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Guideline

Japanese Clinical Practice Guidelines for Management of *Clostridioides (Clostridium) difficile* infection

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1. *C. difficile* testing algorithms

Toxigenic culture and cytotoxicity assays are standard tests for detecting *C. difficile* infection (CDI). Others include immunochromatographic strips, a rapid diagnostic test that detects glutamate dehydrogenase (GDH and toxins simultaneously, and the nucleic acid amplification test (NAAT) that detects *C. difficile* toxin-producing genes. NAAT may not be available in some facilities, so a 2-step method can be adopted where GDH-positive and toxin-negative specimens are selected first, and then toxigenic culture is performed for these specimens. The testing algorithms noted here do not stipulate approaches that individual facilities should opt for based on their characteristics and policies, because testing methods may be influenced by regional and institutional peculiarities. Whichever approach is taken, the diagnosis of CDI should be meticulous and thorough, with consideration given to the possibility that all tests may give false-positive and false-negative results in some instances.

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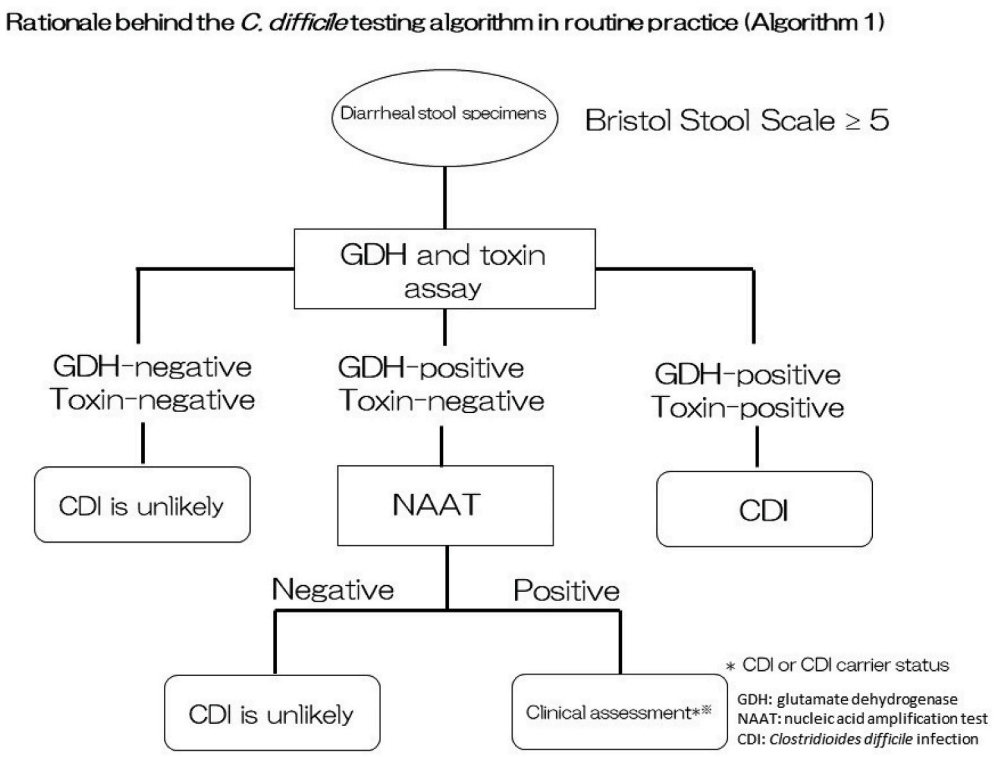
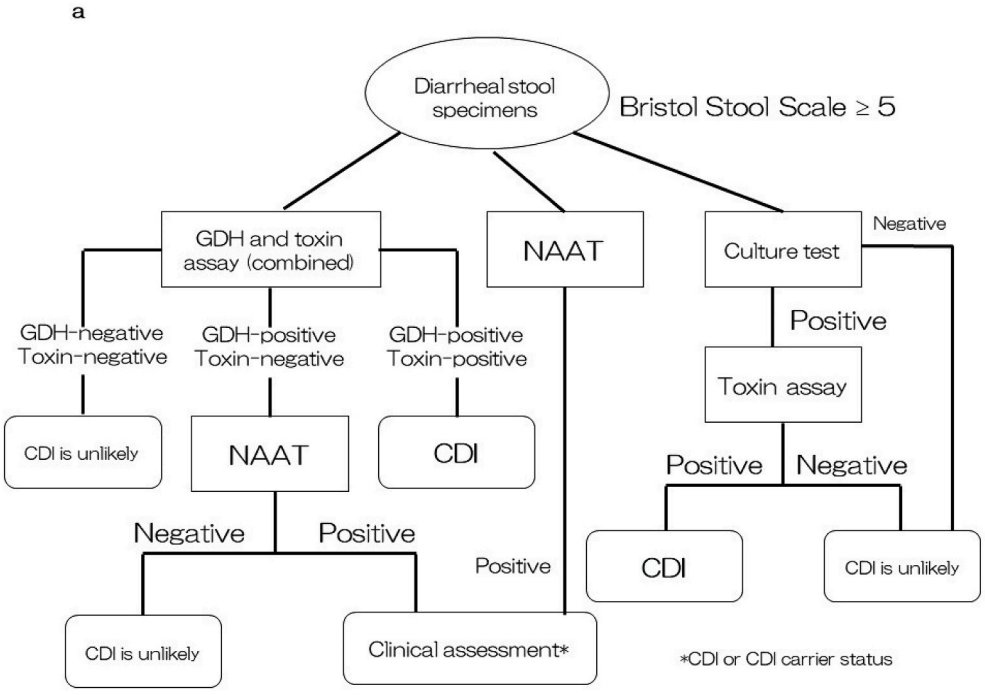
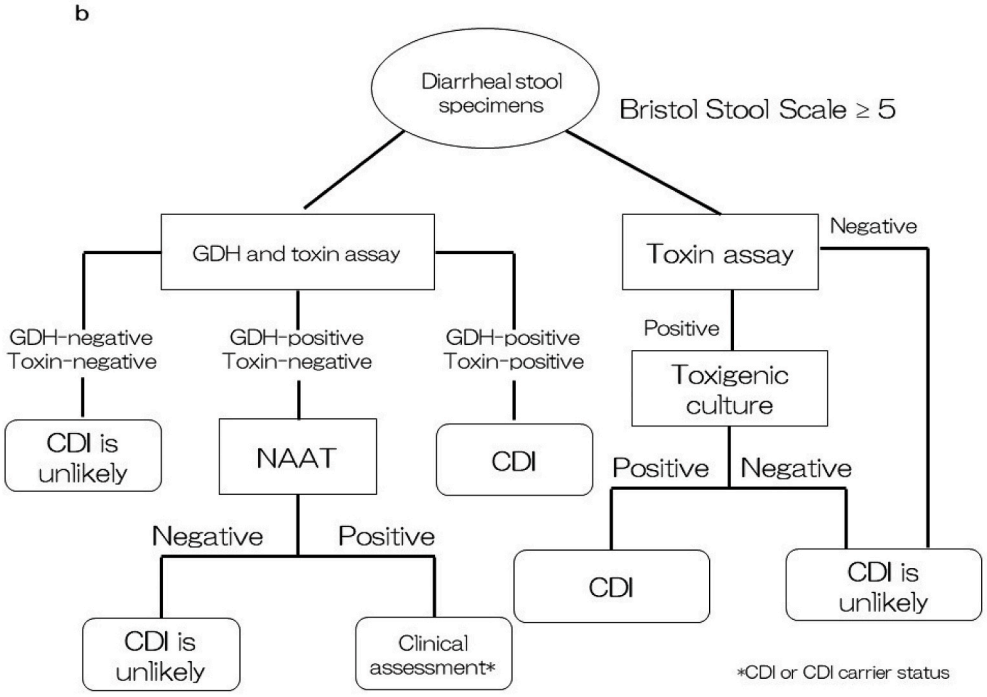


1.1. Rationale behind the C. difficile testing algorithm in routine practice (Algorithm 1)

This algorithm comprises a rapid diagnostic kit for combined GDH and toxin A/B assay, followed by NAAT based on the results of the rapid diagnostic test.

The sensitivity of the GDH assay is relatively high in general, so GDH-positive/toxin-positive results are considered confirmatory for CDI, while GDH-negative/toxin-negative results are considered non-CDI. Conversely, the sensitivity of the toxin assay using diarrheal stool specimens is low, so GDH-positive/toxin-negative results do not distinguish toxigenic strains from non-toxigenic strains. GDH-positive/toxin-negative specimens should therefore be subjected to NAAT. If toxigenicity is confirmed, CDI can be diagnosed by taking disease condition into account; if toxigenicity is not confirmed CDI is unlikely and anti-*C. difficile* medication is not required, in which case other causes of diarrhea need to be identified and/or ruled out.





1.2. Rationale behind the C. difficile testing algorithm during outbreaks (Algorithm 2a and 2b)

During outbreaks, proactive use of high sensitivity tests (i.e., NAAT and toxigenic culture) is recommended because of the possibility of false-negative results in patients with neutropenia who have undergone transplantation. Wider surveillance (including carriers) may be needed to determine the situation with regard to *C. difficile* outbreaks, and molecular epidemiological approaches (e.g., ribotyping) may become necessary. Toxigenic culture is time-intensive, but it offers detailed analysis of strains. Depending on the availability of NAAT in individual facilities, Algorithm 2a (NAAT without waiting for GDH and toxin assay results) or Algorithm 2b (NAAT based on GDH and toxin assay results) should be chosen.

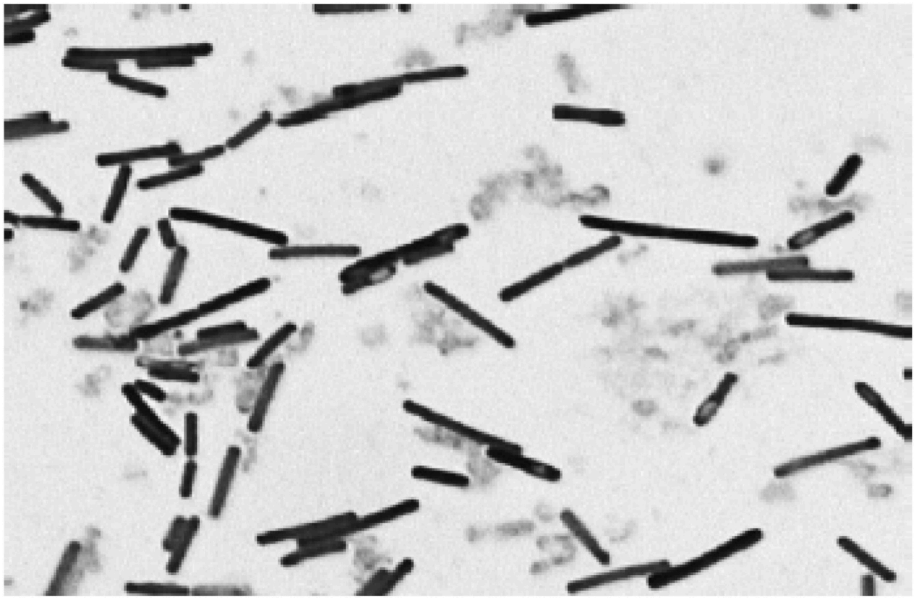
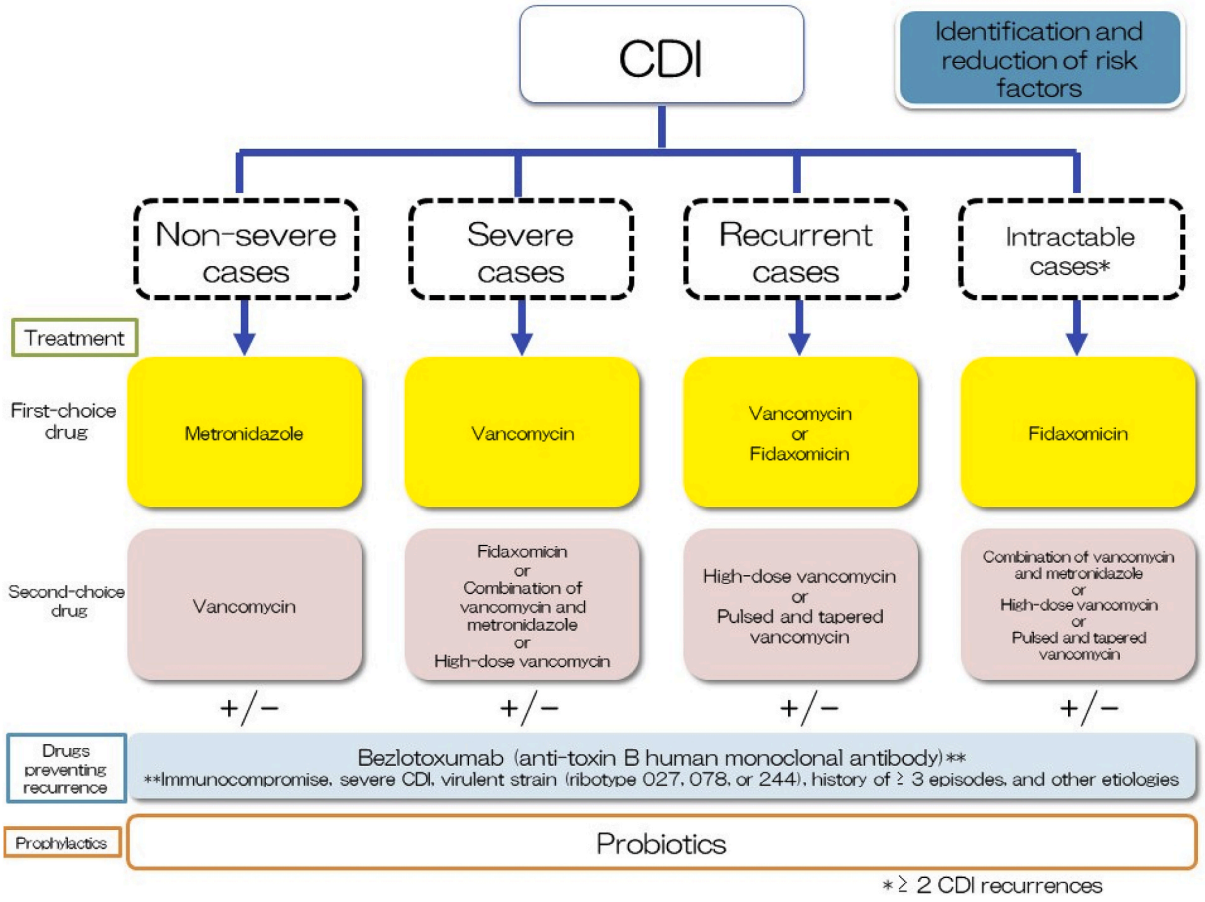


Fig. 1. Gram-stained *C. difficile*.
Gram stain of *C. difficile* showing positive rod-shaped bacteria. Subterminally located spores can be seen in some cells.

