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MEDICAL GUIDELINES

2026 Swiss Society for Infectious Diseases recommendations for *Clostridioides difficile* infection

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Summary

The most recent Swiss Society for Infectious Diseases recommendations for *Clostridioides difficile* infection (CDI) in Switzerland were based on the 2018 American guidelines. Since then, a large number of new studies have been published, and updated international guidelines – both European and American – have introduced substantial innovations in CDI diagnosis and treatment.

This document represents a consensus statement developed by a group of experts appointed by the Swiss Society for Infectious Diseases. The objective of these national guidelines is to provide a comprehensive, evidence-based and context-specific framework for the diagnosis, treatment, prevention and follow-up of CDI across all stages of disease. By synthesising the latest clinical evidence, recent international guideline updates, and national organisational and regulatory considerations, these guidelines aim to harmonise clinical practice, promote high-quality and equitable patient care and support clinicians in making informed, patient-centred decisions within the Swiss healthcare system. These guidelines are endorsed by the Swiss Society for Infectious Diseases.

Introduction

Clostridioides difficile infection (CDI) is a major cause of healthcare-associated morbidity and mortality and represents a persistent and evolving challenge for national healthcare systems [1, 2]. The incidence and severity of CDI disproportionately affect older adults, patients with multiple comorbidities and individuals exposed to antibiotics or healthcare environments, with recurrence occurring in up to one third of cases and contributing substantially to patient burden and healthcare costs [3]. Over recent years, important advances have been made in the understanding of CDI epidemiology, pathophysiology, diagnostics and treatment, prompting significant updates to international recommendations [4–7]. These include refined diagnostic algorithms prioritising detection of free toxins, a shift away from metronidazole as routine therapy, expanded use of fidaxomicin and optimised vancomycin regimens, and the increasing role of faecal microbiota transplantation (FMT) therapies for recurrent disease. FMT has become an established, highly effective intervention, raising regulatory and implementation considerations that vary across countries [4, 8]. New live biotherapeutic products have emerged, and will probably challenge FMT in the future. Despite these advances, heterogeneity in clinical practice persists, particularly with respect to severity assessment, prevention of recurrence, management of severe and complicated CDI, and integration of novel therapies within national regulatory frameworks. The objective of the present national guidelines is to provide an updated comprehensive, evidence-based and context-specific framework for the diagnosis, treatment, prevention and follow-up of CDI across all stages of disease. Previous Swiss Society for Infectious Diseases (SSI) guidelines were based on 2018 international literature which is by now largely outdated. By summarising the most recent clinical evidence, international

guideline updates, and national organisational and regulatory considerations, this document aims to harmonise clinical practice, support high-quality and equitable patient care, and guide clinicians in making informed, patient-centred decisions in the management of CDI.

Methods

A panel of physicians from different medical specialties (infectious diseases, geriatrics, infection control) and different Swiss tertiary care hospitals was constituted. The members of this panel were selected by the Swiss Society for Infectious Diseases committee according to their expertise in the topic. The work was distributed among four working groups (WG): definitions (WG1), risk factors (WG2), treatment (WG3), and prevention and infection control (WG4).

Practical questions to answer were defined for each WG. As a first step, each WG worked independently on literature review, data analyses and elaboration of proposed recommendations. Results of analyses and recommendations were presented during a virtual session attended by all participants. These recommendations were discussed during the session and the draft amended and validated afterwards. In case of substantial disagreement, the issues were referred to each WG for reassessment and elaboration of a revised proposition, which was again submitted for the appreciation of the whole panel. The final recommendations were consensus-based and needed the approval of all the panel. Final recommendations were validated by the Swiss Society for Infectious Diseases guidelines board. The detailed workflow of guideline development and the list of participants of the different WGs are provided in table S1 and S2, respectively, in the appendix. This analysis formed the basis for adapting and contextualising international evidence-based recommendations to the Swiss healthcare setting.

Definitions

Definitions were adapted from the most recent European and American guidelines [4, 5, 7] and are summarised in figure 1.

Clinical symptoms compatible with CDI [9]

- **Diarrhoea** is defined as >3 loose stools, i.e. Bristol stool scale 6–7, in 24 hours.
- **Ileus:** Digestive dysfunction with vomiting or nausea with intolerance of oral intake and absence of stool, plus radiological signs of intestinal distension.
- **Toxic megacolon:** colonic distension greater than 6 cm with signs of sepsis [10]. Distension is typically measured at the transverse colon on radiographic imaging, but US guidelines prioritise a comprehensive clinical and radiographic assessment over strict reliance on this measurement alone [6]. The cut-offs for rectal and caecal measurement are, respectively, >4–5 cm and >9 cm.

Episode of CDI

An episode of CDI is defined as the association of 3 parameters:

- Clinical features including clinical symptoms compatible with CDI and pseudomembranous colitis diagnosed after endoscopy, colectomy or autopsy.
- Microbiological evidence of *C. difficile* (at best, evidence of free toxins): see “Microbiological methods” below.
- No alternate diagnosis.

Microbiological methods

Stool processing:

- The Infectious Diseases Society of America and the American Society for Microbiology state that proper storage is critical to prevent toxin degradation, which can lead to false negative results in toxin-based assays [11].
- Experimental data demonstrate that storage at 4 °C preserves *C. difficile* cytotoxin activity for several days, while storage at –20 °C leads to significant loss of toxin activity, especially with repeated freeze-thaw cycles, and that –80 °C is preferable for long-term storage to maintain toxin integrity [12]. Additional studies confirm that freezing at –20 °C can detrimentally affect toxin stability, particularly in diluted specimens, whereas –80 °C preserves toxin detection by immunoassay [13].

– In routine clinical practice, stool samples for *C. difficile* toxin testing should be refrigerated at 4 °C if processed within 72 hours or frozen at –80 °C for longer storage, and that –20 °C is not recommended due to the risk of toxin degradation and false negative results.
– Rectal swabs may be tested with nucleic acid amplification tests for patients with ileus (inform the laboratory).

The recommended diagnostic approach is a multistep algorithm: initial screening with a sensitive glutamate dehydrogenase (GDH) antigen assay, followed by confirmatory testing for toxins A and B using enzyme immunoassay (EIA) or immunochromatographic methods. Nucleic acid amplification tests may be used as part of the algorithm or alone in symptomatic patients, but nucleic acid amplification tests alone may detect colonisation rather than active infection, so combining nucleic acid amplification tests with toxin testing improves specificity for CDI [14]. Toxigenic culture and cell cytotoxin assays are considered gold standards but are rarely used due to labour intensity and slow turnaround time.

In 2021, the European guidelines suggested an alternative approach emphasising the importance of free toxin detection [4]:

– Free toxins measured by enzyme immunoassay **or**
– Positive nucleic acid amplification test preferably with a low cycle threshold (Ct) value. Based on the literature, several thresholds were proposed between 26 and 27 [15, 16].

Severe forms

Severe forms are defined by one of the following criteria:

– Leucocytosis with a white blood cell count of ≥15,000 cells/ml [4, 5].
– Serum creatinine level >1.5 mg/dl (>132 mcmol/l) [5] or rise in serum creatinine >50% of baseline [4, 5].
– Core body temperature >38.5 °C [4].

Severe-complicated forms

Severe-complicated forms are defined by the presence of one of the following attributed to CDI:

– Hypotension [10].
– Septic shock [10].
– Elevated serum lactate: >2 mmol/l (18 mg/dl) [10].
– Ileus.
– Toxic megacolon.
– Bowel perforation.
– Any fulminant course of disease (i.e. rapid deterioration of the patient).

