantation for *Clostridium difficile* infections. Summary of all studies and larger case series (≥4 patients) published to date (e12–e35) and cumulative analysis.

Reference, year	Country	Patients (*n*)	Successful treatments (*n*)	Response rate (%)	Application (method)	Study design
Eiseman B et al., 1958 (e12)	USA	4	4	100%	Rectal enema	Case series
Bowden TA et al., 1981 (e13)	USA	16	14	88%	Rectal enema (14 patients) Nasoduodenal tube (2 patients)	Case series
Tvede M, Rask-Madsen J, 1989 (e14)	Denmark	6	5	83%	Rectal enema	Case series
Paterson DL et al., 1994 (e15)	Australia	7	7	100%	Rectal enema	Case series
Lund-Tønnesen S et al., 1998 (e16)	Norway	18	15	83%	Colonoscopy	Case series
Gustafsson A et al., 1998 (e17)	Sweden	9	9	100%	Rectal enema	Case series
Aas J et al., 2003 (e18)	USA	18	15	83%	Nasoduodenal tube	Case series
Nieuwdorp M et al., 2008 (e19)	Netherlands	7	7	100%	Colonoscopy	Case series
MacConnachie AA et al., 2009 (e20)	UK	15	11	73%	Nasogastric tube	Case series
Rubin TA et al., 2009 (e21)	USA	12	10	83%	Nasogastric tube	Case series
Rohlke F et al., 2010 (e22)	USA	19	19	100%	Colonoscopy	Case series
Yoon SS, Brandt LJ., 2010 (e23)	USA	12	12	100%	Colonoscopy	Case series
Garborg K et al., 2010 (e24)	Norway	40	33	83%	Duodenoscopy (38 patients) Colonoscopy (2 patients)	Retrospective observational study
Silverman MS et al., 2010 (e25)	Canada	7	7	100%	Rectal enema	Case series
Polak P et al., 2011 (e26)	Czech Republic	15	12	78%	Colonoscopy	Prospective observational study
Mellow MH, Kanatzar A, 2011 (e27)	USA	13	11	85%	Colonoscopy	Case series
Kassam Z et al., 2012 (e28)	USA	27	25	93%	Rectal enema	Case series
Brandt LJ et al., 2012 (e29)	USA	77	70	91%	Colonoscopy	Retrospective observational study
Hamilton MJ et al., 2012 (e30)	USA	43	37	86%	Colonoscopy	Retrospective observational study
Kelly CR et al., 2012 (e31)	USA	26	24	92%	Colonoscopy	Retrospective observational study
Mattila E et al., 2012 (e32)	Finland	70	66	94%	Colonoscopy	Retrospective observational study
Jorup-Rönström C et al., 2012 (e33)	Sweden	32	22	69%	Rectal enema (27 patients) Colonoscopy (5 patients)	Retrospective observational study
Maire F, 2012 (e34)	France	34	34	100%	Colonoscopy	Prospective observational study
van Nood et al., 2013 (e35)	Netherlands	16	15	94%	Nasoduodenal tube	Randomized controlled trial
Summary						
Pooled data (total)		543	484	89%		
Antegrade application (nasogastric/nasoduodenal tube)		101	83	82%		
Retrograde application		442	401	91%[*1]		
Colonoscopy		341	313	92%[*2]		
Rectal retention enema		101	88	87%		

[*1] $p = 0.013$; [*2] $p = 0.005$; statistical testing of retrograde versus antegrade application was performed using two-tailed Pearson's chi-square test

tapering schedule is recommended *(Table 2)*. As an alternative, relapses can be treated with fidaxomicin. Patients in whom relapses recur despite both vancomycin and fidaxomicin treatment are candidates for stool transplantation (synonyms: microbiome transfer, fecal bacteriotherapy).