2. C. difficile treatment algorithm



2.1. Preparation of the Japanese Clinical Practice Guidelines for Management of Clostridioides (Clostridium) difficile infection (CDI)

2.1.1. Principles for preparation

C. difficile is the most common anaerobic pathogen that causes nosocomial or healthcare-associated infections, and *C. difficile* infection manifests variously as diarrhea and pseudomembranous colitis. These clinical practice guidelines were prepared to improve the overall management of CDI.

These guidelines include general information and clinical questions (CQs) about CDI based on the most recent evidence. However, it should be noted that epidemiological data on *C. difficile* in Japan are limited and that there is insufficient evidence overseas and in Japan for the classification of severity as well as on the dosage and administration of new therapies (e.g., probiotics, anti-toxin B human monoclonal antibody, fidaxomicin, and fecal microbiota transplantation) in addition to metronidazole and vancomycin. Thus, recommendations are made based on specialist opinions in order to reflect the clinical setting in Japan.

We hope that these guidelines will help to advance *C. difficile* research in Japan and that the communication of the research results worldwide can lead to guideline revision.

2.1.2. Precautions for use

These clinical practice guidelines serve only as reference to guide the direction of CDI management. Given the paucity of evidence in Japan, clinical practice procedures should be chosen through collaboration between medical professionals and patients, taking into consideration the situation and characteristics of both the individual facilities and individual patients. The guidelines are not mandatory in clinical research or clinical practice, and allow for decision-making at the discretion of medical professionals.

2.1.3. Conflicts of interest (COI)

The COI committees of the Japanese Society of Chemotherapy and the Japanese Association for Infectious Diseases have oversight of potential COI in compliance with the COI guidelines. The COI of editorial board members responsible for producing the Japanese Clinical Practice Guidelines for Management of *Clostridioides (Clostridium) difficile* Infection are as follows.

1) Research funding
2) Fees for lectures and manuscript writing
3) Personal income

Hiroyuki Kunishima received lecture fees from MSD K.K. and Taisho Toyama Pharmaceutical Co., Ltd.

Hiroki Ohge received lecture fees from Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co., Ltd., and MSD K.K.

Hiroki Ohge received scholarship funds from Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., and Shionogi & Co., Ltd.

Atsushi Nakamura received lecture fees from Taisho Toyama

Pharmaceutical Co., Ltd., Pfizer Japan Inc., and MSD K.K.

Hiroshige Mikamo received advisory fees from Toyama Chemical Co., Ltd.

Hiroshige Mikamo received lecture fees from Astellas Pharma Inc., MSD K.K., Daiichi Sankyo Co., Ltd., Shionogi & Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Toyama Chemical Co., Ltd., Asahi Kasei Pharma Corp., and Miyarisan Pharmaceutical Co., Ltd.

Hiroshige Mikamo received manuscript fees from MSD K.K., Taisho Toyama Pharmaceutical Co., Ltd., and Pfizer Japan Inc.

Hiroshige Mikamo received scholarship funds from Asahi Kasei Pharma Corp., Astellas Pharma Inc., MSD K.K., Eneforest Co., Ltd., Shionogi & Co., Ltd., Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Toyama Chemical Co., Ltd., Pfizer Japan Inc., FUJIFILM Pharma Co., Ltd., Hologic Japan Inc., Miyarisan Pharmaceutical Co., Ltd., and Meiji Seika Pharma Co., Ltd.

Yoshitomo Morinaga received scholarship funds from SRL, Inc., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Daiichi Sankyo Co., Ltd., Toyama Chemical Co., Ltd., Astellas Pharma Inc., Mitsui Chemicals, Inc., and MSD K.K.

Katsunori Yanagihara received lecture fees from MSD K.K., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Nippon Becton Dickinson Co., Ltd., bioMérieux Japan Ltd., and Astellas Pharma Inc.

Katsunori Yanagihara received scholarship funds from SRL, Inc., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Daiichi Sankyo Co., Ltd., Toyama Chemical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Astellas Pharma Inc., Mitsui Chemicals, Inc., MSD K.K., Shionogi & Co., Ltd., Nippon Becton Dickinson Co., Ltd., Hitachi High Technologies Co., Ltd., and Beckman Coulter K.K.

Yuka Yamagishi received lecture fees from Sumitomo Dainippon Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., and MSD K.K.

Yuka Yamagishi received scholarship funds from MSD K.K., Asahi Kasei Pharma Corp., Astellas Pharma Inc., Eneforest Co., Ltd., Shionogi & Co., Ltd., Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Toyama Chemical Co., Ltd., Pfizer Japan Inc., FUJIFILM Pharma Co., Ltd., Miyarisan Pharmaceutical Co., Ltd., and Meiji Seika Pharma Co., Ltd.

Hiromichi Suzuki, Kazuaki Matsumoto, Nobuaki Mori, and Sadako Yoshizawa have nothing to declare.

2.1.4. Funding

Formulation of the present guidelines was entirely funded by the Japanese Society of Chemotherapy and the Japanese Association for Infectious Diseases.

*2.1.5**Main bodies responsible for formulation of the guidelines***

Japanese Society of Chemotherapy.

Japanese Association for Infectious Diseases.

*2.1.6. **Committee for development of the Japanese Clinical Practice Guidelines for Management of Clostridioides(Clostridium)difficile infection** (hereafter referred to as the Guidelines Committee)*

Chairman: Hiroyuki Kunishima (Department of Infectious Diseases, St. Marianna University School of Medicine).

Members: Hiroki Ohge (Department of Infectious Diseases,

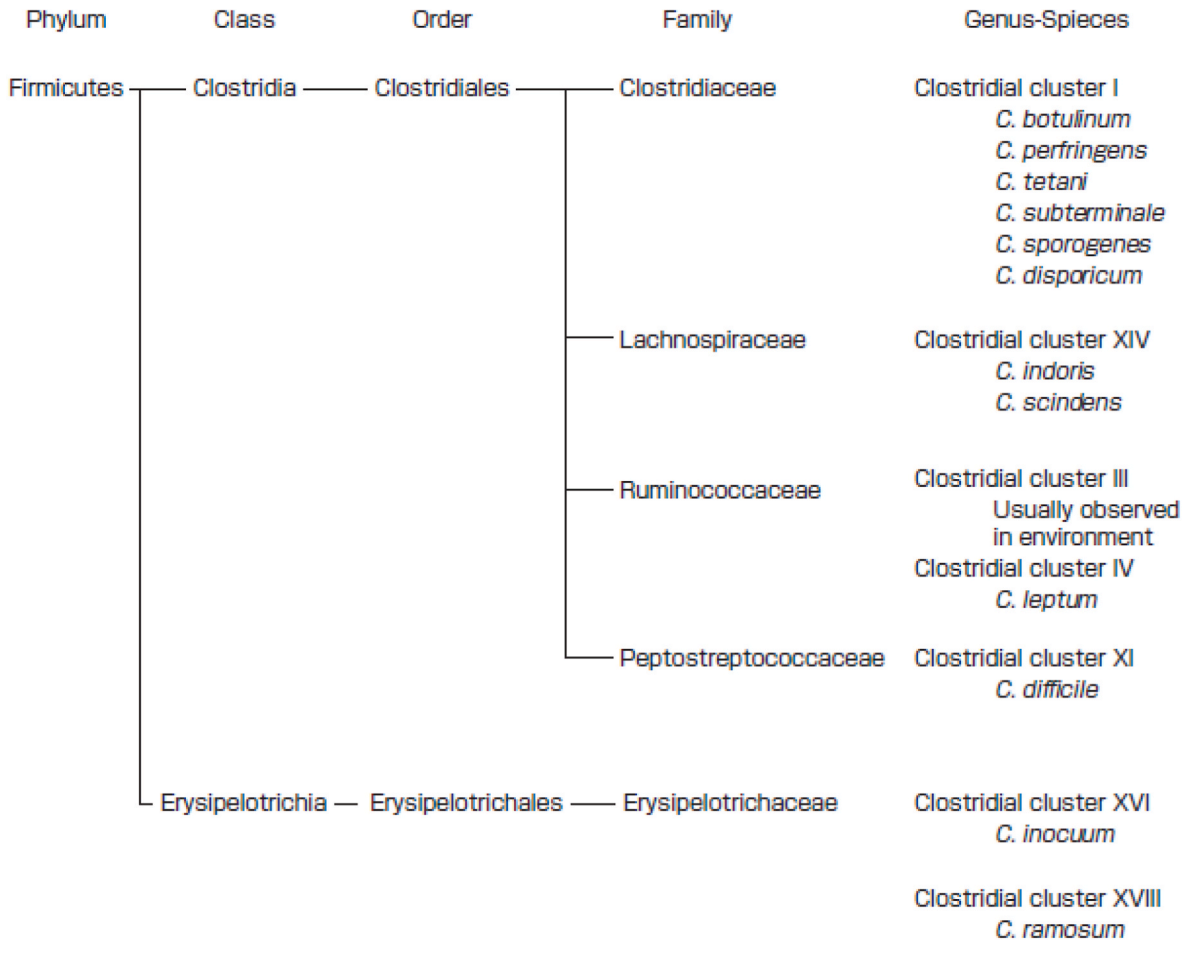


Fig. 2. Classification of *C. difficile* and Clostridial clusters.

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Kazuaki Matsumoto (Division of Pharmacodynamics, Faculty of Pharmacy, Keio University).

Hiroshige Mikamo (Clinical Infectious Diseases, Graduate School of Medicine, Aichi Medical University).

Nobuaki Mori (Division of General Internal Medicine and Infectious Diseases, National Hospital Organization Tokyo Medical Center).

Yoshitomo Morinaga (Department of Microbiology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama).

Katsunori Yanagihara (Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Sciences).

Yuka Yamagishi (Clinical Infectious Diseases, Graduate School of Medicine, Aichi Medical University).

Sadako Yoshizawa (Department of Clinical Laboratory/Department of Microbiology and Infectious Diseases, Toho University School of Medicine).

2.1.7. Guidelines Committee activities

The administrative boards of the Japanese Society of Chemotherapy and the Japanese Association for Infectious Diseases decided to produce the Japanese Clinical Practice Guidelines for Management of *Clostridioides (Clostridium) difficile* Infection, and Hiroshige Mikamo was appointed representative of the Japanese Society of Chemotherapy, Katsunori Yanagihara was appointed representative of the Japanese Association for Infectious Diseases, and Hiroyuki Kunishima was appointed Chairman of the Guidelines Committee.

2.1.8. Development of the Japanese Clinical Practice Guidelines for Management of Clostridioides (Clostridium) difficile infection

2.1.7.1. English title. Japanese Clinical Practice Guidelines for Management of *Clostridioides (Clostridium) difficile* Infection.

2.1.7.2. Objective. The objective of the guidelines is to improve the following outcomes.

- Onset of CDI
- Aggravation of CDI
- Recurrence of CDI
- Deaths due to CDI
- Healthcare-associated CDI

2.1.7.3. Topics. Diagnosis and treatment of CDI, and measures against CDI.

2.1.7.4. Potential users (individuals and facilities). Healthcare professionals including doctors, pharmacists, clinical laboratory technicians, and nurses, and any healthcare facilities involved in the management of patients with CDI.

2.1.7.5. Relationship with existing guidelines. There are no existing guidelines for CDI in Japan, so these represent the first for CDI in Japan.

2.1.7.6. Critical clinical questions. Critical CQ 1: Definition of CDI.
Critical CQ 2: Assessment of severity of CDI.
Critical CQ 3: Recurrence of CDI.
Critical CQ 4: Intractable CDI.
Critical CQ 5: CDI testing.
Critical CQ 6: Treatment of CDI.
Critical CQ 7: Prevention of recurrent CDI.
Critical CQ 8: Use of probiotics for CDI.
Critical CQ 9: Fecal microbiota transplantation for CDI.
Critical CQ 10: Measures against CDI.

2.1.7.7. The search for evidence

2.1.7.7.1. Types of evidence. Existing guidelines, systematic reviews, meta-analyses, and original research articles (i.e., randomized controlled trials (RCTs), non-randomized controlled trials, and observational studies) were searched for, in this order of priority.

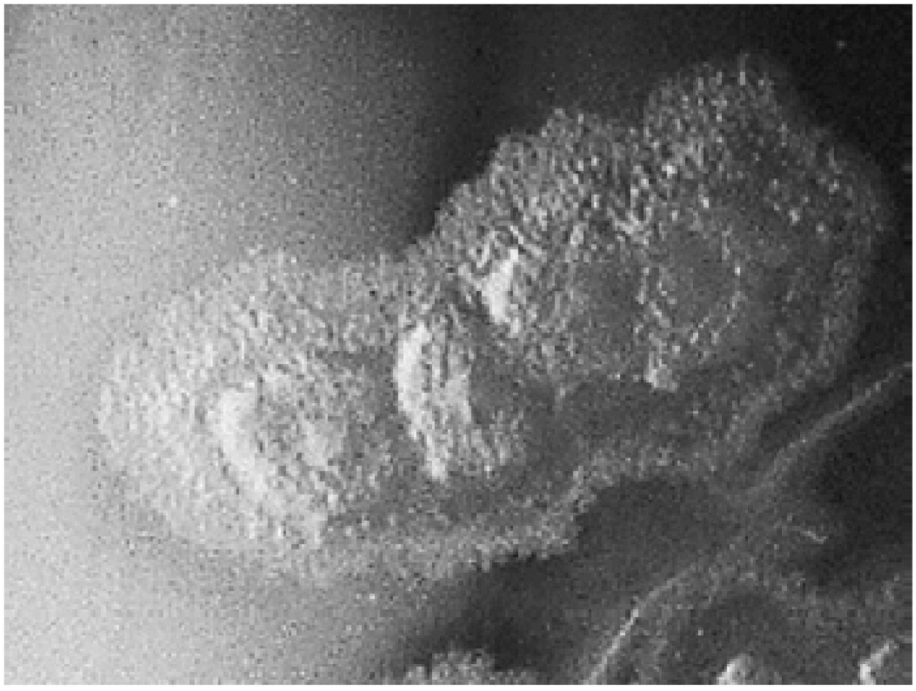


Fig. 3. *C. difficile* colonies on CCFA
Semitransparent or slightly white colonies with a rough mat surface form.

Table 1
C. difficile toxins and virulence-associated factors.

Virulence factor	Gene name	Action	Note
Toxin A (TcdA)	*tcdA*	Degradation of the plasma membrane of host cells Disruption of tight junctions (traditional) enterotoxin	Glucosyltransferase
Toxin B (TcdB)	*tcdB*	Degradation of the plasma membrane of host cells Disruption of tight junctions (traditional) cytotoxin	Glucosyltransferase
TcdC	*tcdC*	Suppression of the transcription of *tcdA* and *tcdB*	Gene mutations result in increased production of toxin A and toxin B in hypervirulent strains
Binary toxin (*C. difficile* transferase, CDT)	*cdtA/cdtB*	Inhibition of actin polymerization Induction of intestinal edema	CDTa is an ADP ribosyltransferase CDTb binds host cells, thereby supporting cytoplasmic entry of CDTa

2.1.7.7.2. Database.
- Medline and Ichushi were used to search for research articles.
- Medline, Ichushi, and the Cochrane Library were used to search for systematic reviews and meta-analysis papers.
- International Guideline Library by the Guidelines International Network, and National Guideline Clearinghouse of the US Agency for Health Research Quality were used to search for existing guidelines.