Treatment response

Treatment response has been clearly defined by the European society [4]:

– Resolution of diarrhoea with maintenance of resolution for the duration of therapy and at least 48 hours after the end of treatment, and no further requirement for CDI therapy *and*
– Improvement of parameters of disease severity (clinical, laboratory, radiological) and no new signs of severe disease.

Treatment response should be observed daily and evaluated after *at least 3 days*, assuming that the patient is not worsening on treatment.

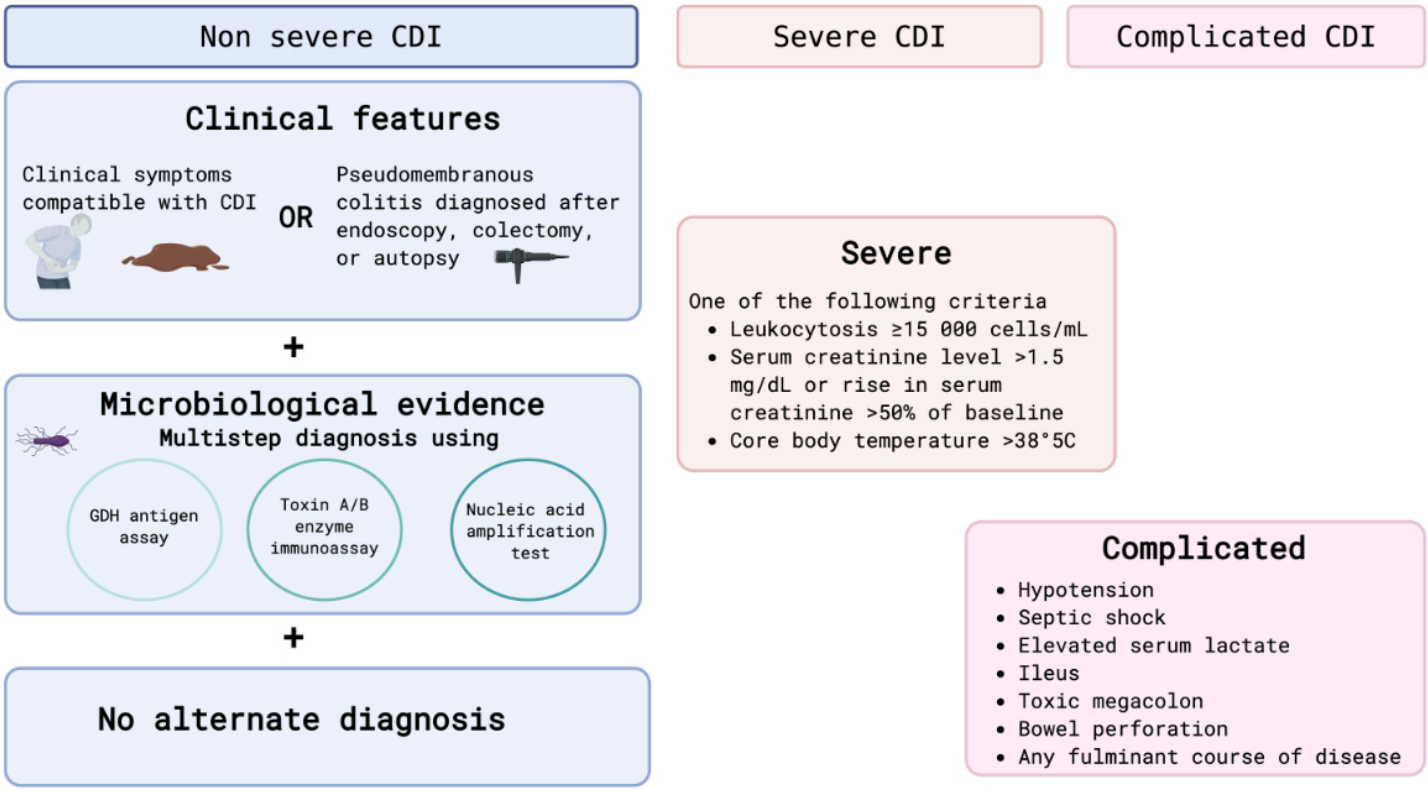
Recurrence

Recurrence is defined as CDI recurrence *within 8 weeks* after complete resolution of the initial episode. After 8 weeks, it is a new first episode.

Refractory CDI

Refractory CDI is defined as a non-response to treatment after 3–5 days of therapy (persistence of >3 loose stools, i.e. Bristol stool scale 6–7, in 24 hours). A refractory CDI should prompt evaluation for co-infections or differential diagnoses, including non-infectious diarrhoea.

Figure 1: Diagnostic approach of *Clostridioides difficile* infection.



SSI recommendation for diagnosis

- An episode of CDI is defined as clinical symptoms compatible with CDI with a microbiological confirmation ideally relying on a multistep algorithm.
- Severe forms are defined by the presence of one of the following criteria: leucocytosis, renal failure or core body temperature higher than 38.5 °C.
- Severe-complicated forms are defined by the occurrence of hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or any fulminant course.

Risk factors

The main factors identified as contributors to the development and severity of CDI are related to microbiota disruption interventions such as exposure to systemic antibiotic use, exposure to spores and alteration of host immunity [17].

The risk arising from systemic antibiotic therapy varies according to its duration: the shorter, the better [18]. Antibiotics have been categorised according to their risk of selecting *C. difficile*, with the high-risk category including clindamycin, fluoroquinolones, second-generation cephalosporins or later, carbapenems, combinations of beta-lactamases and beta-lactamase inhibitors (e.g. piperacillin-tazobactam). Fluoroquinolone use was associated with a higher risk because of the NAP1/BI/027 strain [18–20]. The risk associated with each antibiotic class is summarised in table 1.

Table 1: Antibiotic-specific risk for *Clostridioides difficile* infection in outpatient and inpatient settings, complemented by pharmaco-epidemiological data (FEARS database) [20, 84–86].

Antibiotic classes and their respective agents are ranked according to their association with *C. difficile* infection, first in inpatient, then in outpatient settings. Reported Odds Ratios from pharmaco-epidemiological studies (FEARS database) are included as supplementary information for both settings in the appendix. Results might differ from data derived from in vitro susceptibilities, due to potential confounding exposure, including duration of treatment, IV/PO formulation, co-treatment, and regional variation/molecular shifts (NAP027). However, this table might provide pragmatic evidence that may guide antibiotic selection in either outpatient or inpatient setting. The risk is classified as high, moderate or low: **(H)**: high risk [defined as inpatient OR outpatient OR >5], **(M)**: moderate risk [defined as inpatient OR outpatient OR in range 3–5], **(L)**: low risk [defined as inpatient OR outpatient OR <3]; Blank: no inpatient/outpatient data.