Stool transplantation (microbiome transfer)

The principle behind stool transfer treatment for diarrheal diseases was successfully used as early as the fourth century, during the Eastern Jin Dynasty in China (e50). Since it was first described as treatment for pseudomembranous colitis in 1958 (e12), the number of original and review articles has multiplied (e13–e37). This experimental form of treatment received particular attention after a randomized controlled trial in patients with multiple relapses was successfully completed early because, after 43 patients were enrolled, stool transplantation was significantly superior to standard therapy in terms of sustained response to treatment (e35). Only patients with multiple relapses following established relapse treatment schedules should be offered stool transplantation. This selective search of the literature identified 543 cases, with a treatment response rate of 89% *(Table 3)*. In this pooled comparison of stool transplantation (e12–e35), treatment response following colonoscopic transplantation was higher than that following application via a nasogastric or nasoduodenal tube (92% versus 82%; $p = 0.005$). Colonoscopic stool transfer can be recommended on the strength of better acceptance and avoidance of bacterial contamination of the small intestine with fecal microbes, in addition to its higher success rate. No more than 200 mL should be applied via the upper digestive tract (e36, e37, e51). For retrograde application, the response rate can be improved by using 500 mL or more of suspension (80% versus 97%) (e51). A highly diverse protective donor flora develops within two weeks following stool transplantation, predominantly natural *Bacteroides* species (e52).

In a gastroenterology center with experience of selecting donors and performing the procedure, stool transplantation can be performed as an individual attempt at cure, if strictly indicated *(eFigure)*. To do this, a protocol-based treatment schedule should be followed. Long-term risks that are as yet unknown must be monitored for in long-term follow-up and ruled out. There are, in fact, animal experiments that show a correlation between altered intestinal microbiome and the development of autoimmune diseases and obesity (e53). Overall, the legal questions regarding liability have not yet been sufficiently clarified. Although European guidelines give grade of recommendation A, funding by health insurers in Germany remains problematic.

The concern of all treating physicians should be to perform this procedure according to a standardized protocol that guarantees patients' inclusion in a national stool transplantation register. Such a register, supported by the German Society for Gastroenterology, Digestive, and Metabolic Diseases (DGVS, Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten; www.dgvs.de) is currently being developed online. Not-for-profit "stool banks" such as OpenBiome (www.openbiome.org) in North America show that the application of and access to microbiome transfer can be simplified and standardized (e54, e55). The long-term goal is oral application of standardized bacterial preparations (e14, e54, e55) that would replace stool transplantation in the future. Such preparations are already being developed (e54, e55).

Surgery

Surgery is only necessary for complicated, fulminant CDI (1% to 4%) (e56–e62). A pathophysiological correlate of surgery is reduction of the pathogen population and thus toxin production, in addition to removal of the damaged section of the intestine. It should be considered if CDI is fulminant and peritonitis, toxic megacolon, intestinal perforation, or systemic inflammation with organ failure develops despite suitable antibiotic treatment (8, 9). In these very seriously ill patients, and in CDI patients who should undergo surgery according to general criteria for visceral surgery, 30-day postoperative mortality is reported as between 24% and 80%. There is evidence that mortality following late surgery is similar to mortality without surgery (e56–e71). However, early surgery can reduce the mortality of complicated CDI (e64, e66, e68, e72–e81). Early detection of complicated CDI, before the critical stage is reached, places particular demands on clinical monitoring and ongoing diagnostics (32, e64, e65). Emergency laparotomy is performed more frequently and more rapidly in surgery departments in cases of fulminant CDI. This can reduce mortality 3.4-fold (e59, e56).

In order to provide a clinical definition of fulminant CDI requiring surgery, the criteria for systemic infection and complication can be given a risk score as an aid to classification *(eTable 1)*. This provides a practical basis for individual clinical decisions (e56). Evidence of toxic megacolon, free air, or abscesses in contrast CT of the abdomen are clear indications for surgery. In contrast, if individual segments or even one half of the colon appear intact, this may be an indication for colon-preserving surgery (e61, e65).

Subtotal colectomy with end ileostomy remains the standard operation for fulminant, treatment-refractory CDI (e65, e68, e71, e72, e83). As this is a disease that primarily affects the luminal side of the colon, clearly externally demarcated areas of the colon that might indicate a part of the colon that could safely be preserved are rarely found intraoperatively.