2.1.7.7.3. Basic strategy for search. The PICO format was used to search for interventions.

2.1.7.7.4. Publication period. From 2000 to June 2018.

2.1.7.8. Basic policies for making recommendations. Recommendations were determined based on the outcomes of deliberations by the Guidelines Committee.

In addition to the "level of evidence" and "balance between benefits and harms", "varied sense of perceived value in patients", and "economical viewpoint" were taken into account to make recommendations and determine the strength of recommendations.

2.1.7.9. Finalization. A draft of the guidelines was published at the Annual Meeting of the Japanese Society of Chemotherapy and the Annual Meeting of the Japanese Society of Chemotherapy, to obtain public comments. Public comments raised were assessed by the Guidelines Committee to determine whether modifications were required.

2.1.7.10. Bacteriology

2.1.7.10.1. Bacteriological classification. Clostridioides (Clostridium) difficile is an obligate anaerobic spore-forming gram-positive rod-shaped bacteria (Fig. 1). *C. difficile* cells are 0.5–1.9 by 3.0–16.9 μm and are motile with peritrichous flagella in liquid media [1]. In response to changes in the environment, their morphology changes from vegetative cells to endospores that are resistant to environmental insult.

In bacterial taxonomy, *C. difficile* is classified into the phylum Firmicutes, class Clostridia, order Clostridiales, and family Peptostreptococcaceae (Fig. 2). Because of the historical background of naming anaerobic bacteria, the genus *Clostridium* contains species that are not closely related. To address this, Clostridial clustering that groups closely related species is widely used. Accordingly, *C. difficile* is classified under Clostridial cluster XI, while the human pathogens *Clostridium botulinum*, *Clostridium perfringens*, and *Clostridium tetani* are Clostridial cluster I. The long-known name "*Clostridium difficile*" came under scrutiny, and the new name *Peptoclostridium difficile* was proposed to reflect the family Peptostreptococcaceae [2]. However, because this is likely to affect the well-established abbreviation for *C. difficile* infection of "CDI" in clinical settings globally, *Clostridium difficile* was renamed *Clostridioides difficile* [1].

2.1.7.10.2. Sporulation and germination. C. difficile forms metabolically dormant spores under disadvantageous conditions for growth. The spore core, containing a copy of the chromosomes and essential mRNA and enzymes, and the surrounding 3 outer layers form a barrier that is highly resistant to heat, radiation, dryness, high pressure treatment, and chemicals.

Sporulation is triggered by phosphorylation of the master transcription factor Spo0A by a sensor protein that detects environmental changes. Asymmetric cell division of a vegetative cell produces a mother cell and a forespore, and then the mother cell engulfs the forespore. Finally, the mother cell lyses to release the mature endospore. The water content in the spores is extremely low, contributing to heat resistance under extremely dry cell conditions. Also, a spore coat protein with superoxide dismutase activity contributes to oxygen resistance, and a cysteine-rich spore coat contributes to stability under heat and in the presence of ethanol.

For spores to transform into vegetative cells, bile salts and glycine are required; cold-shock protein C (CspC) acts as a germinant receptor and the entry of fluids into the spore after degradation of the spore cortex activates the expression of genetic material encased protectively within the core [3].

2.1.7.10.3. Culture media and biochemical properties. As a selective medium, a peptone-based medium containing cycloserine and cefoxitin that inhibit growth of other bacteria, with added fructose (cycloserine-cefoxitin fructose agar: CCFA) [4] or mannitol (cycloserine-cefoxitin mannitol agar: CCMA) as a carbon source, is commonly used. For bacterial isolation from clinical specimens, heat or alcohol pretreatment is often performed to enhance growth from spore and inhibit the growth of other bacteria. Use of media containing bile salts is advantageous to spore germination. After culturing on a CCFA plate under anaerobic conditions for 2–3 days, semitransparent or slightly white colonies with a rough mat surface are formed (Fig. 3). *C. difficile* colonies grown on blood-containing medium fluoresce green under long wavelength UV light.

With respect to biochemical characteristics, *C. difficile* can use glucose, fructose, and mannitol but not arabinose, galactose, glycogen, inositol, inulin, lactose, maltose, or sucrose [5]. After fermentation, *C. difficile* produces acetic acid, butyric acid, isobutyric acid, isovaleric acid, valeric acid, isocaproic acid, isobutanol, hexanol, folic acid, and lactic acid. A large volume of gas is produced on culture with peptone yeast extract glucose medium (PYG). *C. difficile* produces hydrogen and ammonia, but the production of hydrogen sulfide is strain-dependent. Lecithinase reaction and lipase reaction on CCFA containing egg yolk are negative. Hemolytic reaction on blood agar is negative, and indole reaction is negative.

Glutamate dehydrogenase (GDH) produced by *C. difficile* is used as a target for the diagnosis of CDI. GDH is the enzyme that catalyzes the conversion of glutamate to α-ketoglutarate and ammonia using NAD as cofactor, and it is highly expressed irrespective of toxin production [6].

2.1.7.10.4. Virulence factors of C. difficile. Virulent *C. difficile*

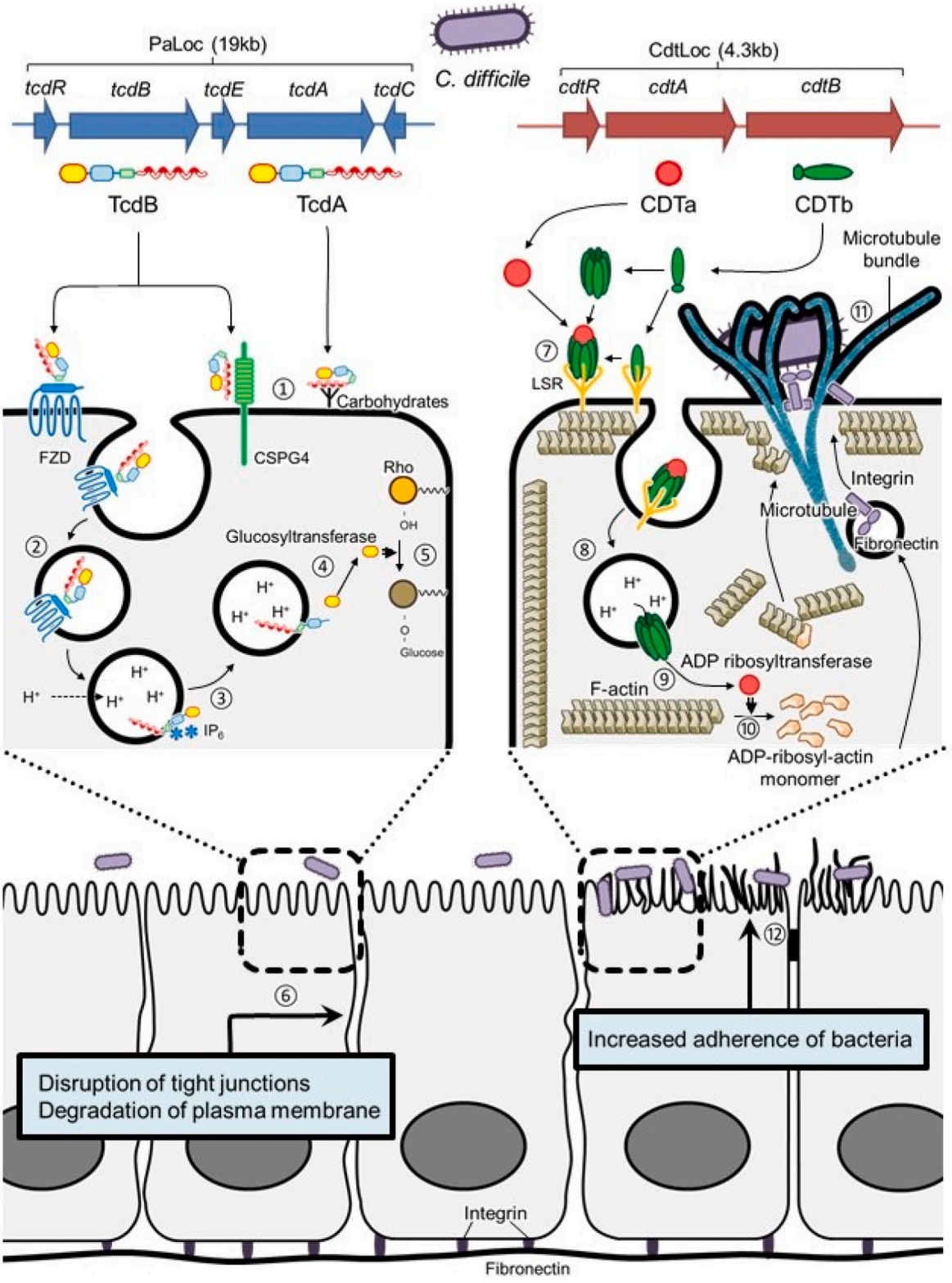


Fig. 4. Mechanism of action of *C. difficile* toxins.

produces toxins (Table 1). Toxin A (TcdA; 308 kDa) and toxin B (TcdB; 270 kDa) has been considered as an enterotoxin characterized by the induction of diarrhea and a cytotoxin that damages cells, respectively. However, they show approximately 48% similarity in their amino acid sequence, and both have glucosyltransferase activity [7].

Toxin A^+/toxin B^+ strains and toxin A^-/toxin B^+ strains cause CDI, but toxin A^-/toxin B^- strains do not cause any symptoms. Genes encoding toxin A and toxin B are located in a 19.6-kb pathogenicity locus (PaLoc) with 3 genes involved in the expression of these toxins (Fig. 4) [6,8]. In nontoxigenic strains, PaLoc is replaced by a 75- or 115-bp noncoding sequence, and thus these strains are not pathogenic [9]. Although it has been believed that toxin A^+/toxin B^- strains do not

exist, a PaLoc variant strain harboring only *tcdA* (toxin A gene) was identified, for which the integration site in the genome is located far from the well-known PaLoc integration site [10].

During *in vitro* culture, the production of toxins is the most active from the late exponential growth phase to the stationary phase, but decreases in the late stationary phase. Because the expression of *tcdC* in PaLoc is upregulated in the late stationary phase, the increased production of TcdC results in the inhibition of the transcription of *tcdA* and *tcdB* [11]. PCR-ribotypes (hereinafter ribotypes) 027 and 078, which have caused CDI outbreaks in Europe and North America, harbor mutations in *tcdC* that regulate production of toxins A and B, resulting in hyperproduction of these toxins [12,13]. It is implicated that TcdR upregulatesgene expressions in PaLoc, and TcdE involves in the releasing process of toxins from *C. difficile* cells [14].

Both toxins translated are composed of 4 functional domains (i.e., a glucosyltransferase domain, a protease domain, a binding domain, and a domain associated with host cell entry) through which its pathogenicity is exerted (Fig. 4). The binding domain contains repetitive sequences called the combined repetitive peptides (CROPs) that contribute to the binding to host cells and are also a target of immunotherapy [15]. Toxin A uses carbohydrates on the plasma membrane, while toxin B uses chondroitin sulfate proteoglycan 4 (CSPG4) [16] and Frizzled proteins (FZD) [17] as their receptors. CROPs and the adjacent non-CROPs region of toxin B are responsible for binding to CSPG4 and FZD, respectively. Following endocytosis of these toxins, the protease domain and the glucosyltransferase domain are transported into the cytosol, and the protease activated by inositol hexakisphosphate (IP6) cleaves and releases the active form of glucosyltransferase [8]. Then, following glycosylation and inactivation of Rho, which is required for the maintenance of plasma membrane structure [18], epithelial cells become unable to maintain the normal cytoskeletal structure, and ultimately cytotoxicity and disruption of tight junctions occur [8]. It is still controversial whether toxin A and toxin B are involved differently in the pathology of CDI; toxin B was shown to be essential for virulence of *C. difficile* in an animal study [19].

Some *C. difficile* strains produce a third toxin, reffered as a binary toxin or *C. difficile* transferase (CDT). CDT is composed of 2 proteins that have different functions: CDTa, an ADP ribosyltransferase activity, and CDTb that serves as a binding component to host cells. Both are encoded in the Cdt locus (CdtLoc) but not in PaLoc (Fig. 4) [6]. CDTb released from the cells binds to the lipolysis-stimulated lipoprotein receptor (LSR) on the host cell. CDTa binds to CDTb heptamers. Once internalized into the cell, CDTb heptamers form pores in the endosomal membrane, and CDTa is translocated into the cytosol through the center of the haptamers. Actin filaments that have undergone ADP-ribosylation by CDTa cannot polymerize themselves and also inhibit polymerization of normal actin filaments, resulting in disturbance of the structural integrity and the microtubule system, that lead to forming microtubule-based protrusions [20]. The impairment of recycling of extracellular matrix (ECM) proteins also induces accumulation of integrins and fibronectin around the microtubule-based protrusions at the apical side. Microtubule-based protrusions can provide advantages on the bacterial adherence [21]. The role of CDT in the pathology of CDI has not been fully elucidated, but it is known that CDI caused by CDT-producing strains is more severe and has high mortality [22]. Results from an animal study showed that CDT alone did not cause onset of CDI but caused marked intestinal edema [23].

There are several non-toxin virulence factors involved in the motility and adhesion of *C. difficile* [8,14,24,25]. The cell wall protein CWP66, Spo0A, and an S-layer protein in the cell surface structure, as well as CWP84, an enzyme responsible for processing of S-layer proteins, are all known to be involved in adhesion.

Toxin A (TcdA) and toxin B (TcdB), which are composed of 4 functionally-different domains, bind to carbohydrates and CSPG4 on the host plasma membrane, respectively, through their CROPs region (①). Binding of Toxin B to FZD is via its non-CROPs region. After internalization of toxins into the host cell (②), and with the involvement of IP6 (③), the glucosyltransferase is cleaved, activated, and released into the cytosol (④). Rho on the plasma membrane is inactivated (⑤) and epithelial cells become unable to maintain the normal cytoskeletal structure, resulting in cell damage and disruption of tight junctions (⑥).

The binary toxin comprises CDTa and CDTb; CDTa binds to heptameric CDTb that binds to the LSR on the surface of cell membrane(⑦). After being internalized into the host cells (⑧), CDTa translocates into the cytosol through a pore created by heptameric CDTb (⑨). CDTa then induces ADP-ribosylation of actin (⑩) to destabilize the cytoskeleton. As a result, microtubule-based protrusions form (⑪) to enhance bacterial adherence (⑫).

A heat shock protein GroEL of *C. difficile* that is produced in response to stress enhances adhesion to host cells. Fibronectin-binding proteins and collagen-binding proteins are responsible for binding to ECM-associated proteins of host cells. A metalloprotease that degrades ECM-associated proteins is also implicated in bacterial invasion. Type IV pili are involved in bacterial aggregation and biofilm formation, and the production of antibodies against pili and polysaccharides has been confirmed in the host. Flagella enhance bacterial adhesion to intestinal tissue in ribotype 027 strains but not in non-epidemic strains, suggesting variable traits among strains. Increased production of toxin A and toxin B was confirmed in strains lacking flagella, indicating a negative correlation between the expression of flagella and toxin production [14].