Antibiotic class		Antibiotic name (risk)	Estimates	Source
Penicillins	Non-antistaphylococcal	Amoxicillin (L)	OR: 1.96 [95% CI: 1.88–2.04]	Outpatients [87]
			ROR: 6.74 [95% CI: 5.92–7.67]	Pharmacovigilance [89]
		Penicillin (L)	OR: 1.8 [95% CI: 1.59–2.03]	Outpatients [87]
			ROR: 2.91 [95% CI: 1.09–7.77]	Pharmacovigilance [89]
	Antistaphylococcal	Flucloxacillin	ROR: 56.08 [95% CI: 22.13–142.10]	Pharmacovigilance [89]
	Beta-lactamase inhibitor combinations	Amoxicillin/clavulanate (H)	OR: 8.53 [95% CI: 8.23–8.85]	Outpatients [87]
			ROR: 16.84 [95% CI: 15.01–18.89]	Pharmacovigilance [89]
		Piperacillin/tazobactam (H)	OR: 6.99 [95% CI: 1.81–27.02]	Outpatients [87]
			ROR: 17.35 [95% CI: 15.30–19.69]	Pharmacovigilance [89]
Cephalosporins	1st generation	Cefazolin (L)	OR: 2.3 [95% CI: 1.9–2.6]	Inpatients [88]
			ROR: 17.26 [95% CI: 13.30–22.39]	Pharmacovigilance [89]
	2nd generation	Cefuroxime (H)	OR: 9.59 [95% CI: 8.79–10.45]	Outpatients [87]
			OR: 6.4 [95% CI: 5.1–7.9]	Inpatients [88]
			ROR: 15.03 [95% CI: 13.02–17.37]	Pharmacovigilance [89]
	3rd generation	Cefpodoxime (H)	OR: 9.17 [95% CI: 6.99–12.04]	Outpatients [87]
			ROR: 37.3 [95% CI: 25.54–54.49]	Pharmacovigilance [89]
		Ceftriaxone (H)	OR: 6.93 [95% CI: 5.16–9.29]	Outpatients [87]
			OR: 4.0 [95% CI: 3.5–4.6]	Inpatients [88]
			ROR: 10.07 [95% CI: 8.80–11.53]	Pharmacovigilance [89]
		Ceftazidime	ROR: 21.31 [95% CI: 14.86–30.56]	Pharmacovigilance [89]
	3rd generation + beta-lactamase inhibitor	Ceftazidime/Avibactam	ROR: 8.24 [95% CI: 4.26–15.93]	Pharmacovigilance [89]
		Ceftolozane/Tazobactam	ROR: 5.89 [95% CI: 3.05–11.38]	Pharmacovigilance [89]
	4th generation	Cefepime (M)	OR: 4.45 [95% CI: 1.18–16.80]	Outpatients [87]
			OR: 2.8 [95% CI: 2.1–3.6]	Inpatients [88]
			ROR: 12.51 [95% CI: 9.30–16.83]	Pharmacovigilance [89]
	5th generation	Ceftaroline	ROR: 5.29 [95% CI: 1.98–14.19]	Pharmacovigilance [89]
Carbapenems		Meropenem (H)	OR: 5.1 [95% CI: 4.4–6.0]	Inpatients [88]
			OR: 3.31 [95% CI: 0.81–13.61]	Outpatients [87]
			ROR: 16.46 [95% CI: 13.65–19.85]	Pharmacovigilance [89]
		Imipenem/Cilastatin (H)	OR: 5.1 [95% CI: 4.4–6.0]	Inpatients [88]
			ROR: 12.23 [95% CI: 9.77–15.32]	Pharmacovigilance [89]
		Ertapenem (M)	OR: 3.51 [95% CI: 1.47–8.40]	Outpatients [87]
			OR: 2.5 [95% CI: 2.0–3.2]	Inpatients [88]
			ROR: 10.77 [95% CI: 8.51–13.63]	Pharmacovigilance [89]
Lincosamides		Clindamycin (H)	OR: 25.39 [95% CI: 24.11–26.72]	Outpatients [87]
			OR: 1.9 [95% CI: 1.5–2.5]	Inpatients [88]
			ROR: 30.41 [95% CI: 28.24–32.75]	Pharmacovigilance [89]
Fluoroquinolones		Ciprofloxacin (H)	OR: 6.83 [95% CI: 6.56–7.1]	Outpatients [87]
			ROR: 8.82 [95% CI: 8.16–9.54]	Pharmacovigilance [89]
		Moxifloxacin (M)	OR: 4.71 [95% CI: 4.14–5.37]	Outpatients [87]
			ROR: 8.08 [95% CI: 7.25–9.01]	Pharmacovigilance [89]
		Levofloxacin (L)	OR: 2.49 [95% CI: 2.35–2.64]	Outpatients [87]
			ROR: 4.12 [95% CI: 3.71–4.59]	Pharmacovigilance [89]
		Norfloxacin	ROR: 13.2 [95% CI: 7.43–23.43]	Pharmacovigilance [89]
Aminoglycosides		Tobramycin (M)	OR: 4.2 [95% CI: 1.32–13.39]	Outpatients [87]
			ROR: 1.05 [95% CI: 0.67–1.62]	Pharmacovigilance [89]
		Amikacin	ROR: 13.04 [95% CI: 6.95–24.46]	Pharmacovigilance [89]
		Gentamicin (L)	OR: 2.73 [95% CI: 1.17–6.37]	Outpatients [87]
			ROR: 10.61 [95% CI: 7.90–14.27]	Pharmacovigilance [89]

Macrolides	Clarithromycin (L)	OR: 1.83 [95% CI: 1.62–2.07]	Outpatients [87]
		ROR: 5.46 [95% CI: 4.73–6.29]	Pharmacovigilance [89]
	Erythromycin (L)	OR: 1.53 [95% CI: 1.21–1.93]	Outpatients [87]
		ROR: 4.34 [95% CI: 3.20–5.88]	Pharmacovigilance [89]
	Azithromycin (L)	OR: 1.31 [95% CI: 1.26–1.37]	Outpatients [87]
		ROR: 2.71 [95% CI: 2.27–3.24]	Pharmacovigilance [89]
Tetracyclines	Doxycycline (L)	OR: 0.96 [95% CI: 0.89–1.02]	Outpatients [87]
		ROR: 2.96 [95% CI: 2.35–3.71]	Pharmacovigilance [89]
	Minocycline (L)	OR: 0.79 [95% CI: 0.67–0.93]	Outpatients [87]
Other	Cefiderocol	ROR: 17.25 [95% CI: 6.36–46.84]	Pharmacovigilance [89]
	Fosfomycin (H)	OR: 5.68 [95% CI: 2.89–11.17]	Outpatients [87]
		ROR: 16.37 [95% CI: 10.89–24.61]	Pharmacovigilance [89]
	Metronidazole	ROR: 15.18 [95% CI: 13.85–16.64]	Pharmacovigilance [89]
	Colistin	ROR: 6.39 [95% CI: 2.38–17.13]	Pharmacovigilance [89]
	Tigecycline	ROR: 6.62 [95% CI: 4.72–9.28]	Pharmacovigilance [89]
	Linezolid (M)	OR: 3.58 [95% CI: 2.36–5.44]	Outpatients [87]
		OR: 1.2 [95% CI: 1.0–1.5]	Inpatients [88]
		ROR: 2.28 [95% CI: 1.79–2.92]	Pharmacovigilance [89]
	Sulfamethoxazole/trimethoprim (L)	OR: 2.16 [95% CI: 2.05–2.27]	Outpatients [87]
		OR: 2.0 [95% CI: 1.6–2.6]	Inpatients [88]
		ROR: 4.43 [95% CI: 3.55–5.51]	Pharmacovigilance [89]
	Nitrofurantoin (L)	OR: 1.77 [95% CI: 1.65–1.89]	Outpatients [87]
		ROR: 1.55 [95% CI: 0.83–2.88]	Pharmacovigilance [89]
	Vancomycin	ROR: 3.98 [95% CI: 3.39–4.66]	Pharmacovigilance [89]
	Daptomycin (L)	OR: 0.4 [95% CI: 0.2–0.6]	Inpatients [88]
		ROR: 2.05 [95% CI: 1.46–2.87]	Pharmacovigilance [89]
	Aztreonam	ROR: 1.24 [95% CI: 0.84–1.82]	Pharmacovigilance [89]

Abbreviations: OR = odds ratio; ROR = reporting odds ratio.