Besides a colon-preserving diversion stoma (e61, e72, e87), a blow-hole colostomy or ileostomy is another interesting approach. This can be performed laparoscopically and allows for intensive antegrade colon lavage using vancomycin (e85). The selective search of the literature on case series and observational studies with more than 12 patients investigating

colon-preserving surgery versus subtotal colectomy *(eTable 2)* shows slightly lower postoperative mortality following colon-preserving surgery (40.3% versus 30%; *p* = 0.078) (e63–65, e67, e68, e84, e85, e88–e91). Overall long-term prognosis is poor even following successful surgery, with a five-year survival rate of less than 20%. Reversal of ileostomy appears to be possible in only 20% of patients (e69).

KEY MESSAGES

- Hypervirulent epidemic strains of ribotype 027 have spread to cover almost all of Germany. The frequency of severe *Clostridium difficile* infections that are subject to mandatory reporting is increasing steadily.

- Multistep diagnosis and risk-adapted treatment stratification according to the European guidelines updated in 2014 allow for rapid, effective, standardized action in patients with CDI. The combination of a sensitive screening test followed by a confirmation test for the toxigenic infection is recommended for diagnosis.

- Conservative therapy primarily involves oral administration of metronidazole, vancomycin, or fidaxomicin. Special challenges are posed by patients in whom oral therapy is impossible, in relapses, and in complicated, fulminant cases.

- As individual attempts at cure, patients with multiple relapses can be treated very successfully using "stool transplantation" in centers with experience in this area. Colonoscopic stool transplantation should be preferred over administration via gastrointestinal tube.

- Surgery is necessary only for patients with very severe, fulminant CDI. Standard surgery is subtotal colectomy with end ileostomy. Colon-preserving surgery is only possible when treatment is initiated in good time.

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Clostridium Difficile Infection

Guideline-Based Diagnosis and Treatment

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Classification of preoperative clinical severity of *Clostridium difficile* infection (according to [e56])

Criterion	Points
Age >80 years	1
Severe clinical course	1
>10 episodes of diarrhea in 24 hours	1
WBC >20.000 / µL	1
CRP >150 mg/L	1
Urea >15 mg/dL	1
Albumin <20 g/L	1
Score	**Mortality**
0 to 1	22%
2 to 3	55%
4 to 5	89%

WBC, white blood count; CRP, c-reactive protein

eTABLE 2

Review of the literature on 30-day postoperative mortality of patients with very severe, fulminant CDI and subtotal colectomy with ileostomy vs. colon-preserving surgery (case series with ≥12 patients)

First author, no. of cases	Subtotal colectomy	Colon-preserving surgery	p-value
Perera et al. (e63), n = 35	13/32 (40.6%)	3/3 (100%)	N/A
Pepin et al. (e67), n = 130	47/124 (40.0%)	1/6 (16.7%)	N/A
Ali et al. (e68), n = 36	14/28 (50.0%)	3/8 (37.5%)	N/A
Koss et al. (e65), n = 14	1/9 (11.1%)	4/5 (80.0%)	N/A
Byrn et al. (e64), n = 73	24/64 (37.5%)	1/9 (11.1%)	N/A
Seder et al. (e84), n = 69	29/68 (42.6%)	0/1 (0%)	N/A
Medich et al. (e88), n = 12	0/5 (0%)	4/7 (57.1%)	N/A
Hall et al. (e89), n = 36	13/34 (38.2%)	0/2 (0%)	N/A
Dudukgian et al. (e90), n = 14	4/11 (36.4%)	1/3 (33.3%)	N/A
Chan et al. (e91), n = 15	7/12 (58.3%)	2/3 (66.7%)	N/A
Neal et al. (e85), n = 84	21/42 (50.0%)	8/42 (19.0%)	N/A
Total	173/429 (40.3%)	27/89 (30.3%)	0.078

N/A: Not available. Statistical testing performed using two-tailed Pearson's chi-square test.
CDI: *Clostridium difficile* infection