2.1.7.10.5. C. difficile strain typing methods. Distributions of common clinical isolates and epidemic strains of *C. difficile* differ among geographical regions. *C. difficile* genome analysis provides epidemiological and bacteriological insight, and it illustrates genetic diversity and

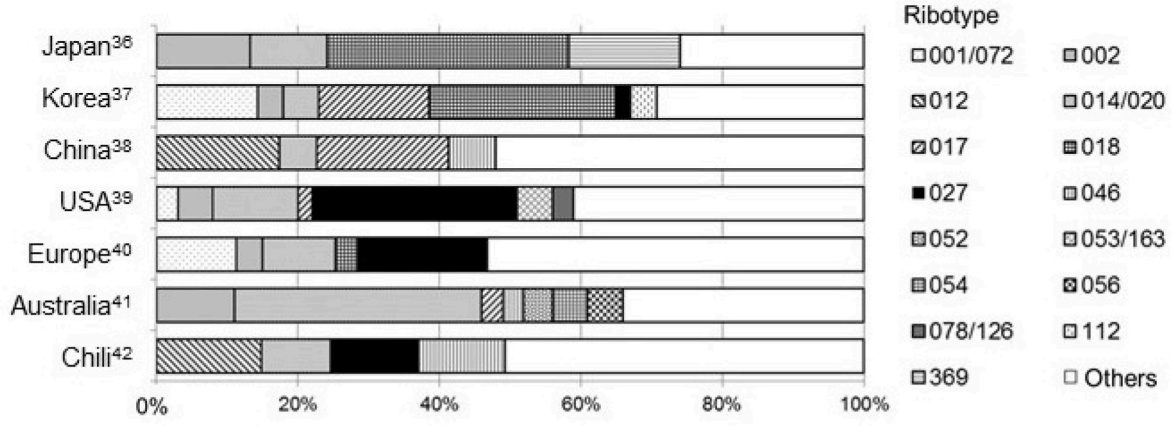


Fig. 5. Ribotypes in different regions.

Table 2
Antimicrobial susceptibility of *C. difficile*.

Antimicrobials		Susceptibility-related information							Breakpoints, μg/mL	
		Country and region of investigation								
		Japan [49] n = 130	Japan [54] n = 73	Japan [55] n = 157	Japan [60] n = 100	Japan [61] n = 50	Canada [56] n = 1, 310	Europe [53] n = 953	EUCAST [51]	CLSI [52]
Vancomycin	Range	0.5–4	1–8	0.12–2	0.5–1	0.5	≤0.25–4	0.125–16	Susceptible ≤2 Resistant 2<	ECV WT ≤ 2 NWT 4≤
	MIC_{50}	1	2	0.5	0.5	0.5	1	1		
	MIC_{90}	2	4	1	0.5	0.5	2	2		
Metronidazole	Range	0.125–1	0.1–0.25	0.06–1	0.12–1	0.12–0.5	0.12–4	0.125–8	Susceptible ≤2 Resistant 2<	Susceptible ≤8 Intermediate 16 Resistant 32 ≤
	MIC_{50}	0.25	0.19	0.25	0.25	0.25	0.5	0.25		
	MIC_{90}	0.5	0.25	0.5	0.5	0.5	2	2		
Fidaxomicin	Range				0.03–0.5	0.015–0.25	<0.015 −2	0.002–0.25	No Recommendation*	No Recommendation
	MIC_{50}				0.12	0.12	0.25	0.06		
	MIC_{90}				0.25	0.12	0.5	0.125		
Tigecycline	Range							0.03–1	ECOFF 0.25	No recommendation
	MIC_{50}							0.06		
	MIC_{90}							0.06		
Moxifloxacin	Range				1->128	2->64	0.5->32	0.125->64	ECOFF 4	Susceptible ≤2 Intermediate 4 Resistant 8 ≤
	MIC_{50}				8	2	2	2		
	MIC_{90}				>128	16	>32	32		
Clindamycin	Range	0.5->256	1->256	0.25->32	1->128	1->64	<0.12->64	0.125->64	No recommendation	Susceptible ≤2 Intermediate 4 Resistant 8 ≤
	MIC_{50}	8	>256	>32	8	8	8	4		
	MIC_{90}	>256	>256	>32	>128	>64	>64	>64		
Rifampicin	Range							0.001->16	ECOFF 0.004	No recommendation
	MIC_{50}							0.002		
	MIC_{90}							>16		

EUCAST, The European Committee on Antimicrobial Susceptibility Testing; CLSI, Clinical and Laboratory Standards Institution; ECOFF, epidemiologic cut-off value; ECV, epidemiologic cutoff value; WT, wild type; NWT, non-wild type.
*No recommendation made because results of available studies varied greatly.

the degree of evolution.

Ribotyping is a classification technique using PCR-based restriction fragment length polymorphism (RFLP) analysis in the intergenic spacer (ITS) region between the 16S rRNA gene and the 23S rRNA gene, and ribotypes so determined are designated with three-digit numbers. Ribotypes found in Japan include 018 [26], while ribotypes found overseas include 017, 019, 023, 027, 033, 078, 126, 176, and 244 [27], with differences noted due to the region and year of the study.

Pulse-field gel electrophoresis (PFGE) assesses similarities among *C. difficile* strains based on DNA patterns fragmented by restriction endonuclease digestion. PFGE is used mainly in North America, and strains with >80% similarity are generally regarded as a single type [6].

Restriction endonuclease analysis (REA) is also used to assess similarities among strains based on electrophoresis patterns of DNA fragments after restriction endonuclease digestion. REA has a higher discrimination ability because of the higher number of DNA fragments, although more technical experience is required to make reproducible and accurate judgements using REA than PFGE [9,27].

Toxinotyping is a PCR-RFLP-based technique that classifies *C. difficile* strains based on the PaLoc sequence encoding toxin A and toxin B. The reference strain VPI 10463 is defined as toxinotype 0, and 34 toxinotypes (designated with Roman numerals I-XXXIV) have been identified [27]. Toxinotypes correlate relatively well with ribotypes, and the most prevalent toxinotypes worldwide are toxinotypes V (ribotype 078), III (ribotypes 027/126), VIII (ribotype 017), and IV (ribotype 023) [27].

Multilocus sequence typing (MLST) determines the sequence types (STs) of *C. difficile* strains based on the base sequences of 7 housekeeping genes, changes in which are thought to reflect evolutionary conservation. Although STs are weakly correlated with ribotypes, there are common features of ribotypes classified into a single ST [28].

Surface-layer protein A encoding gene (*slpA)* typing determines the *slpA* type depending on the sequence of its variable region, either directly sequenced or via assessing the electrophoresis pattern of PCR products from restriction endonuclease digestion relative to known patterns. The *slpA* types correlate well with serogroups, but the use of this typing method is limited compared with the other methods [29].

Recently, whole genome analysis using next generation sequencing has been used to investigate virulent and epidemic lineages [30]. Ribotype 027 strains are of toxinotype III and ST1, while ribotype 078 strains are of toxinotype V and ST11. Some strain names reflect the

Table 3
Bristol stool scale.

Score	Types of stool
1	Separate hard lumps
2	Sausage-shaped but lumpy
3	Like a sausage but with cracks on its surface
4	Like sausage or snake, smooth and soft
5	Soft blobs with clear-cut edges
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces, entirely liquid

typing results; for example, a strain designated as 027/BI/NAP1 indicates ribotype 027, REA classification B1, and PFGE classification NAP1.

2.1.7.10.6. Regional characteristics of outbreaks and ribotypes. Outbreaks due to the same *C. difficile* clone have occurred mainly in North America and Europe since 2003, and infections have occurred in individuals in the community without history of medical facility exposure who were thought to be at low risk and higher mortality rates were reported [31,32]. The ribotype of this clone is 027 (027/BI/NAP1 strain) characterized by increased production of toxin A and B, production of CDT, increased sporulation tendency, aberrant forms of *tcdC*, and resistance to fluoroquinolone [30]. Ribotype 078 strains also caused similar outbreaks [33]. However, outbreak strains in Japan are mostly ribotype 018, not ribotype 027 or 078 [26,34,35].

It is known that ribotype 027 have spread worldwide by two lineages. The first lineage originated in Pittsburgh and caused outbreaks in the USA, and laterwas transmitted to Switzerland and South Korea. The other lineage had a greater reach, causing outbreaks in Europe and Australia [30]. Each region has characteristic proportions of *C. difficile* ribotypes [36–42] (Fig. 5). Ribotypes 027 and 078 strains are rarely observed in Asia, with a frequency in isolates of 0–1% in Japan [43–46]. The commonly reported ribotypes in Japan are 018, 001, 014, 002, 017, and 369 [34,36], and the proportions of CDT positive strains are 0–6.8% [36,43,45,47–49]. A downward trend in the proportion of ribotype 027 strains has recently been seen in both Europe and North America [39,50].

2.1.7.10.7. Susceptibility to antimicrobials and disinfectants. *C. difficile* is susceptible to vancomycin, metronidazole, fidaxomicin, and tigecycline. The breakpoints of major antimicrobials recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [51] differ from corresponding agents recommended by the Clinical and Laboratory Standards Institution (CLSI) [52]. The proportions of strains resistant to vancomycin or metronidazole range from 0 to a variable percentage (Table 2) [49,53–56], and the minimum inhibitory concentration (MIC) of fidaxomicin and tigecycline are ≤2 μg/mL and ≤1 μg/mL, respectively [53,56]. *C. difficile* is resistant to β-lactams and macrolides. Susceptibility to quinolones varies depending on the strain, and many ribotype 027 strains in Europe and North America have a high MIC, and isolates in previous outbreaks and recent isolates in Asia have a low MIC.

Similarly, many ribotype 078 strains are resistant to fluoroquinolone. Ribotype 018 and 369 strains are often resistant to quinolone, while ribotype 014 strains are often susceptible to quinolone [36,39]. Mutations in *ermB* can be seen in clindamycin-resistant strains, while mutations in *gyrA* and *gyrB* can be seen in quinolone-resistant strains.

Autoclaving (121 °C for ≥15 min), dry heat sterilization (180 °C for ≥30 min, or 160 °C for ≥60 min), as well as formalin and gamma sterilization are all effective methods for spore inactivation. Among common disinfectants, ethanol and benzalkonium chloride are not effective, whereas sodium hypochlorite, glutaraldehyde, and peracetic acid are effective [57,58]. Also, UV radiation is used to decontaminate the environment [59]. [60,61].

*A table of "non-toxin virulence factors" is not included due to issues associated with reuse of published materials in References 14 and 25.

Table 4
Definitions in CDI surveillance.

Classification	Definition
Healthcare facility-onset (HO) CDI	Healthcare facility-onset (HO) CDI Symptom onset >3 days after admission to a healthcare facility (reported as the number of cases per 10,000 patient-days).
Community-onset, healthcare facility-associated (CO-HCFA) CDI	Symptom onset in the community <28 days after discharge from a healthcare facility (reported as the number of cases per 1,000 patient admissions).
Community-associated (CA) CDI	Symptom onset in the community >12 weeks after last discharge from a healthcare facility.

2.1.7.11. Pathology of CDI

2.1.7.11.1. Pathology. Most manifestations of CDI are enteritis. The main symptom is diarrhea sometimes associated with abdominal pain and fever. Endoscopic examination sometimes reveals findings of pseudomembranous change and bleeding, and less frequently perforation, toxic megacolon, and paralytic ileus.

The first step in the manifestation of CDI is invasion of *C. difficile* into the intestine, and the main transmission routes are contact with symptomatic carriers, use of healthcare facilities, and contact with asymptomatic carriers [62,63]. Asymptomatic carriers include infants with *C. difficile* colonization in the intestine [63]. *C. difficile* also exists in the environment such as in rivers, seawater, and soil, and it has been confirmed in the intestines of pets and livestock [30,40,63,64]. *C. difficile* enters into the body orally via hands that have been contaminated after contact with such environments or animals. Infection with toxigenic strains is prerequisite for the onset of CDI, and interventions that disturb the intestinal flora (e.g., exposure to antimicrobials or medical procedures) and the host immune condition (including antibody production) are involved in its onset. In a host with low susceptibility to CDI, *C. difficile* is eliminated or the host remains an asymptomatic carrier [50].

Incidence and prevalence

CDI incidence rates (per 10,000 patient-bed-day) were reported as 5.5 (0-3-6.3)[40] on average in Europe, 7.4 in the USA, [65] and 5.3 in Asian countries, [66] with a range of 0.8–4.7 in Japan [26]. CDI prevalence was 6.9/1,000 patient admissions in the study in the USA, but 0.3–5.5 in Japan [26]. Differences in the distribution of pandemic strains and in detection methods commonly used are thought to have influenced the slightly lower incidence and prevalence in Japan [26,66]. Approximately 95% of CDI patients had previously used medical facilities including inpatient, outpatient, and long-term care facilities [67,68]. CDI incidence increases with age, but a study carried out in the USA showed that many community-associated CDI cases involved young individuals under 45 years old [68].

Extraintestinal CDI is extremely rare, accounting for 0.17% of all CDI cases in Finland [69]. Examples of extraintestinal CDI include

Table 5
Risk factors for CDI.

Older age	Systematic reviews [1,4,5,7] Meta-analyses [2,3] Prospective cohort study [6]
Antimicrobial use	Meta-analyses [3,18,19,21,39] Systematic reviews [4,20]
Previous history of hospital admission	Meta-analysis [13]
History of gastrointestinal surgery	Prospective cohort studies [14,15] Systematic review [16]
Comorbidities (e.g., inflammatory bowel disease and chronic kidney disease)	Meta-analysis [3] Systematic reviews [4,10,11] Retrospective cohort study [12]
Nasogastric tube feeding	Systematic review [34]
PPI use	Meta-analyses [22–25,27,28] Systematic review [26]
H2RA use	Meta-analyses [27,30]
NSAID use	Meta-analysis [35]
Decreases in 25(OH)D	Meta-analysis [36]

bacteremia, intraperitoneal infection, perianal abscess, wound infection, and catheter-associated urinary tract infection [69–71]. Patients with extraintestinal CDI show characteristics such as inpatient status, presence of comorbidities, and *C. difficile* often isolated with other organisms [69–71].

Colonization

C. difficile can colonize the intestine. The proportion of asymptomatic carriers was high in newborns and infants, reported to range from 20% to as high as 90% [65,72–76]. Different strains can be found in the same host depending on the season, and colonization with both toxigenic and non-toxigenic strains has been observed [65,77]. The proportion of asymptomatic carriers increases to 1%–3% by 2–3 years of age [65,72,73]. The proportion of asymptomatic carriers in adults without recent healthcare facility exposure is reported to be 2%–15% [65,72,73]. The proportion of asymptomatic colonization increases in inpatients (by approximately 30%) and in the elderly in long-term care facilities (by approximately 50%) [72]. A negative correlation was found between prolonged hospital stay and colonization rate [78]. A possible reason for why CDI rarely occurs in infants despite a high colonization rate is insufficient expression of toxin A receptors in the intestinal epithelia [79], although the molecular mechanism and involvement of other toxins has not yet been fully elucidated.