Seventy to eighty percent of CDI occur in adults aged ≥65 years [1]. Recurrences are more frequently observed in older populations, affecting 20–30% of patients [21]. Over 80% of CDI-related mortalities occur in individuals aged ≥75 years, particularly those with prior comorbidities, hospitalisations and frailty [21].

Systemic antibiotics are the strongest risk factor but are often unavoidable. Other risk factors include use of proton-pump inhibitors and other acid-suppressing agents, which represent the next strongest modifiable risk factors; prior healthcare exposure, including long-term care residency and prolonged hospitalisation; and host-related factors such as inadequate antibody responses to *C. difficile* toxins, chemotherapy or corticosteroid use, severity of underlying illness, comorbidities, immunosenescence and reduced functional status [22–24]. Prior *C. difficile* colonisation or infection is also recognised as a significant risk factor [25, 26]. All risk factors are summarised in table 2.

Table 2: Risk factors for primary *Clostridioides difficile* infection, recurrent *Clostridioides difficile* infection and outcomes. "Yes" means the risk factor is preventable, "No" means the risk factor is not preventable.

Risk category	Preventable?	Risk factor	Evidence / effect size*	Notes & References
Microbiota disruption	Yes	Systemic antibiotics	OR range: ~3.55 (95% CI: 2.56–4.94) compared to no antibiotics.	Association strength depends on antimicrobial class, cumulative antibiotic exposure (duration, recurrence) [90, 91]. See table 1.
	Yes	Proton-pump inhibitors	aOR range: ~1.14–4.50 in hospital populations. Risk: 36/1000 people [89].	Underlying indication (e.g. severe illness) may confound [92, 93]. Dose and duration matters [94]. Association disappears when only looking at RCTs (bias control, but shorter use and underpowered) [95, 96].
	Yes	H2-receptor antagonist	aOR range: ~0.98–3.0 in hospital populations. Risk: 26/1000 people [89].	Demonstrated a lower risk than proton-pump inhibitors [92].
Spore exposure	No	Prior *C. difficile* colonisation or infection	[25, 26]	
	No	Prior hospitalisation / prior care facility residence	OR: 2.18 [95% CI: 1.86–2.56]: prior hospitalisation in the last 6 months [97].	Also reflects healthcare-associated risk. Trajectory (ICU > wards) and length of stay (risk +1.3% per day) matter [84].
Host immunity	No	Age ≥65 years	One of the most consistent risk factors. RR: ~1.63 (95% CI: 1.24–2.14) for rCDI.	Probably due to immunosenescence. Age is non-modifiable but helps stratify risk [93].
	Yes	Chemotherapy, in the prior month, [22, 98, 99]		Also reflects disruption of the mucosal barrier. But may also reflect non-CDI diarrhoea [100].
	Yes	Steroids [22–24]	Risk factor for community-acquired and complicated *C. difficile* infection (OR: 2.09) and rCDI (2.45).	
	No	Comorbidities	Haematological malignancy (OR range: ~1.74–12.9), chronic liver diseases (OR range: ~1.30–1.34), chronic kidney disease (OR range: ~1.58–1.93), cardiovascular diseases [26, 93].	Cumulative effect of comorbidities on the risk, that may also reflect increased healthcare exposure.
Poor outcomes / severity / mortality	Yes	Prolonged exposure to antibiotics prior to CDI [101]		
	No	Advanced age [101, 102]	Older age consistently shown to raise mortality risk.	Combined with comorbidities increases risk further [90].
	No	Male sex [103]		
	No	Neutropenia [103]		
	No	Multiple comorbidities (e.g. liver disease, kidney disease, cardiovascular disease)	Identified as likely risk factors for both primary and recurrent CDI.	Indicator of reduced physiological reserve [93].
	No	Hospital/ICU stay [101]	ICU stay associated with increased mortality in CDI cohorts.	Reflects severity of underlying illness and exposure [93].
	No	Severe form of CDI, *C. difficile* ribotype 078 [104]		

Abbreviations: CDI = *Clostridioides difficile* infection; rCDI = recurrent *Clostridioides difficile* infection; OR = odds ratio, aOR = adjusted odds ratio; ICU = intensive care unit; RR = risk ratio

Treatment

General measures [4]

- Stop unnecessary antibiotics.
- Rehydrate and correct electrolytes.
- Avoid antiperistaltic drugs.
- Reassess indication for proton-pump inhibitor.
- Probiotics not recommended.

Drugs currently available

Metronidazole

A multicentre RCT compared vancomycin and metronidazole [27]. Clinical success with metronidazole was 72.7%, lower than vancomycin (81.1%) (p = 0.02). In severe CDI, metronidazole clinical success was 66.3% vs 78.5% for vancomycin (p = 0.059). Post hoc analysis found lower odds of success with metronidazole compared with vancomycin; factors favouring success overall included treatment-naive status and mild/moderate disease. In a prospective cohort of 75 primary, uncomplicated CDI patients [28], treatment with metronidazole was associated with significantly higher recurrence – 40.9% vs 15.1% – on univariate analysis and remained an independent predictor on Cox regression (HR: 3.27, 95% CI: 1.31–8.19). The authors concluded that metronidazole should be avoided for primary treatment, aligning with guidelines favouring vancomycin or fidaxo-

micin. A network meta-analysis further confirmed that metronidazole is inferior to vancomycin, and fidaxomicin for sustained symptomatic cure [29]. Initial treatment failure rates are higher with metronidazole compared to vancomycin (RR: 1.58, 95% CI: 1.10–2.27) [30]. These differences are more pronounced in older patients, those with comorbidities and those with severe disease, in whom metronidazole is associated with higher risk of treatment failure, recurrence and mortality [6, 31].

Finally, there is a documented rise in metronidazole resistance among *C. difficile* isolates, including elevated minimum inhibitory concentrations (MIC) and emergence of plasmid-mediated resistance, particularly in epidemic ribotypes [32, 33]. The pharmacokinetic profile of metronidazole is suboptimal: oral administration results in low faecal concentrations, and its bioactivity is further reduced by interaction with the gut microbiota [32, 33]. This leads to subinhibitory exposure, promoting bacterial adaptation and potential treatment failure.

While metronidazole is substantially less expensive than vancomycin or fidaxomicin, the lower efficacy and increasing resistance outweigh its cost advantage in most clinical scenarios. Cost-effectiveness analyses suggest that lower recurrence rates with fidaxomicin and vancomycin may offset their higher upfront costs [34].

The cumulative evidence from randomised trials, meta-analyses and antimicrobial resistance data supports removing metronidazole from the routine treatment of CDI due to its lower efficacy, higher rates of treatment failure and recurrence, rising resistance, suboptimal pharmacokinetics, consistent with updated international guideline recommendations favouring vancomycin and fidaxomicin.