2.1.7.11.2. Definition of CDI

Executive summary

1. *C. difficile* infection (CDI) is defined as the presence of diarrheal symptoms with a consistency of Bristol Stool Scale type ≥5 (Table 3), positive stool test results for toxins, isolation of toxigenic strains from stool, or the presence of pseudomembranous colitis detected on colonoscopy or colon pathology in individuals aged ≥2 years. CDI in individuals aged <2 years was not defined in the guideline.
2. Stools of Bristol Stool Scale type ≥5, 3 bowel movements at a time or at a higher frequency than normal for the individual in 24 h is generally considered diarrheal symptoms.
3. Paralytic ileus and toxic megacolon sometimes occur without diarrheal symptoms.
4. Definitions of CDI with different timings of infection and symptom onset, as used in epidemiological research, are given in Table 4.

Literature review

C. difficile is a typical pathogen known to cause healthcare facility-associated infectious diarrhea, and community-associated cases have also been reported recently. A small number of cases of extraintestinal CDI (e.g., bacteremia and wound infection) have been reported with a frequency of 0.17% [69]; most cases of CDI are intestinal. *C. difficile* causes disease by producing toxins, although there are asymptomatic *C. difficile* carriers. The proportion of asymptomatic carriers was found to <2% in adults without recent healthcare facility exposure [80], but was around 20% in inpatients in acute hospitals [62,81]. Such asymptomatic carriers and individuals infected with non-toxigenic *C. difficile* are not subjected to treatment, and thus CDI must be diagnosed based on both clinical symptoms and test results.

Recently, CDI incidence in children has been rising [82]. Generally, infants <12 months old carry *C. difficile* in their intestines, but many of the strains are non-toxigenic, and colonization in the intestine is temporary resulting in a lower proportion of asymptomatic carriers with increasing age [77,83,84]. Accordingly, the proportion of *C. difficile* carriers is high in children <2 years old, and thus conducting CDI testing in children <2 years old is not recommended unless causes of noninfectious diarrhea are eliminated.

It is recommended that the type of diarrhea be assessed using the Bristol Stool Scale [85] because description and recognition vary among examiners. When CDI is suspected, a stool sample with a consistency of Bristol Stool Scale type ≥5 should be sent for testing. It must be noted that Bristol Stool Scale type does not correlate with toxigenicity of the

Table 6
Comparison of CDI risk associated with antimicrobials Risk of *Clostridium difficile* infection or colitis according to specific antibiotic comparisons.

Comparison	No. of RCTs	No. of patients	RR (95% CI)	*I* [2] (%)	*I* [2] subgroup (%)
Cephalosporins vs. all	35	10,703	1.09 (0.84–1.42)	27	83.3
Cephalosporins vs. penicillins/carbapenems/fluoroquinolones	29	9,312	1.10 (0.84–1.44)	36	94.1
Cephalosporins vs. other[a]	6	1,391	1.00 (0.33–3.06)	0	0
Cephalosporins vs. penicillins	11	2,246	**2.36 (1.32–4.23)**	0	NA
Cephalosporins vs. fluoroquinolones	8	2,203	**2.84 (1.60–5.06)**	0	NA
Cephalosporins 4G vs. 3G	7	2,153	1.06 (0.39–2.89)	0	NA
Cephalosporins 3G vs. 1/2G	4	2,509	0.47 (0.17–1.29)	20	NA
Carbapenems vs. all	22	10,956	**2.26 (1.64–3.11)**	0	0
Carbapenems vs. penicillins/cephalosporins/fluoroquinolones	19	7,997	2.32 **(1.67–3.24)**	0	0
Carbapenems vs. other[b]	3	2,959	1.48(0.42–5.23)	26	62.4
Carbapenems vs. penicillins	4	1,322	2.53(0.87–7.41)	0	NA
Carbapenems vs. cephalosporins	10	4,497	**2.24 (1.46–3.42)**	0	NA
Carbapenems vs. fluoroquinolones	5	2,178	**2.44 (1.32–4.49)**	0	NA
Meropenem vs. imipenem	2	537	0.62 (0.08–5.00)	0	NA
Fluoroquinolones vs. all	20	8,104	**0.52 (0.37–0.75)**	0	46.6
F1uoroquinolones vs. carbapenems/cephalosporins/penicillins	17	6,894	**0.49(0.34–0.70)**	0	69.3
Ruoroquinolones vs. other[c]	3	1,210	2.05(0.38–11.05)	0	0
Ruoroquinolones vs. penicillins	4	2,513	1.34(0.55–3.25)	0	NA
Penidll ins vs. all	24	7,682	**0.48(0.32–0.72)**	0	0
Penicillins vs. carbapenems/cephalosporins/fluonaquinolones	19	6,066	**0.52 (0.34–0.79)**	0	0
Penicillins vs. other[d]	5	1,616	**0.31(0.10–1.00)**	0	0
Clindamycin vs. all	5	1,146	**3.92 (1.15–13.43)**	0	NA
linezolid vs. all[e]	5	4,151	0.99 (0.44–2.26)	0	NA
Vancomycin vs. all[e]	5	4,196	1.16 (0.45–2.99)	0	NA

RCTs. randomised controlled trials; RR, relative risk: CI. confidence interval; NA, not applicable; 4G, fourth-generation; 3G. third-generation; 1/2G. first-/second-generation. Statistically significant associations are shown in bold.

[a] Tetracycline, clindamycin, linezolid, aminoglycosides.
[b] Tigecycline, aztreonam.
[c] Aztreonam, macrolides, tigecycline.
[d] Macrolides, clindamycin.
[e] The comparisons refer to RCTs comparing linezolid or vancomycin with other anti-Gram-positive antibiotics only.

Table 7
Systematic reviews and meta-analyses on CDI risk associated with PPI use.

Design	Year of publication	Number of studies analyzed	N	RR or OR	95% confidence interval	I [2] (%)	References
S	2007	12	18,468	OR 1.94	1.37–2.75	–	(118)
M	2012	23	288,620	RR 1.69	1.40–1.97	91.9	(109)
S/M	2012	47	–	OR 1.65	1.47–1.85	89.9	(110)
M	2012	30	202,965	OR 2.15	1.81–2.55	87.0	(111)
M	2012	42	313,000	OR 1.74	1.47–2.05	85.0	(119)
M	2016	23	186,033	OR 1.81	1.52–2.14	82.0	(112)
S	2016	33	342,532	OR 1.69–3.33	–	–	(113)
S/M	2017	12	74,132	OR 1.386	1.15–1.67	42.8	(114)
M	2018	50	342,532	OR 1.26	1.12–1.39	80.6	(115)
S/M	2018	67	303,235	OR 2.34	1.94–3.82	93.0	(116)

M, meta-analysis; S, systematic review; RR, risk ratio; OR, odds ratio.

strains or severity of CDI [86]. The World Health Organization defines diarrhea as "The passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)" [87]. Accordingly, the definition of CDI in overseas guidelines includes the wording "3 or more unformed stool in 24 h" [65,88]. However, many CDI patients are elderly and cannot use the toilet independently, so stool frequency often cannot be measured accurately for these patients. Thus, the guidelines here recommend to test for CDI based on the type of stool, irrespective of the frequency of passage when measuring frequency is difficult. It should be noted that paralytic ileus and toxic megacolon can occur without diarrheal symptoms in severe cases.

Information regarding CDI epidemiology, which is currently limited in Japan, needs to be accumulated. In this guidelines, different types of CDI cases are defined [65,88] so that data collected in Japan can be compared with international data. Types not defined above should be deciphered clinically. It is advisable for all healthcare facilities be fully aware of the status of healthcare facility-onset CDI, in particular.

2.1.7.11.3. Risk factors for CDI

Executive summary

1. Older age and use of antimicrobials are important risk factors for CDI.
2. Previous history of hospital admission, previous history of gastrointestinal tract surgery, comorbidities such as chronic kidney disease and inflammatory bowel disease, nasogastric tube feeding, and the use of acid suppressing agents such as proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RA) are considered risk factors for CDI.
3. CDI testing should be considered for outpatients with diarrhea who have a previous history of antimicrobial use.

Literature review

CDI is diagnosed only after physicians suspect infection and specimens are tested accordingly. CDI is not frequently tested for in Japan, so the occurrence of CDI may be underestimated. Increased understanding of risk factors for CDI will increase CDI testing and diagnosis rates.

Numerous risk factors (Table 5) have been reported in systematic reviews and meta-analyses [26,89–92], with 26 factors listed in a systematic review by Eze et al. [92]. Among them, older age, various comorbidities, previous history of hospital admission, antimicrobial use, and use of acid suppressing agents were identified in many studies. Risk factors shown in a systematic review on the epidemiology of CDI included older age, serious comorbidities, antimicrobial use, PPI use, and extended hospital stay before gastrointestinal surgery [26].

Older age, reported as a risk factor for CDI [89,92–94], was recently identified as a risk factor for infections due to ribotype 027 strain [90]. Given that older age is also associated with the presence of comorbidities, previous history of hospital admission, and prolonged hospital stay [95], it can be regarded as a surrogate marker of various risk factors [96]. Comorbidities such as chronic kidney disease, inflammatory bowel disease, and malignant tumors are risk factors for CDI [92]. In patients with inflammatory bowel disease, disturbance of gut microbiota, use of antimicrobials and immunosuppressants, and hospital admission were associated with CDI onset [97], and the number of inflammatory bowel disease patients with CDI is increasing [98,99]. Inflammatory bowel disease was found to be an important risk factor for community-associated (CA)-CDI (odds ratio [OR], 3.72; 95% confidence interval [CI], 1.52–9.12) [91]. A meta-analysis reported that history of hospital admission in the past 3 months carried a risk of colonization (relative risk [RR], 1.63; 95% CI, 1.13–2.34) and that CDI risk was high in patients with colonization by toxigenic *C. difficile* strains (RR, 5.86; 95% CI, 4.21–8.16) [100]. Prospective cohort studies and a systematic review showed high CDI rates after gastrointestinal surgery [101–103] at 0.7%–1.8%, which is higher than that after non-gastrointestinal surgery. Esophageal and gastric surgery had an OR of 2.14 (95% CI, 1.05–4.35) and lower gastrointestinal surgery had an OR of 2.01 (95% CI, 1.06–3.08). Analysis of the diagnosis procedure combination (DPC) [104] revealed a lower CDI rate after gastrointestinal surgery in Japan (0.28%) compared with overseas, although the Japanese figure could have been underestimated.

External risk factors for CDI, as well as host factors, need to be considered. Use of antimicrobials disturbs normal gut microbiota, and thus it is closely associated with CDI pathology. Several systematic reviews and meta-analyses have shown antimicrobial use as a risk factor for CDI [92,105–108]. Clindamycin, carbapenems, cephalosporins, and fluoroquinolones in particular were shown to be associated with CDI. Also, a meta-analysis by Slimings et al. showed that use of β-lactamase inhibitor combination penicillins is a risk factor for HO-CDI (OR, 1.54; 95% CI, 1.05–2.24) [105]. A meta-analysis of RCTs showed that clindamycin was associated with more CDI episodes than cephalosporins/penicillins (RR, 3.92; 95% CI, 1.15–13.43), and similarly carbapenems were associated with more CDI episodes than fluoroquinolones (RR, 2.44; 95% CI, 1.32–4.49) and cephalosporins (RR, 2.24; 95% CI, 1.46–3.42; Table 6) [108].

In total, 11 systematic reviews and meta-analyses have been reported for acid suppressing agents (7 for PPIs [109–115], 1 for H2RA [116], and 3 for acid suppressing agents [117–119]. PPI use as a risk factor for CDI was proven statistically in meta-analyses, but it has not yet been validated due to study heterogeneity (Table 7). Also, in a study using the Bradford Hill Criteria to examine the association between PPI use and CDI shown in meta-analyses performed from 2016 to 2017, causality could not be proved due to differences in patient characteristics across the individual studies and difficulties in controlling for confounding factors in observational studies [120].

H2RA was shown to be a risk factor for CDI in a meta-analysis of 5 observational studies (OR, 1.44; 95% CI, 1.22–1.70) [117]. CDI risk increased in inpatients on both antimicrobials and H2RA (number needed to harm 58; 95% CI, 37–115). A meta-analysis comparing CDI risk with use of different acid suppressing agents showed that PPIs increased CDI risk by 38.6% compared with H2RAs [114]. Nasogastric feeding was thought to be associated with CDI because tube insertion as a procedure increases the possibility of acquiring *C. difficile*, and deficient dietary fiber intake enhances *C. difficile* growth [34]. A systematic

Table 8
Risk factors for CDI recurrence.

Older age (≥65 years)	Meta-analysis [161] Systematic reviews [139,140,162] Prospective validation study [136] Retrospective observational study [163]
Antimicrobial use (concomitant use during treatment of the initial CDI episode, or after CDI treatment)	Meta-analysis [161] Systematic reviews [92,139,140] Prospective validation study [136]
Serious comorbidities (e.g., kidney failure)	Prospective validation study [136] Meta-analysis [164] Systematic reviews [92,140] Database analysis [165]
History of CDI	Randomized controlled trials [159,166] Meta-analysis of randomized controlled trials [158]
Use of PPIs	Systemic reviews of studies [92,139,140] Meta-analysis [109,116,141,161]
Severity of initial CDI episode	Prospective validation study [136] Long-term population-based cohort study [146]
Low anti-toxin A level	Prospective observational study [155]

review of 11 observational studies by Wijarnpreecha et al. showed the pooled RR of CDI in patients on nasogastric feeding was 1.87 (95% CI, 1.06–3.28), while the RR when only cohort and case-controlled studies were analyzed was 1.9 (95% CI 1.05–3.77) [121]. A meta-analysis by Permpalung et al. showed that a history of non-steroidal anti-inflammatory drugs (NSAIDs) is a risk for CDI (OR, 1.41; 95% CI, 1.06–1.87), and subgroup analysis showed that CDI risk was increased in patients using non-selective NSAIDs and in those aged ≥50 years; the duration of NSAID use did not affect CDI risk [122]. The association of 25-hydroxyvitamin D [25(OH)D] with CDI has become of interest because an association was recently shown between high blood 25(OH)D and reduced risk of CDI in patients with inflammatory bowel disease. A meta-analysis showed that blood 25(OH)D level was lower in CDI patients than in non-CDI patients, and patients with lower 25(OH)D level (<20 ng/mL) had higher odds (OR, 1.61; 95% CI, 1.02–2.53) of developing severe CDI [123]. Although 25(OH)D is thought to act as an immune modulator in CDI, the mechanism remains unclear.

The epidemiology of CA-CDI in Japan has not been well studied to date, but an increase in CA-CDI cases overseas has been seen since 2000 [67,124]. Risk factors for CA-CDI were reported in 3 meta-analyses [91,106,125]. According to Furuya-Kanamori et al., antimicrobial use (OR, 6.18; 95% CI, 3.80–10.04) and corticosteroid use (OR, 1.81; 95% CI, 1.15–2.84) were associated with increased risk of CA-CDI, and comorbidities such as inflammatory bowel disease (OR, 4.11; 95% CI, 1.78–9.49), renal failure (OR, 2.59; 95% CI, 1.2–5.59), hematologic malignancy (OR, 1.74; 95% CI, 1.01–3.01), and diabetes mellitus (OR, 1.14; 95% CI, 1.04–1.26) were associated with CA-CDI [91]. The other 2 meta-analyses investigated antimicrobials and CA-CDI risk and found the highest ORs of 20.43 (95% CI, 8.50–49.09) [106] and 16.8 (95% CI, 7.5–37.8)[125] for clindamycin, and the second highest ORs of 5.65 (95% CI, 4.38–7.28) [106] and 5.50 (95% CI, 4.26–7.11) [125] for fluoroquinolones; penicillins, macrolides, and sulfonamide/trimethoprim had weaker associations [106,125]. Antimicrobial use is considered a risk factor for CA-CDI; however, given the low rate of antimicrobial use in CA-CDI cases (78%) compared with HO-CDI cases (94%) [124], it should be noted that some patients with CA-CDI are not exposed to antimicrobials. Generally, though, because accessibility to healthcare facilities is good and antimicrobials are often prescribed to outpatients in Japan, CA-CDI is likely to occur. Thus, CDI testing should be considered in outpatients with diarrhea and a history of antimicrobial use.

2.1.7.11.4. Definition of recurrence

Executive summary

In this guideline, CDI recurrence is defined as "re-occurrence of CDI within 8 weeks of the onset of a previous episode, albeit with appropriate treatment". Furthermore, relapse is defined as CDI recurrence caused by genetically identical *C. difficile* strains, while reinfection is caused by genetically different *C. difficile* strains. Distinguishing relapse from reinfection may be important when searching for outbreak strains and assessing treatment efficacy. However, distinguishing between the two is based solely on the results of genetic testing, and it is impossible to determine relapse or reinfection in daily practice. Therefore, CDI recurrence here includes both relapse and reinfection.

Literature review

Despite appropriate treatment, CDI recurs in approximately 30% of patients [126–128]; the recurrence rate is reportedly higher in patients with a recurrent CDI episode (40%–65%) that in those with the initial CDI episode (10%–20%) [73,129]. Relapse caused by the same strain and reinfection with a different strain are both categorized as recurrence. According to a study by Figueroa et al., in 90 patients with recurrent CDI after the first episode of CDI or first recurrence (1 prior episode of CDI within 3 months), 75 (83%) developed relapse caused by the same strains as the prior episode, and the remaining 15 (17%) developed reinfection with different strains [128]. In other studies, approximately half of the recurrent cases were of reinfection [126,130,131]. Durovic et al. reported that 45.8% of reinfection cases—defined as a new episode occurring ≥8 weeks after the prior episode—were actually relapse cases caused by the same strain [132]. Thus, some cases may involve reinfection by the same strain from contaminated environment while others may involve relapse caused by endogenous strains; however, distinguishing one from the other is difficult.

Figueroa et al. reported a mean time to recurrence after completing CDI treatment of 12.6 days [128]. Johnson et al. reported a mean time to relapse of 14.5 ± 10 days and that to reinfection of 42.5 ± 39 days [126,133]. The MODIFY I and MODIFY II randomized double-blind placebo-controlled Phase III trials that examined bezlotoxumab (human anti-toxin B monoclonal antibody) revealed the placebo group had a recurrence rate of 28% (109/395) in MODIFY I and 26% (97/378) in MODIFY II, 79% of which occurred within 4 weeks after resolution of CDI [133]. Taken together, CDI recurrence often occurs relatively early after the previous episode has resolved, and therefore we consider the definition we use here—re-occurrence of CDI within 8 weeks after the onset of a previous episode, albeit with appropriate treatment—is reasonable.

2.1.7.11.5. Recommendations by related clinical practice guidelines.

The guidelines from American College of Gastroenterology (ACG), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Association for Professionals in Infection Control and Epidemiology defined recurrent CDI as re-occurrence of CDI within 8 weeks of the onset of a prior episode, albeit with appropriate treatment [73,134,135]. The 2017 guidelines from the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) define recurrent CDI as CDI diagnosed within 2–8 weeks of a prior positive test result [65].

2.1.7.11.6. Risk factors for recurrence

Executive summary

The following are recommended as risk factors for recurrence: older age (≥65 years), history of antimicrobial use after diagnosis of CDI, serious comorbidities (e.g., kidney failure), previous history of CDI episode, and use of PPIs.

Literature review

CDI is known to recur in approximately 30% of CDI patients even after appropriate treatment, so understanding the risk factors will

Table 9
Severity criteria summary.

		Guidelines								
		IDSA/ SHEA (2010)	ACG(2013)	ESCMID (2014)	WSES(2015)	ASID(2016)	Zae et al. (2007)	Neal et al.(2011)	Miller et al.(2013)	Mikamo et al. (2017) (MN criteria)
Patient characteristics	Age (years)						>60: 1		≥60, <80: 1, ≥80: 2	≥65: 1
	Presence of immunosuppression ± chronic disease							Yes: 1		
	Causes during CDI treatment: antimicrobial use during ≥1day of CDI treatment								Yes: 2	
Physical findings	Fever		Yes (≥38.5 °C)	Yes(≥38.5 °C)	Yes (≥38.5 °C)	Yes(≥38.5 °C)	>38.3 °C: 1	>38.5 °C: 1		≥37.0 °C, < 37.5 °C: 1, ≥37.5 °C, < 38.5 °C: 2, ≥38.5 °C: 3
	Chills		Yes							
	Diarrhea (frequency/day)									≥3, <9: 1, ≥10: 2 (+1 point for each condition in the case of bloody stool)
	Abdominal symptoms (distension, pain)	Yes(pain)						Yes; 1		Yes (distension or pain); 1
	Ileus	Yes	Yes	Yes	Yes	Yes				
	Peritonitis/perforation			Yes	Yes	Yes		Presence of symptoms: 3		
	Hemodynamic instability	Yes	Yes	Yes	Yes	Yes				
	Respiratory insufficiency		Yes	Yes						
	Alteration of consciousness		Yes					Yes: 5		
	ICU admission		Yes	Yes		Yes				
Laboratory test findings	Leukocyte count (/μL)	≥15,000	≥15,000	≥15,000, or neutrophils content >20%	≥15,000	≥15,000, or neutrophils content >20%	>15,000: 1	>15,000, or < 1,500 ± band cell content >10%: 2	≥16,000, <25,000: 1, ≥25,000: 2	≥12,000, <15,000: 1, ≥15,000, <20,000: 2, ≥20,000: 3
	Serum creatinine	≥1.5 × BL value	Kidney failure	≥1.5 × BL value or 133 μM	Rapid increase	≥1.5 × BL Value		>1.5 × BL Value: 2	≤1.2: 0, ≥1.21, ≤1.79: 1, ≥1.8: 2	
	eGFR level (mL/min/1.73m2)									≥50, <80: 1, ≥30, <50: 2, <30: 3
	Serum albumin(g/dL)		<3.0	<3.0	<2.5	<2.5	<2.5: 1	<3.0: 1	≥2.6, <3.5: 1, <2.5: 2	≥2.5, <3.0: 1, ≥2.0, <2.5: 2, <2.0: 3
	Serum lactate(mmol/L)		>2.2	≥5	Increase	Elevated levels				
Imaging findings	Pseudomembranous colitis			Yes		Yes	Yes			Imaging findings (intestinal dilation, wall thickening, adipose tissue consolidation around the intestine, ascites of unknown origin other than CDI, presence of the pseudomembrane: 2
	CT findings							Findings (presence of signs of colitis affecting the entire intestine, ascites ± intestinal wall thickening): 2		
	Megacolon/distention of the large intestine	Yes		Yes		Yes/Yes				
	Intestinal wall thickening			Yes		Yes				
	Adipose tissue consolidation around the intestine			Yes		Yes				
	Ascites of unknown origin			Yes		Yes				

(*continued on next page*)

Table 9 (*continued*)

		Guidelines									
		IDSA/ SHEA (2010)	ACG(2013)	ESCMID (2014)	WSES(2015)	ASID(2016)	Zae et al. (2007)	Neal et al.(2011)	Miller et al.(2013)	Mikamo et al. (2017) (MN criteria)
Treatment	ICU treatment Administration of vasopressin Ventilatory support of respiratory function due to CDI						Yes; 2	Yes; 1 Yes; 5 Yes; 5		
Severity classification		Meeting ≥1 item: severe disease	Meeting ≥1 item: severe disease	Meeting ≥1 item: severe disease	Meeting ≥1 item: severe disease	Meeting ≥1 item: severe disease	≥2 points: severe	1-3 points: mild-moderate; 4–6 points: severe; ≥ 7 points: severe and complicated;	0-10 points: prediction of cure by score (e.g., 100% for 0 points, 64.4% for 7 points, 49.2% for 10 points)	≤4 points: mild; 5–9 points, moderate; 10–13 points, severe; ≥ 14 points, extremely severe

BL value: baseline value.

contribute to prevention of recurrence. Several systematic reviews and meta-analyses have identified risk factors for CDI recurrence, but because the effect of confounding factors cannot be ruled out in the individual studies themselves, a large-scale prospective study is warranted.

Table 8 summarizes risk factors for CDI recurrence that have been reported. Similar to the initial CDI episode, the risk of recurrence increases with older age and use of non-CDI-associated antimicrobials, and the recurrence rate is even higher with a prior CDI episode [136–138]. A systematic review by Chakra et al. showed that, among the 24 studies analyzed, the risk factors of CDI recurrence were age (in 9 studies), use of antimicrobials after CDI diagnosis (in 7 studies), and use of PPIS (in 3 studies) [139]. Similarly, Deshpande et al.'s review of 33 studies showed the risk factors as age ≥65 years (RR, 1.63; 95% CI, 1.24–2.14; $P = 0.0005$), antimicrobial use after CDI treatment (RR, 1.76; 95% CI, 1.52–2.05; $P < 0.00001$), PPI use (RR, 1.58; 95% CI, 1.13–2.21; $P = 0.008$), kidney failure (RR, 1.59; 95% CI, 1.14–2.23; $P = 0.007$), and use of quinolones (RR, 1.42; 95% CI, 1.28–1.57; $P < 0.00001$) [140]. A meta-analysis of 16 observational studies by Tariq et al. showed use of acid suppressing agents (OR, 1.52; 95% CI, 1.20–1.94; $P < 0.001$) as a risk factor [141].

In terms of Japanese studies, Riley et al. found in a systematic review of 12 CDI studies that only 2 reported on risk factors for CDI recurrence (i.e., malignancy, intensive care unit [ICU] admission, and PPI use) [26]. Recurrence risk prediction based on risk factor scoring was evaluated in several studies, but no rational method has yet been developed due to small sample size and the complexity of judgement involved [136,142–147]. Therefore, a large-scale prospective study examining a simpler prediction method is needed in the future. Other risk factors include the following: use of steroids, shown in a retrospective cohort study by Abdelfatah et al. [148]; tube feeding, shown in a prospective cohort study by Larrainzar-Coghen et al. [149]; and long-term hospitalization, found in a retrospective cohort study by McDonald et al. [150]. A retrospective cohort study by Matsumoto et al. examined 14 patients with CDI recurrence and 39 without CDI recurrence and showed that time to starting anticancer agents and steroids after completing CDI treatment was significantly shorter in the group with recurrence than in the group without recurrence, and they recommended that administration of these agents be delayed as long as possible after CDI onset [151].

Also, more recently, inflammatory bowel disease was reported as a host factor associated with increased risk of CDI, including recurrent CDI [152,153]. Also, characteristics of *C. difficile* strains are also associated with recurrence; for example, 027/BI/NAP1 strain, which caused recent epidemics in Europe and North America but not in Japan, were associated with a higher rate of recurrence [154]. Patients can have multiple recurrent episodes, and host immunity, such as impaired production of anti-toxin A antibodies, was shown to be associated with recurrence [155].

A strong association between toxin B and virulence has been shown [19], and a phase II randomized double-blind placebo-controlled double study showed the protective effect of anti-toxin B antibody against recurrence (OR, 0.11 and $P = 0.05$, by multivariable analysis) [156]. The MODIFY I and II phase III studies mentioned earlier demonstrated that anti-toxin B monoclonal antibody administration significantly inhibited CDI recurrence 12 weeks after administration [157]. [158–160].

With respect to the association of CDI recurrence with therapeutic agents, overseas studies showed that fidaxomicin significantly reduced recurrence within 4 weeks after the end of treatment compared with vancomycin [158,159]. Also, decreased diversity of the gut microbiome was shown in CDI patients with multiple recurrent CDI episodes [160], and use of antimicrobials after CDI episodes increased the risk of recurrence. Patients whose intestinal environment after CDI treatment has not yet been restored sometimes have repeated recurrent episodes, and fecal microbiota transplant is sometimes used to restore the gut

Table 10
Recommendations for vancomycin and metronidazole in the treatment of the initial CDI episode (non-severe and severe) and recurrent episodes.

		Recommendation	Strength of recommendation
Initial episode	Judged as non-severe	• Administer a single 500-mg dose of metronidazole (oral or infusion) 3 times daily for 10 days.	Strong recommendation (A)
		• If metronidazole cannot be used (e.g., allergic reaction, adverse reaction, or pregnancy and/or breast feeding), administer a single 125-mg dose of oral vancomycin 4 times daily for 10 days.	Strong recommendation (A)
	Judged as severe	• Administer a single 125-mg dose of oral vancomycin 4 times daily for 10 days.	Strong recommendation (A)
		• If vancomycin cannot be used (e.g., allergic reaction or adverse reaction), administer a single 500-mg dose of metronidazole (oral or infusion) 3 times daily for 10 days.	Weak recommendation (B)
		• If administration of a 125-mg dose of oral vancomycin 4 times daily is not effective, or if shock, hypotension, toxic megacolon, or paralytic ileus occurs, administer a single 500-mg dose of vancomycin (oral, or infusion in 100 mL saline) 4 times daily for 10 days.	Weak recommendation (C)
		• If treatment with vancomycin is not effective, consider combination therapy with metronidazole.	Weak recommendation (C)
Recurrent episodes	–	• Administer a single 125-mg dose of oral vancomycin 4 times daily for 10–14 days.	Weak recommendation (B)
		• If administration of a 125-mg dose of oral vancomycin 4 times daily is not effective, or if shock, hypotension, toxic megacolon, or paralytic ileus occurs, administer a single 500-mg dose of vancomycin (oral, or infusion in 100 mL saline) 4 times daily for 10–14 days.	Weak recommendation (C)
		• If episodes occur repeatedly, consider pulsed and tapered dosing of vancomycin.	Weak recommendation (C)

microbiome.

2.1.7.11.7. Definition of severity

Executive summary

There are several versions of the definition of CDI severity, but none can be recommended.

Literature review

CDI often causes diarrheal symptoms, but the frequency of bowel movements varies greatly. CDI can cause various symptoms; for example, some patients have minimal diarrhea but have fever and abdominal pain. Generally speaking, CDI cases with little diarrhea due to paralytic ileus, toxic megacolon, intestinal perforation, or death are regarded as severe, but they can be considered as cases with complications of CDI. There is no standard definition for CDI, and definitions recommended in several guidelines or by several groups can be used as references (Table 9) (see Table 10).