Vancomycin and fidaxomicin

Following on international guideline recommendations [4, 7], recent meta-analyses and systematic reviews of RCTs clarify the comparative efficacy and safety profile of fidaxomicin over vancomycin in CDI. Pooled data from six RCTs demonstrate that fidaxomicin yields significantly higher global cure rates (risk ratio [RR]: 1.18, p <0.00001) and markedly lower recurrence rates (RR: 0.59, p <0.0001) compared to vancomycin, while initial clinical cure rates and adverse event profiles remain comparable between agents [35]. These findings are consistent across diverse patient populations, including those with non-severe and severe CDI, although the benefit in severe CDI may be less pronounced and vancomycin may retain a slight advantage in initial cure for severe cases [36]. Subgroup analyses indicate that the reduction of recurrence rates with fidaxomicin is particularly relevant for older adults and those with comorbidities, such as cancer or renal impairment, where recurrence risk and healthcare utilisation are highest [37]. In a recent open-label RCT of hospitalised CDI patients receiving concomitant antibiotics, clinical cure was numerically higher with fidaxomicin than vancomycin (73% vs 62.9%) but not statistically significant. Recurrence within 30 days was rare and similar between groups (3.3% vs 4.0%; only 4 total rCDI cases) [38]. The overall recurrence rate was lower than anticipated in both arms, the global mortality reached 6.8% with no differences between the groups.

Extended administration regimens

Pulsed tapered administration of vancomycin is advocated in some guidelines for specific situations. Meta-analytic data indicate that taper-and-pulse regimens achieve higher resolution rates (83%) compared to taper alone (68%) or pulse alone (54%) in recurrent CDI, though the evidence is limited by study heterogeneity and small sample sizes [39, 40]. A small case series provides a long-term follow-up of 20 patients treated with vancomycin 125mg qd for 8 weeks from 2013 to 2017, confirming an efficient treatment, with only one relapse per 220 patient-months. However, among 13 patients discontinuing this treatment, the same authors observed 31% (n = 4) relapses in the 6 weeks following treatment discontinuation [41]. A more recent RCT compared pulsed tapered administration of vancomycin versus its standard dosing for a first episode or a first recurrence of CDI among 12 Canadian hospitals, with 256 patients. At day 56, recurrence occurred in 20/135 patients (14.8%) in the vancomycin pulse and taper group compared to 23/130 (17.7%) in the vancomycin pulse group [42]. The American Gastroenterological Association clinical practice guidelines propose this solution as an alternative to faecal microbiota-based therapies [43]; the ESCMID suggest this option if the preferred option is not available for first and later recurrences [4].

Extended-pulsed fidaxomicin regimens have also shown superior sustained cure rates in older inpatients compared to standard vancomycin courses [44]. Economic evaluations consistently report that the higher acquisition cost of fidaxomicin is offset by reduced recurrence and hospital readmission costs, resulting in cost-effectiveness or cost savings in most analyses, especially among high-risk subgroups and those receiving concomitant antibiotics [37]. Direct cost studies confirm that fidaxomicin use is associated with lower hospital admission-related expenses, sup-

porting its economic value in routine clinical practice. There are no RCTs directly comparing pulsed/tapered vancomycin to fidaxomicin or other regimens for recurrent CDI, and animal models suggest that pulsed dosing may not facilitate clearance of *C. difficile* colonisation [40].

Focusing on the gut microbiota, the two regimens are however not comparable; vancomycin, including pulsed regimens, causes profound and persistent microbiota disruption with 2–4 log_{10} reductions in key bacterial groups (Bacteroides, Firmicutes), decreased diversity (26.2 vs 349.1 Operational Taxonomic Units [OTUs] in mice), loss of colonisation resistance persisting 18 days post-treatment, and increased susceptibility to vancomycin-resistant enterococci and multidrug-resistant organisms [45–48]. In contrast, fidaxomicin preserves microbiota diversity (134.2 OTUs), maintains colonisation resistance, allows persistence of major microbiome components during treatment and promotes faster recovery with significantly higher Shannon diversity up to day 55 in clinical trials [44, 46, 47, 49].

Tigecycline

Tigecycline is not recommended as a first-line therapy for CDI, but available evidence suggests it may be considered as an adjunctive or alternative option in severe CDI when oral administration is not possible, and in refractory CDI [4]. Retrospective cohort studies and meta-analyses indicate that tigecycline may improve clinical cure rates and reduce complicated disease courses in severe CDI, but does not significantly impact mortality or relapse rates compared to standard therapy [50–53]. Case reports and small series suggest safety and efficacy in patients with severe, refractory CDI with rapid symptom improvement and low recurrence rates [53, 54].

In summary, tigecycline may be considered for severe, severe-complicated or refractory CDI as adjunctive therapy [4], but is not supported for routine use in initial or non-severe cases due to insufficient high-quality evidence.

Bezlotoxumab

Bezlotoxumab has been discontinued by Merck, the manufacturer, and is no longer available as of January 2025.

Faecal microbiota transplantation (FMT)

FMT is a highly effective therapy for recurrent *Clostridioides difficile* infection (rCDI) compared to standard-of-care antibiotics. Multiple RCTs and meta-analyses justify the use of FMT in rCDI. The landmark trial by van Nood et al. demonstrated that FMT delivered via nasoduodenal tube after vancomycin pretreatment resulted in cure rates of 81%, compared to 31% for vancomycin alone and 23% for vancomycin plus bowel lavage, establishing FMT as superior to antibiotics for rCDI [55]. A double-blind RCT by Kelly et al. found that donor FMT via colonoscopy achieved clinical cure in 90.9% of patients with multiply recurrent CDI, compared to 62.5% with autologous FMT ($p = 0.042$), with no serious adverse events attributable to FMT [56]. A single-centre RCT by Hvas et al. showed FMT was superior to both fidaxomicin and vancomycin for rCDI, with clinical resolution rates of 92% for FMT, 42% for fidaxomicin and 19% for vancomycin [57]. The Kao et al. RCT demonstrated noninferiority of oral capsule FMT compared to colonoscopic FMT, with both modalities achieving high cure rates for rCDI [58]. Real-world multicentre data confirm similar effectiveness for capsule and colonoscopic FMT with cure rates of 81–86% at 1–2 months [59]. Meta-analyses and systematic reviews consistently report pooled cure rates of 76–92% for FMT in rCDI, with a number needed to treat (NNT) of 3 and no significant increase in serious adverse events [60, 61]. FMT is effective regardless of delivery route or preparation, and capsule formulations are as effective as colonoscopic delivery [58, 59, 62].

American as well as European societies recommend FMT for immunocompetent adults with multiple recurrences of CDI, typically after failure of standard antibiotic regimens such as vancomycin or fidaxomicin [4–6, 43, 63]. This is also proposed in a recent review published by van Prehn et al. [3].

Emerging evidence supports the use of FMT in earlier stages of CDI, including first recurrence and even first episode. A recent RCT demonstrated that FMT is non-inferior to vancomycin for primary CDI with similar cure rates (78.4% vs 61.2%, 95.2% CI: −0.7–35.1%) and no increase in adverse events [64]. In this study, FMT was performed without any prior antibiotic treatment. Another double-blind, placebo-controlled trial found that FMT after vancomycin for first or second CDI episode resulted in a 90% cure rate, significantly higher than placebo [65]. The American Gastroenterological Association notes that select non-severely-immunocompromised patients at high risk for recurrence or with severe/refractory disease may benefit from FMT after the initial episode or first recurrence, though shared decision-making is recommended [43].

Cost-effectiveness analyses indicate that FMT is a cost-effective strategy for first recurrent CDI with favourable incremental cost-effectiveness ratios and high probability of cost-effectiveness at standard willingness-to-pay thresholds [66]. FMT is well tolerated with no significant difference in serious adverse events compared to control and only minor, transient gastrointestinal symptoms reported in most cases [67].