Many guidelines use a scoring system based on clinical data (e.g., age, temperature, abdominal findings, and hemodynamics), laboratory test data (leukocyte count, serum albumin level, and serum creatinine level), and imaging data. However, there are huge variations in the scoring systems in terms of the items used for scoring, in the cutoff values used, and in the allocation of points, and there are no data comparing the different guidelines available (Table 9). The first major guidelines published were the SHEA/IDSA guidelines in 2010 [167], followed by the CDI guidelines from the ACG in 2013 [73]. The relatively quick publication in the same country of the later CDI guidelines was to reflect Fujitani et al.'s finding that hypoalbuminemia showed the highest association of disease severity (OR, 13.69) [168]. As shown in Table 9, definitions of CDI severity also appeared in the guidelines published by the ESCMID in 2014 [135], the World Society of Emergency Surgery (WSES) in 2015 [169], and the Australasian Society of Infectious Diseases (ASID) in 2016 [170]. The guidelines published by SHEA/IDSA 2017 do not define CDI severity [65]. The criteria for severe CDI are not stringent in any guidelines, and almost all CDI cases satisfy the criteria and the criteria have not yet been verified after guideline publication.

Also, several research groups have proposed severity criteria (Table 9). A randomized study by Zar et al. at the University of Illinois comparing vancomycin and metronidazole defined severe CDI as those cases meeting 2 severity criteria [171]. Neal et al. examined patients who had undergone surgery for severe CDI at the University of Pittsburg to determine the definition of CDI [172]. Miller et al. proposed that CDI severity be determined based on responsiveness to treatment, where 0–2 points were allocated depending on the values of the variables (age, treatment with systemic antimicrobial during CDI treatment for >1 day, temperature, leukocyte count, albumin level, and creatinine level), and prediction of cure was made individually for a total score of 1–10 points [173]. This severity score is called the ATLAS score and it has been tested in a few studies. In a retrospective study of 64 inpatients with CDI, Mulherin et al. showed that patients with ATLAS score ≥4, ≥5, or ≥6 points were categorized as severe according to the SHEA/IDSA criteria for severe CDI and that the ATLAS score was useful for evaluating the severity of CDI, with a sensitivity of 58.3%–87.5% and a specificity of 67.5%–87.5% [174]. Also, Hernández-García et al. conducted a prospective observational study examining CDI severity using the ATLAS score in 102 patients at 2 healthcare facilities in Mexico, and they showed 100% mortality for patients with an ATLAS score of 8–10 points, 100% survival for patients with an ATLAS score ≤3 points, and good association between an ATLAS score of 4–7 points and the need for colectomy [175]. Figh et al. retrospectively examined 271 inpatients with CDI and showed that death correlated well with the severity score index proposed by Velazquez-Gomez et al. [176] (Pearson's correlation coefficient r = 0.9536, P = 0.002) and the ATLAS score (Pearson's correlation coefficient r = 0.9103, P = 0.0001); mean ATLAS score was 3.3 in those who survived and 5.2 in those who did not [177]. Despite several sets of severity criteria already in use, the MN criteria were proposed in 2017 in Japan.

This is an 8-item criteria where 0–3 points are allocated to each item, and a total score of ≤4 points is judged as mild, 5–9 points as moderate, 10–13 points as severe, and ≥14 points as extremely severe [178]. This was the first CDI severity classification proposed at a Japanese professional society, and it was developed based on preceding studies and overseas guidelines while taking into account the Japanese situation [178]. However, validation using an adequate number of Japanese patients is needed to finalize the details for each item and to determine the cutoff values [179]. Criteria items vary among the various scoring systems in use, except for albumin level and leukocyte count, which are common to all scoring systems (Table 9).

When CDI severity, most studies have examined all-cause deaths, and very few have investigated risk factors for CDI-associated deaths. When we performed a Pubmed search using "*Clostridium difficile*", "mortality", and "risk" as keywords, we found the following risk factors for death in CDI patients reported in the English articles retrieved: age, comorbidities, hypoalbuminemia, renal impairment; leukocytosis, and ribotype (027, 002).

With respect to age, the impact on death increased with advancing age [180–183]. A study by Stewart et al. that included young subjects showed increased risk in older age groups, with an OR of 1.17 (95% CI, 1.1–1.24) for those aged 26–50 years, an OR of 1.81 (95% CI, 1.71–1.92) for those aged 51–70 years, and an OR of 2.45 (95% CI, 2.31–2.61) for those aged >70 years [184]. Particularly high risk of death was reported for patients aged ≥75 years in studies by Labbé et al. (OR, 3.18; 95% CI, 1.26–8.02) [185] and Lamontagne et al. (OR, 6.5; 95% CI, 1.7–24.3) [186], for patients aged ≥80 years in studies by Morrison et al. (OR, 5.51; 95% CI, 2.5–13.5) [187] and Kassam et al. (OR, 4.12; 95% CI, 3.39–4.99) [188], and for patients aged ≥85 years in a study by Inns et al. (RR, 1.95; 95% CI, 1.53–2.47) [189]. The study by Kassam et al. included the largest number of CDI patients (n = 374,747), and showed an OR of 2.51 (95% CI, 2.06–3.06) for those aged 61–80 years and an OR of 4.12 (95% CI, 3.99–4.99) for those aged ≥80 years [188]. A multicenter case-control study by Takahashi et al. examined 1,026 Japanese patients and found an OR of 2.08 (95% CI, 1.19–3.62) for those aged 75–84 years and an OR of 1.86 (95% CI, 0.98–3.55) for those aged ≥85 years [190].

With respect to the impact of comorbidities on mortality, a higher Charlson comorbidity index score was associated with higher morbidity in studies by Cadena et al. (OR, 1.2; 95% CI, 1.02–1.19) [191], Das et al. (HR, 1.09; 95% CI, 1.16–1.22) [181], and Chintanaboina et al. [192]; risk was particularly high when the Charlson comorbidity index score was ≥7 points in the study by Labbé et al. [185]. In terms of specific comorbidities as risk factors, a retrospective study of 70 CDI patients aged ≥80 years by Cober et al. identified coronary artery disease (OR, 5.5; 95% CI, 1.3–23.0)[193], a retrospective study of 536 CDI patients by Kim et al. identified malignant tumors (OR, 2.05; 95% CI, 1.05–3.98) [194], and a study by Takahashi et al. identified heart failure (OR, 2.12; 95% CI, 1.26–3.55) and respiratory failure (OR, 1.98; 95% CI, 1.19–3.32) [190]. A multicenter prospective study by Vendetti et al. investigated 7,318 CDI patients aged 1–18 years and identified an association with malignant tumor (OR, 3.57; 95% CI, 2.36–5.40), cardiovascular disease (OR, 2.06; 95% CI, 1.28–3.30), and presence of severe illness (OR, 3.88; 95% CI, 2.44–6.19) [183]. A large-scale retrospective study by Kassam et al. involving 374,747 CDI patients found the following risk factors: kidney failure (OR, 2.93; 95% CI, 2.76–3.13), liver disease (OR, 2.00; 95% CI, 1.78–2.25), malignant tumor (OR, 1.89; 95% CI, 1.74–2.50), inflammatory bowel disease (OR, 1.72; 95% CI, 1.49–1.99), and cardiopulmonary disease (OR, 1.46; 95% CI, 1.38–1.56) [188]. A retrospective study by Xu et al. of 307 CDI patients identified connective tissue disease as a risk factor (HR, 5.531; 95% CI, 1.391–22.000) [195].

Among laboratory test findings, serum albumin level, serum creatinine level, and leukocyte count have mainly been assessed for associations with risk of death. Serum albumin level was examined in many studies. Walker et al. showed a decrease in albumin level by ≥ 5 g/dL as a risk factor for death (HR, 1.3; 95% CI, 1.28–1.4)[182], although many studies showed serum albumin level <3.0 g/dL or < 2.5 g/dL as a risk factor for death. Serum albumin level <2.5 g/dL was shown to be a risk factor for 30 day-mortality in a cohort study of 129 patients conducted by Wilson et al. (OR, 3.13; 95% CI, 1.26–7.75) [196] and a retrospective study of 536 patients conducted by Kim et al. [194]. Takahashi et al. investigated 1,026 Japanese patients and showed an albumin level <2.5 g/dL as a risk factor for 28 day-mortality (OR, 3.5; 95% CI, 1.33–9.22) [190]. A single-center retrospective study by Xu et al. involving 307 patients showed an albumin level <2.5 g/dL as one of the risk factors for 30 day-mortality (HR, 3.935; 95% CI, 1.376–11.250) [195]. A case-control study by Smith et al. of 200 patients with cirrhosis and CDI showed an albumin level <3.0 g/dL was associated with 30 day-mortality (OR, 1.631; 95% CI, 1.03–2.59) [197]. With respect to serum creatinine level, the following levels were reported as a risk factor for death: > 1.5 mg/dL by Solomon et al. (OR, 6.5; 95% CI, 1.5–29.1) [198], >2.0 mg/dL by Pant et al. (OR, 5.07; 95% CI, 1.8–13.9) [199], and >2.3 mg/dL by Cloud et al. (OR, 6.6; 95% CI, 1.4–32) [200]. Persistent high leukocyte count was found to be a risk factor for death (OR, 1.1; 95% CI, 1.0–1.2) in a study including 70 CDI patients aged ≥80 years by Cober et al. [193]. In terms of the cutoff leukocyte count for death, > 15,000/μL was reported by Kim et al. (OR, 2.88; 95% CI, 1.46–5.69) [194], >20,000/μL by Solomon et al. (OR, 11.5; 95% CI, 2.4–55.9) [198], >20,000/μL by Cloud et al. (OR, 30.0; 95% CI, 5.0–144) [200], ≥35,000/μL by Sailhamer et al. (OR, 2.9; 95% CI, 1.3–6.6)[201], and ≥50,000/μL by Lamontagne et al. (OR, 18.6; 95% CI, 3.7–94.7)[186]. Other laboratory test findings have also been shown as risk factors, such as increased blood urea nitrogen level by Bishara et al. (HR, 1.013; 95% CI, 1.006–1.013) [202] and a 3-mmol/L increase by Walker et al. (HR, 1.013; 95% CI, 1.006–1.013) [182]. Walker et al. also reported a decrease by ≥ 3 mmol/L (HR, 1.14; 95% ci, 1.07–1.2) and a c-reactive protein level ≥50 mg/L (HR,1.18; 95% CI, 1.12–1.2) as risk factors [182].

In relation to prognosis by ribotype, a single-center retrospective study showed poor prognosis for CDI caused by clade 5 (078/ST 11), as evidenced by a 14-day mortality rate of 25% (16/63), which was significantly higher (P < 0.001) than 20% (111/560) seen for clade 2 (027/ST 1) and 12% (137/1,168) for clade 1[182]. The NAP-1 strain was identified in 59 of a total of 235 CDI samples, but comparison of NAP-1 isolates with non-NAP-1 isolates obtained in the same period showed no association between the NAP-1 strain and poor prognosis [200]. Ribotype 027 was found to be a risk factor for death in a single-center retrospective study conducted in Canada by Labbé et al. (OR, 2.06; 95% CI, 1.00–4.22) [185] and in a retrospective study including 1,144 patients by Rao et al. (OR, 2.02; 95% CI, 1.19–3.43; P = 0.009) [203], as well as a risk factor for hospital mortality in a study of 292 patients by Bauer et al. (OR, 1.02; 95% CI, 0.53–1.96) [204]. A retrospective cohort study with 1,426 patients by Inns et al. showed the best prognosis for ribotype 015 with an RR of 0.46 (95% CI, 0.26–0.83), compared with an RR of 1.34 (95% CI, 1.02–1.7) for ribotype 027 [189]. A prospective case-control study including 139 patients by Wong et al. showed ribotype 002 as a risk factor (HR, 28; 95% CI, 1.1–7.0) [205].

A study that analyzed 374,747 inpatients with CDI in the USA revealed a mortality of 8% and 8 risk factors for death (age, cardiovascular disease, malignant tumor, diabetes mellitus, inflammatory bowel disease, acute kidney failure, liver disease, and ICU admission). The *Clostridium difficile*-Associated Risk of Death Score (CARDS) was developed using these 8 risk factors (total score, 0–18 points), and analysis showed 100% mortality with a total score of 18 points and 1.2% mortality with a total score of 0 points [188].

Risk of death was also examined in a particular subgroup of CDI patients, namely, those who needed to undergo colectomy for CDI. Kulaylat et al. retrospectively examined 532 patients identified in the American College of Surgeons National Surgical Quality Improvement Project between 2005 and 2014 and found a 30-day mortality rate of 32.7%, and age ≥80 years (OR, 5.5; P = 0.003), preoperative mechanical ventilation (OR, 3.1; P = 0.001), steroid use (OR, 2.9; P < 0.001), presence of cardiopulmonary disease (OR, 2.0; P = 0.001), and acute kidney failure (OR, 1.7; P = 0.03) [206].

2.1.7.11.8. Definition of intractable CDI

Executive summary

Here, intractable CDI is defined as one of the following.

Table 11
Pulsed and tapered vancomycin.

	Dose and duration
①[65]	125 mg 4 times daily for 10–14 days → 125 mg twice daily for 1 week → 125 mg once daily for 1 week → 125 mg once every 2–3 days for 2–8 weeks
②[244]	125- mg 4 times daily for 1 week → 125 mg 3 times daily for 1 week → 125 mg twice daily for 1 week → 125 mg once daily for 1 week → 125 mg once every 2 days for 1 week → 125 mg once every 3 days for 1 week

1. CDI causing ≥2 recurrent episodes after treatment of the initial CDI episode.
2. CDI causing diarrheal symptoms that cannot be alleviated despite standard duration of treatment with vancomycin or oral fidaxomicin, or CDI causing shock, paralytic ileus, toxic megacolon, or perforation despite oral vancomycin or oral fidaxomicin.

Literature review

There is no clear consensus on the definition of intractable CDI [65,73,135]. Intractable CDI cases include those where standard *C. difficile* treatments do not achieve complete cure and results in recurrent CDI episodes or do not resolve clinical features. The standard treatments for *C. difficile* covered by the national health insurance system in Japan are metronidazole (oral or infusion), vancomycin (oral), and the recently added fidaxomicin (oral).

1. CDI causing ≥2 recurrent episodes after treatment of the initial CDI episode

Relapse is more likely to occur after treatment of recurrent CDI episodes than for the initial episode [166,207,208]. The number of previous recurrent episodes is a risk factor for recurrent CDI [129,166]. Among risk factors for recurrence, age ≥65 years was more likely to be associated with a second or more recurrence episodes [207]. Fekety et al. showed that risk of recurrence significantly increased to a recurrence rate of >50% with ≥2 previous recurrent episodes (OR, 3.87; CI, 1.12–13.34, P = 0.03) [166].

Recurrence rate did not differ between oral vancomycin and oral fidaxomicin [209] but was significantly lower with fidaxomicin [159,210]. The rate of second recurrence in patients with one previous recurrence was significantly lower when treated with fidaxomicin compared with vancomycin (20% vs 36%, P = 0.045) [207]. Pulsed and tapered dosing of oral vancomycin were shown to be effective for preventing CDI recurrence [129,211], and they are used to treat patients with repeated recurrent episodes [127]. Bezlotoxumab (human anti-toxin B monoclonal antibody) also prevents recurrent CDI [157] and is covered by health insurance when CDI is likely to be exacerbated or in cases with a high risk of recurrence.