Long-term follow-up studies, including prospective registry data with a median follow-up of 30–44 months, show a low incidence of new-onset medical conditions after FMT, with no clustering of diseases associated with dysbiosis and no increased risk of inflammatory bowel disease, irritable bowel syndrome, allergy, diabetes or psychiatric disorders [68–71]. Most new diagnoses reported in long-term studies were adjudicated as unlikely to be related to FMT.

Infectious complications are rare, especially with current donor screening protocols, though isolated cases of transmission of multidrug-resistant organisms have been reported, prompting enhanced regulatory oversight [72]. In mildly or moderately immunocompromised patients, FMT appears to have a safety and effectiveness profile comparable to immunocompetent populations, with a serious adverse event rate of approximately 10% [43, 73].

In summary, FMT is strongly supported by randomised trials and major society guidelines for multiple recurrent CDI, and emerging evidence supports its use in first recurrence and select cases of initial CDI. FMT offers high efficacy, safety and cost-effectiveness, and should be considered as part of a patient-centred, evidence-based approach to CDI management.

In Switzerland, FMT is considered a drug, and manufacture therefore requires Swissmedic approval through a GMP process with a market authorisation. Lausanne University Hospital (CHUV) is a Swissmedic-certified centre for FMT (frozen capsules and liquid formulations) (Contact: min.tmf@chuv.ch).

Rationale for severe and severe-complicated forms

Severe CDI

Recent meta-analyses and randomised controlled trials indicate that fidaxomicin is non-inferior to vancomycin for initial clinical cure in severe CDI; however, a 2024 meta-analysis found that vancomycin was statistically more effective than fidaxomicin for severe CDI (risk ratio [RR]: 0.94, 95% CI: 0.90–0.98, p <0.01), although the absolute difference was modest [36]. Fidaxomicin consistently demonstrates lower recurrence rates and improved long-term mortality in general CDI populations, but these benefits are not clearly established in severe CDI subgroups, with no significant difference in recurrence rates between fidaxomicin and vancomycin for severe CDI specifically [30, 35, 74]. In a large propensity-matched analysis, combined clinical failure or recurrence rates were similar (fidaxomicin 31.9% vs vancomycin 25.5%, p = 0.071), as were 30-, 90- and 180-day mortality rates [75]. When oral administration is not possible, intravenous metronidazole or tigecycline can be combined with vancomycin local delivery [4].

Complicated CDI

Smaller retrospective studies in critically ill or fulminant CDI patients treated with fidaxomicin report response rates comparable to those in general medical wards, but sample sizes are limited and treatment failure rates remain high [6]. As a result, most of the current recommendations are based on expert opinions rather than strong experimental proofs. The majority of clinical trials and real-world studies exclude fulminant CDI, leaving a significant evidence gap for fidaxomicin in this population. For complicated CDI, defined by hypotension, shock, ileus or megacolon, oral vancomycin (500 mg four times daily, with or without rectal administration) plus intravenous metronidazole 500 mg every 8 hours is recommended as first-line therapy for fulminant CDI; for patients with ileus, rectal vancomycin (500 mg every 6 hours) should be added to ensure adequate colonic drug delivery. Early surgical consultation is advised for patients with clinical deterioration or evidence of toxic megacolon [4, 7, 43]. Fidaxomicin has not been adequately studied in this population.

FMT in severe and complicated forms

Clinical trial and cohort data support the use of FMT in severe and complicated forms of CDI), particularly when standard medical therapy fails. In a retrospective analysis, sequential FMT combined with vancomycin achieved a cure in 100% of severe and 87% of fulminant CDI cases during the same admission, and a randomised trial showed 100% success for multiple faecal microbiota transplantations plus vancomycin versus 75% for a single FMT plus vancomycin, with no serious adverse events reported [76].

A meta-analysis of 16 studies (including one randomised trial) found a pooled clinical cure rate of 61% after a single FMT in severe/fulminant CDI, with major adverse events in 10.9%, colectomy in 8.2%, and an all-cause mortality of 15.6% [77]. Observational studies report that FMT in severe/fulminant CDI reduces mortality and colectomy rates compared to standard care, with an NNT of 2–3 to prevent one death [78]. FMT can be safely administered via colonoscopy, even in toxic megacolon, using careful technique [6].

Most protocols recommend continuing anti-CDI antibiotics (vancomycin or fidaxomicin) alongside FMT, and repeating FMT every 3–5 days until clinical and endoscopic resolution [6]. Overall, FMT is effective and safe as salvage therapy for severe and complicated CDI, with improved survival and low rates of serious adverse events when performed with appropriate donor screening and procedural precautions.

Empirical antibiotic therapy

- Start if microbiological confirmation is delayed or in complicated CDI.
- Avoid empirical use of fidaxomicin.

Confirmed CDI treatment

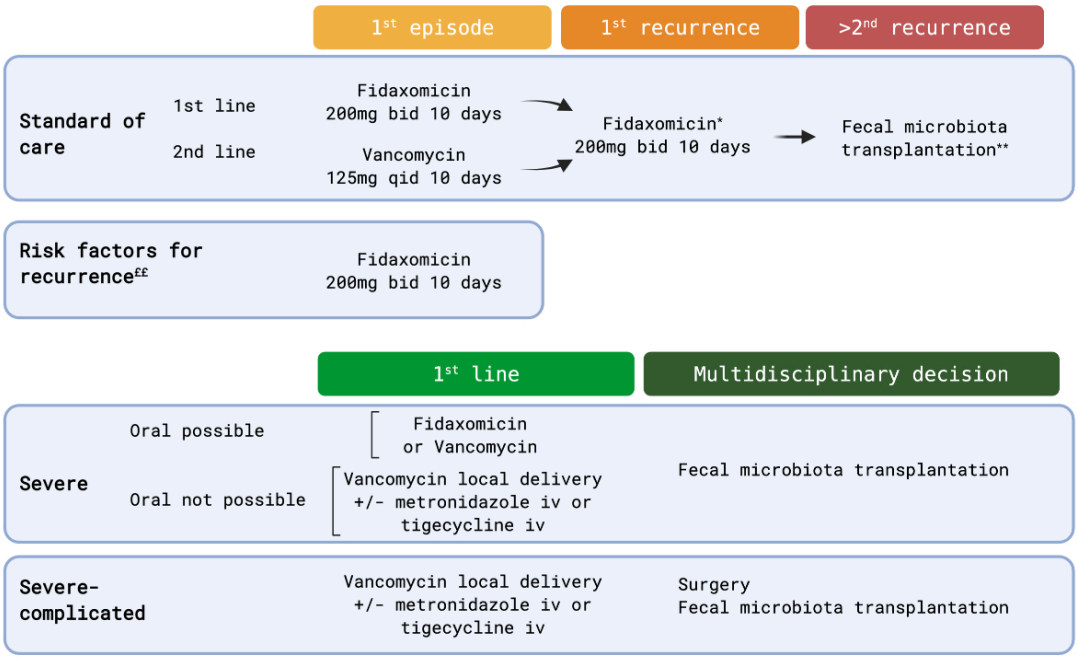
The treatment of documented CDI varies according to the type of episode (first episode, first recurrence or multiple recurrences), the presence of risk factors for recurrence, and disease severity. For a first episode, the standard first-line therapy is fidaxomicin; as an second-line option, vancomycin may be used. In patients with risk factors for recurrence, fidaxomicin is preferred for the initial episode because of its lower recurrence risk. For a first recurrence, treatment depends on prior therapy: if fidaxomicin was used initially, vancomycin is recommended, whereas fidaxomicin can be used if vancomycin was given during the first episode. All these choices are in line with the current European recommendations [4]. For second or subsequent recurrences, FMT is recommended. If the preferred options are unavailable, alternatives include vancomycin for an initial episode and vancomycin taper-and-pulse regimens for recurrent disease.

Management also depends on disease severity. In severe CDI with oral treatment possible, either fidaxomicin or vancomycin is recommended as first-line therapy, with FMT considered through multidisciplinary decision-making. If oral therapy is not possible, local delivery of vancomycin combined with intravenous metronidazole or tigecycline may be used. In severe-complicated CDI, treatment includes local vancomycin delivery with intravenous metronidazole or tigecycline, and escalation to surgical management or FMT may be required following multidisciplinary evaluation.

The algorithm based on severity, risk factors for recurrence, type of episode is depicted in figure 2.

Figure 2: Suggested treatment algorithm for *Clostridioides difficile* infection.

* Consider Extended fidaxomicin: 200 mg twice a day on day 1–5, 200 mg every 48 hours on day 7–25. / ** Can be discussed earlier in selected patients. FMT is always performed after a full 10 days' treatment of vancomycin or fidaxomicin. / § Vancomycin taper pulse: 2 weeks 125 mg four times a day, 1 week 125 mg twice a day, 1 week 125 mg daily, 1 week 125 mg every 48 hours, 1 week 125 mg every 72 hours. / £ In multiple recurrences, vancomycin taper pulse is extremely less effective than FMT and should be considered only if FMT is not available. / ££ If one risk factor for recurrence is present.



New drugs

There are two microbiota-derived standardised live biotherapeutic product treatments licensed for CDI. Both FDA-approved products (SER-109 and RBX2660) demonstrated substantial reduction of recurrence risk in rCDI compared with placebo, with recurrence rates of ~12% vs 40% and treatment success rates of ~71% versus ~58%, respectively.

SER-109 (VOWST™) consists of faecal viable Firmicutes spores (purified suspension from healthy donors) that are applied orally four capsules daily for three consecutive days. SER-109 is FDA-approved since 2023 for the prevention of recurrent CDI in adults with rCDI after antibiotic treatment. In a randomised, placebo-controlled phase III trial (ECOSPOR III), orally applied SER-109 (4 capsules daily for 3 days) demonstrated superiority over placebo in reducing the risk of rCDI. The proportion of patients with rCDI up to 8 weeks after dosing was 12% in the SER-109 group compared with 40% in the placebo group. The relative risk (RR) of recurrence was 0.32 (95% CI: 0.18–0.58) for SER-109 vs placebo (p <0.001) [79]. Engraftment was rapid and correlated with favourable outcomes. Post hoc analyses showed lower risks regardless of baseline characteristics, comorbidities, co-medications and ribotype [80].

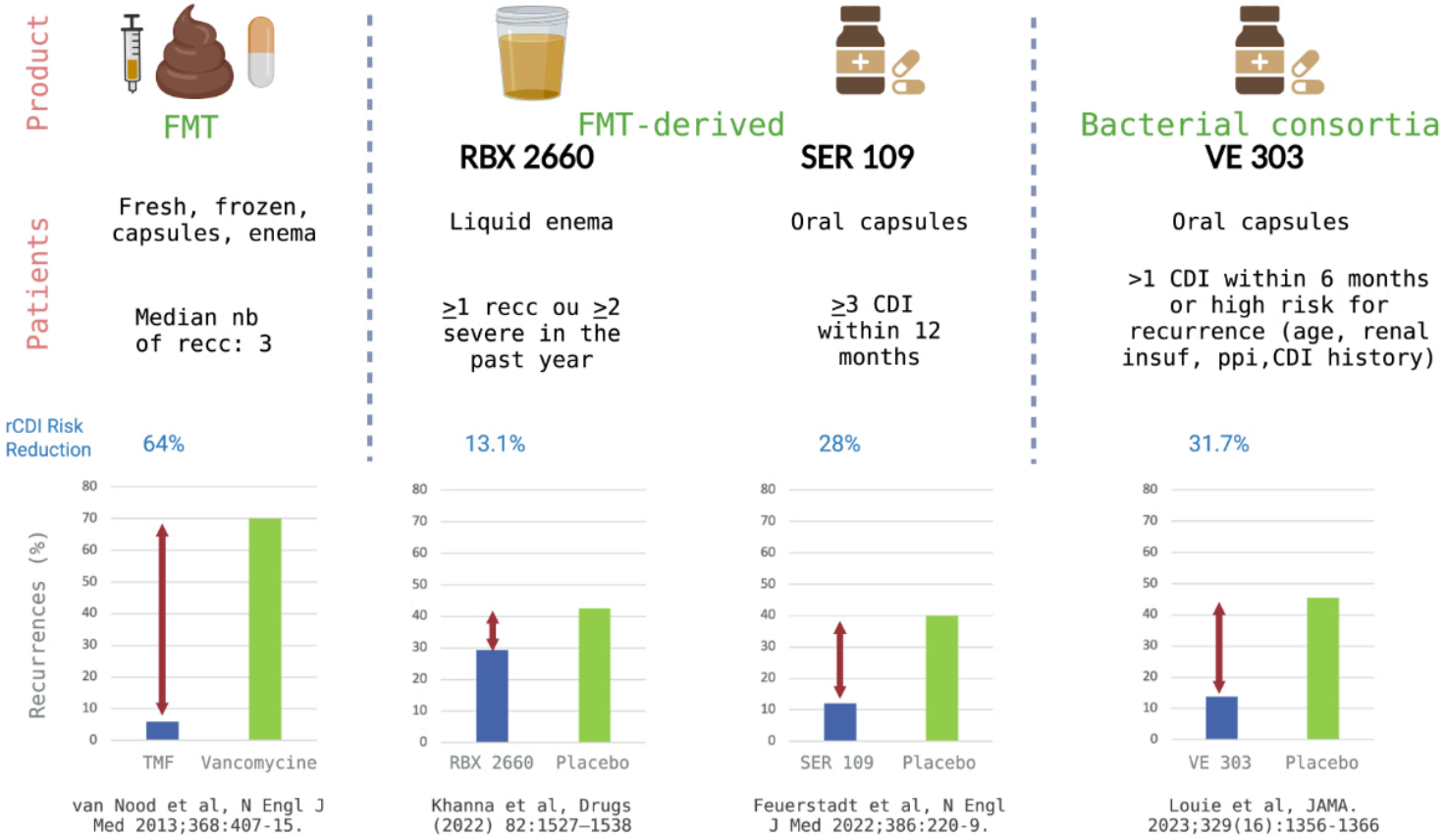
RBX2660 (REBYOTA™) consists of cryopreserved broad consortia of live microbes from screened healthy donors, applied rectally as a single-dose microbiota suspension (150 ml). RBX2660 is FDA-approved since 2022 for the prevention of recurrent CDI in adults with rCDI after antibiotic treatment. In a randomised, double-blind, placebo-controlled phase 3 trial, a single-dose enema of RBX2660 achieved treatment success rates of 70.6% versus 57.5% for placebo at 8 weeks with an estimated treatment effect of 13.1% and a posterior probability of superiority of 0.991 [81]. There were more side effects with RBX2660 but most were mild gastrointestinal disorders such as diarrhoea and abdominal pain and overall safety was good.

One further live biotherapeutic product has received orphan drug designation from the FDA for CDI treatment: VE303 (Vedanta Biosciences®) is a defined bacterial consortium composed of 8 well-characterised, nonpathogenic, nontoxigenic, commensal strains of *Clostridia*, administered orally in capsules. The FDA has granted VE303 Orphan Drug designation for the prevention of rCDI

in individuals with prior rCDI. A phase 2, double-blind, placebo-controlled dose-ranging study in adults with laboratory-confirmed CDI showed a significantly reduced risk of recurrence of 13.8% for high-dose VE303 versus 45.5% for placebo. This equates to an adjusted absolute risk reduction (ARR) of 30.5% (p = 0.006) [82]. A phase 3 study of VE303 for patients with rCDI is currently recruiting.

A comparison of the efficacy of these live biotherapeutic products compared to classic FMT from the pivotal van Nood trial is presented in figure 3.

Figure 3: Efficacy of RBX2660, SER109 and VE303 compared to classic FMT.



Other investigational microbiota-derived oral therapeutics include MET-2 and VP20621, which have been tested in phase 1 studies but to date still lack clinical efficacy data from clinical trials.

All these products offer consistent composition and rigorous safety screening, addressing limitations of conventional FMT. There are no head-to-head trial data available for these new products against FMT and none have been approved by the EMA or Swissmedic. Current international guidelines do not include these novel compounds yet. Therefore, we await further data and approval before we can make recommendations for their use.

SSI recommendation for treatment

- Fidaxomicin is the first-line treatment for the first episode.
- In the absence of risk factors for recurrence, vancomycin can be proposed as an alternative.
- In severe episodes, vancomycin and fidaxomicin can both be proposed.
- In severe-complicated forms and when oral administration is not possible, vancomycin local delivery combined with metronidazole or tigecycline intravenously is proposed.
- FMT is recommended after the second recurrence but several lines of evidence suggest a potential role earlier.

– Live biotherapeutic products are not yet recommended.

Prevention and infection control

Primary prevention of *C. difficile* infection

We concur with the "Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update" by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) [5] that there is insufficient evidence to recommend administration of probiotics for primary prevention of CDI at this point.

Prevention of *C. difficile* transmission in healthcare settings

Table 3 provides an overview of recommendations on infection prevention and control measures to prevent transmission of *C. difficile* in healthcare settings. These recommendations are based on the "Guidance document for prevention of CDI in acute healthcare settings" published on behalf of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [83]. In general, these measures are supported by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) "Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update" [5], in part with differing strengths of recommendations and quality assessments.

Table 3: Overview of recommendations on infection prevention and control measures to prevent transmission of *Clostridium difficile* in healthcare settings.

Infection control measure		Endemic setting		Outbreak setting	
		Recommendation	Quality of evidence	Recommendation	Quality of evidence
Surveillance in combination with timely feedback		Yes/strong	Very low	Yes/strong	Very low
Screening of asymptomatic patients		No/conditional	Low	No/conditional	Not applicable
Hand hygiene	Switch from hand rub to hand washing	No/conditional	Very low	Yes/conditional	Very low
	Increase compliance	Yes/conditional	Very low	Yes/conditional	Very low
Use of personal protective equipment (gloves/gowns)		Yes/conditional	Very low	Yes/strong	Very low
Implement contact precautions		Yes/strong*	Very low	Yes/strong	Very low
Environmental cleaning/disinfection	Daily and terminal environmental sporicidal disinfection	Yes/conditional	Very low	Yes/strong	Very low
	"No touch" disinfection systems»	Yes/conditional	Very low	Yes/conditional	Very low
Antibiotic stewardship	Restriction of antibiotic agents/classes	Yes/strong	Moderate	Yes/strong	Low
	Reducing the duration of antibiotic therapy	Yes/strong	Very low	Yes/strong	Very low
Education	Of healthcare workers	Yes/strong	Very low	Yes/strong	Not applicable
	Of patients and visitors	Yes/strong	Not applicable	Yes/strong	Not applicable

* The authors acknowledge that institutions may choose to forgo contact precaution measures, providing strict surveillance of CDI rates and implementation of other prevention measures.

Further details are beyond the scope of this guideline.

Note: For the initial fidaxomicin prescription, contact with the patient insurance company may be required because reimbursement is currently limited to specific situations: no response to metronidazole and vancomycin, or multiple recurrences (≥2), or follow-up treatment of patients who were previously treated as inpatients with fidaxomicin. These limitations are not in line with the current literature.

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Appendix

Table S1: Workflow of the guideline development.

Task	Who	What
Design / conceptualization; level: leading committee		
Definition of working groups (WG) and group leaders	SSI executive committee	Definition of 4 WG: definitions, risk factors, treatment and hygiene/prevention.
Constitution of the WGs	Group leaders	Designation of 4 group leaders among the scientific committee according to their expertise in the field.
Determination of questions to answer	Group leaders	For each WG, a subset of practical questions to answer (i.e. relevant for clinical practice) were defined.
Analysis / Interpretation; level: each working group (WG)		
Literature review	Group leaders and senior reviewers	Selection of relevant articles (literature search) for each topic and questions to answer.
Compilation of evidences	Group leaders and senior reviewers	Analyses of selected articles. Constitution of a core of evidence-based elements to answer the questions.
Proposition of recommendation	All WG members (group leaders, senior reviewers)	Review of the core of evidence-based elements and proposition of recommendation based on these elements.
Discussion for recommendations; level: all participants		
Presentation of results and preliminary recommendations	Plenary webex: all participants (group leaders, senior reviewers). All participants were required	Presentation of the results by each WG.
Analysis of the recommendations	All participants (group leaders, senior reviewers)	Results and recommendations were analyzed by all the participants. All the comments were then gathered to be discussed in the last plenary Webex. The participants were invited to send by email their potential comments or disagreements.
Plenary session final discussion	Plenary Webex: all participants (group leaders, senior reviewers). All participants were required	All comments were discussed to reach a consensus.
Preparation of manuscript; level: all participants		
First draft of individual chapters	Each group leader	Each WG, redaction of their dedicated chapter after discussion of the evidence in the WG
First draft of the complete manuscript	B Guery	Introduction and methodology, merging of all different chapters, harmonization of style and length, finalization of tables / figures.
Review / editing of manuscript	All participants	Manuscript was sent by email to all participants for review. Approval of all participants was required for co-authorship.
Finalization of the manuscript	B Guery	Implementation of edits of the participants. Implementation following the changes suggested in the final plenary Webex.

Table S2: Composition of the working groups (WG).

Last name, first name	Specialty	Role
WG 1: definitions		
Prendki, Virginie	Geriatrics, Infectious diseases	Group leader
Guery, Benoit	Infectious diseases	Senior reviewer
WG 2: risk factors		
Brugger, Silvio D	Infectious diseases	Group leader
Prendki, Virginie	Geriatrics, Infectious diseases	Senior reviewer
Martischang, Romain	Infectious diseases	Senior reviewer
WG 3: treatment		
Guery, Benoit	Infectious diseases	Group leader
Albrich, Werner	Infectious diseases	Senior reviewer
Brugger, Silvio D	Infectious diseases	Group leader
WG 4: hygiene and prevention		
Tschudin-Sutter, Sarah	Hygiene, Infectious diseases	Group leader
Stroffolini, Giacomo	Hygiene, Infectious diseases	Senior reviewer