Taken together, anti-CDI agents at standard dosage and administration are unlikely to achieve cure in a second or more recurrent episode following treatment of the initial episode. As such, we include CDI causing ≥2 or more recurrent episodes after treatment of the initial CDI episode in the definition of intractable CDI.

2. CDI causing diarrheal symptoms that cannot be alleviated despite standard duration of treatment with vancomycin or oral fidaxomicin, or CDI causing shock, paralytic ileus, toxic megacolon, or perforation despite oral vancomycin or oral fidaxomicin.

Responsiveness to oral vancomycin and to oral fidaxomicin are similar [159,210]. However, in patients with severe CDI, higher mortality was reported with oral metronidazole compared with other anti-*C. difficile* agents [209,212]. If oral metronidazole does not alleviate clinical features, therapy is commonly switched to oral vancomycin [163]. The therapeutic effects of anti-*C. difficile* agents are mainly judged by the number of passages of loose stools [159,171,210,213] and changes in other clinical features [214,215]. The median time to resolution of symptoms caused by oral vancomycin or oral fidaxomicin was approximately 3 days [159,216], and response to oral vancomycin was seen by day 6 after starting the therapy [213,217].

Response rates to oral vancomycin shown in previous RCTs were 81%–98% [159,171,210,213,215,218,219], while those to oral fidaxomicin shown in randomized double-blind controlled studies were 88%–92% [159,210]. Bauer et al. analyzed 2 randomized double-blind controlled trials and showed a leukocyte count ≥15,000/μL and a serum creatinine level ≥1.5 mg/dL as factors for resistance to treatment [165]. However, it is noteworthy that CDI patients with severe illness such as toxic megacolon, paralytic ileus, and shock were excluded from among subjects of these clinical studies examining oral vancomycin and oral fidaxomicin.

In patients resistant to oral vancomycin and oral fidaxomicin, none of the following showed clear therapeutic effect: intravenous immunoglobulin [220], high-dose vancomycin [221], or fecal microbiota transplantation [222]. In patients with severe CDI who met ≥3 of the following criteria—hypoalbuminemia (serum albumin level <2.5 g/dL), heart rate >90 bpm, mean arterial pressure <60 mmHg, leukocyte count ≥15,000/μL, serum creatinine ≥1.5 times baseline level, and temperature 38 °C—high-dose oral vancomycin plus intravenous metronidazole improved prognosis compared with oral vancomycin alone (mortality rate; 16% vs. 36%), with Day 10 clinical success resulted in only 57% of patients treated with oral vancomycin plus intravenous metronidazole and in 61% of patients treated with oral vancomycin alone [223]. A retrospective study by Sailhamer et al. showed a mortality rate of 35% (69/199) in patients with CDI requiring ICU therapy or colectomy, and colectomy as a factor improving prognosis [201]. A systematic review also showed the efficacy of colectomy in severe CDI [224]. However, the therapeutic effect of surgery has been examined in retrospective studies only and thus further validation is needed.

Consequently, the definition of intractable CDI we use includes CDI causing diarrheal symptoms that cannot be alleviated by cessation of oral vancomycin or oral fidaxomicin, or CDI causing shock, paralytic ileus, toxic megacolon, or perforation despite oral vancomycin or oral fidaxomicin.

2.1.7.11.9. Treatment (metronidazole and vancomycin)

Executive summary

Literature review

a Pharmacotherapy for non-severe and severe CDI

A meta-analysis examined the effectiveness of vancomycin and metronidazole in CDI treatment to determine recommended pharmacotherapies for non-severe and severe cases [225]. When comparing vancomycin with metronidazole, the RR of clinical effects was 1.08 (95% CI, 0.99–1.17), RR of recurrence was 0.86 (95% CI, 0.62–1.18), and RR of adverse events was 0.66 (95% CI, 0.25–1.77). Subgroup analysis by severity showed the RR of clinical effects was 1.09 (95% CI, 1.00–1.19) in the non-severe group and 1.19 (95% CI, 1.02–1.39) in the severe group. In the entire cohort and in the non-severe group, there were no significant differences in clinical effects between vancomycin and metronidazole, but in the severe group, the clinical effects of vancomycin were significantly higher than those of metronidazole.

Metronidazole has an advantage of being inexpensive. A prospective study showed the frequency of occurrence of vancomycin-resistant enterococci (VRE) as similar in CDI patients treated with oral metronidazole and those treated with oral vancomycin [226], although increased vancomycin use for CDI may increase the frequency of VRE

Table 12
Concentrations of sodium hypochlorite and the corresponding targets for disinfection.

Concentration	Target for disinfection	Notes
1,000 ppm	Contaminated linen, devices, and bedpans	30-min immersion in sodium hypochlorite solution after general washing/cleaning. If immersion is impossible, thorough wiping with sodium hypochlorite after general washing/cleaning.
	Contaminated environment	Thorough wiping with sodium hypochlorite. For rust-prone materials, additional wiping with water is required.
5,000–10,000 ppm	Excrement	Eliminate contamination with sodium hypochlorite pre-saturated wipes.

Table 13
Diagnostic algorithms and their characteristics.

Authors	Algorithm	Reference for comparison	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Planche et al. [277], N = 10,634	GDH test → Toxin assay	TC[a]/CCA[b]	58–84	>99	59–81	>99
	GDH test → NAAT	TC/CCA	91–98	96–98	90–92	96–99
	Toxin assay → NAAT	TC/CCA	59–85	>99	90–93	>96
Walkty et al. [278], N = 428	GDH test → Toxin assay	TC	41	100	100	91
	GDH test → NAAT	TC	68	100	100	95
	GDH test → Toxin assay → NAAT	TC	70	100	100	95

[a] Toxigenic culture.
[b] Cell cytotoxic assay.

occurrence [227].

Taken together, in these guidelines, we recommend metronidazole for non-severe cases and vancomycin for severe cases as first-line therapy.

b Neurotoxicity of metronidazole

In a review of metronidazole (tablet), the Pharmaceuticals and Medical Devices Agency (PMDA) raised caution about the occurrence of adverse events when metronidazole is administered for >10 days or at high dose (≥1,500 mg/day). This was based on the incidence of serious central and peripheral neuropathy reported for patients who received metronidazole for ≥10 days (central neuropathy in 10 patients and peripheral neuropathy in 5 patients). Also, a survey on metronidazole use in the clinical setting found that the incidence of adverse events tended to be higher in patients who received ≥1,500 mg/day than in those who received <1,500 mg/day. High dosage and long duration of metronidazole treatment was associated with toxicosis in dogs [228]. In humans, a study in 34 patients showed the mean time to the onset of encephalopathy symptoms was 61.3 days (2–210 days) and the mean total dose was 95.9 g (3.9–367.5 g) in Japan [229]; overseas studies have shown neuropathy occurred with a total dose of 25–1,080 g [230] or 21–135 g [231]. Because of this association of adverse effects with high dosage and long treatment durations, these guidelines recommend metronidazole for treatment of non-severe initial episodes of CDI.

On the other hand, these factors may not be associated with adverse effects given that one study showed a wide variation in metronidazole dosage and treatment duration in 64 patients (mean duration 54 days, mean daily dose 719 mg [250–2,000 mg], and mean total dose 93.4 g [0.25–1,095 g]) [232]. One of the reasons for encephalopathy is increased blood trough metronidazole level in patients with liver and kidney disease. Metronidazole undergoes metabolism via hydroxylation, oxidation, and glucuronidation mainly in the liver, and the resulting metabolites are excreted by the kidney. One case of encephalopathy has been reported in a patient with liver disease (Child-Pugh class C) that occurred after metronidazole treatment for the initial episode of CDI (500 mg, 3 times daily, for 14 days) and for a recurrent CDI episode (500 mg, 3 times daily, for 3 weeks) after completing the initial CDI treatment [233]. Another case was reported of neurotoxicity in a patient with liver cirrhosis on day 19 of metronidazole therapy (1,500 mg/day) [234]. Also, patients with Child-Pugh class A or B cirrhosis and patients with Child-Pugh class C cirrhosis had approximately 1.5 times and 2 times the area under the curve (AUC) of metronidazole compared with healthy individuals, respectively [235]. A high blood metronidazole level (35.1 μg/mL) was reported in a patient with Child-Pugh class C cirrhosis who developed neurotoxicity after receiving a total dose of >60 g over a 55-day period [236], suggesting that patients with severe liver disease should be carefully monitored for adverse effects due to increases in blood trough metronidazole level. Encephalopathy has also been reported in patients with severe kidney disease [237]. The AUC of metronidazole remained unchanged, but the AUC values of its main metabolites, an active metabolite (hydroxy metronidazole) and an oxidative metabolite, increased with impairment in kidney function [238]. Given the neurotoxicity of metronidazole metabolites reported [239], caution should be exercised to avoid adverse effects when using metronidazole in patients with severe kidney failure [239]. Taken together, metronidazole should be administered carefully, such as by decreasing the dose or increasing the dosing interval, in patients with severe liver or kidney disease.

c Standard dose of vancomycin

No difference in efficacy was found between a group who received vancomycin 125 mg 4 times daily and those who received vancomycin 500 mg 4 times daily [221]. Further, Lam et al. compared patients with severe CDI who received vancomycin ≤500 mg or <500 mg daily and found cure rates of 64% and 60% (P = 0.76), respectively, with recurrence rates of 12% and 2% (P = 0.09), respectively [240]. Thus, routine use of a single dose above 125-mg is not recommended. Japanese studies showed that the MIC_{90} of vancomycin for *C. difficile* is 0.5 μg/mL[60,61], and given the fecal concentration of vancomycin reported in patients receiving 125 mg 4 times daily was approximately 30–10,000 times higher than the MIC_{90} value [241–243], this dosage is deemed adequate.

d High-dose vancomycin and intracolonic vancomycin

Although there is no high level of evidence to support recommending a high dose vancomycin regimen (500 mg 4 times daily), it is recommended by many guidelines [65,73,135,169,170,244] and empirically used in the clinical setting for patients with shock, hypotension, toxic megacolon, or paralytic ileus. When high-dose vancomycin is ineffective, or repeated CDI episodes occur after treatment, switching to different agents needs to be considered because of the possibility of vancomycin-resistant *C. difficile*. When oral administration of other agents is impossible, intracolonic vancomycin has been used, and its effectiveness was shown in 33 of 47 (70%) of patients with severe CDI in a retrospective study by Kin et al. [245], and similarly in 26 patients reported by Akamine et al. [246], 17 patients by Saffouri et al. [247], 9 patients by Apisarnthanaraket al. [248], 8 patients by Olsonet al. [249], 8 patients by Shetler et al. [250], and 24 patients by Malamood et al. [251]. A vancomycin dose of 500 mg was administered 4 times daily in many cases of these studies [246–249], but this regimen is not universally accepted, with a single dose ranging from 250 mg to 1000 mg and frequency of dosing ranging from 2 to 4 times daily.

Gonzales et al. reported higher fecal vancomycin levels in CDI patients receiving 500 mg than in those receiving 125 mg as well as lower fecal vancomycin levels with a stool frequency ≥4 times a day compared with a stool frequency ≤3 times a day [242]. Fecal vancomycin level may be decreased in patients with frequent passage of watery stool, and a dose increase should be considered when the current dose is not effective.

The trough concentration of vancomycin exceeded 30 μg/mL in a patient with kidney failure with resulting damage to intestinal epithelial cells in patients who received vancomycin 500 mg 4 times daily [252]. Pettit et al. reported daily dose >500 mg, intestinal lesion, and kidney dysfunction as risk factors for increased blood vancomycin level [253], indicating that blood vancomycin level should be measured on suspicion of adverse effects when vancomycin is administered at high doses in

Table 14
Summary of the characteristics of tests used to diagnose CDI, as reported in systematic reviews and meta-analyses.

Test	Authors	Number of studies	Sensitivity, %[a]	Specificity, %[a]
GDH test	Crobach et al. [281]	11	88 (60–97)	89 (72–97)
	Shetty et al. [285]	13	92 (80–100)	93 (83–100)
	Burnham et al. [6]	7	94 (90–100)	94 (76–98)
Toxin assay	Crobach et al. [281]	60	73 (32–99)	98 (65–100)
	Planche et al. [284]	18	87 (69–90)	97 (92–100)
	Burnham et al. [6]	21	74 (42–99)	98 (84–100)

[a] Values in parentheses indicate range.

patients with intestinal lesions or kidney dysfunction.

e Combination therapy with metronidazole and vancomycin

Bass et al. reported no difference in the incidence of clinical cure in patients with severe CDI between oral vancomycin monotherapy and combination therapy (57% vs 65%, P = 0.49) [254]. On the other hand, Rokas et al. showed a significant difference in mortality in patients with severe CDI between the two therapies (36% vs 16%, P = 0.03) [223]. Both were retrospective studies and since no RCTs have been conducted, further studies are necessary on combination therapy with metronidazole and vancomycin. Therapies for patients with severe CDI who are not responding vancomycin are limited, and combination therapy is one of the limited options available.

f Pulsed and tapered vancomycin

Table 11 shows details of 2 pulsed and tapered vancomycin regimens. According to Tedesco et al., pulsed and tapered vancomycin prevented recurrence in 22 patients who had had several recurrent episodes [255]. In an observational study, McFarland et al. found a significant decrease in recurrence rate after pulsed and tapered vancomycin [129]. However, this was not compared with other monotherapies (e.g., fidaxomicin monotherapy) and the safety data are not yet available. The incidence of VRE may increase due to increased vancomycin use [227,256]. The pulsed and tapered vancomycin can be an alternative when other therapies are not effective.

2.1.7.11.10. Infection control measures

Executive summary

Patients with CDI or suspected CDI should be isolated in private rooms whenever possible, with appropriate contact prevention measures taken, such as practising stringent hand hygiene and using personal protective equipment (PPE) such as gloves, gowns, and aprons. If isolation in a private room is not possible, cohorting should be considered. Healthcare professionals, and any visitors, must wear PPE when entering patient rooms. During outbreaks, or at facilities where the *C. difficile* infection rate is increasing, hands should be cleaned with soap and water after touching patients while providing care, and visitors must abide by the same instructions.

Literature review

The incidence rate of CDI was reported to be higher in 2-bed rooms (17%) than in single-bed rooms (7%), indicating that infection risk increased on exposure to roommates with positive *C. difficile* culture [81]. It is widely recommended that patients with confirmed or suspected CDI be isolated in private rooms, ideally in those with a washroom, whenever possible [73,167,169,257,258]. A prospective study involving 100 patients with suspected CDI showed that the time to diagnosis was 2.07 days in 10 patients with a CDI diagnosis, and that 69% of healthcare professionals who had already been exposed to the patients before their diagnosis of acquired *C. difficile* [259]. Thus, it is advisable for contact isolation precaution to be instituted for patients with suspected CDI until the final diagnosis is obtained.

Where the number of single-bed rooms is limited, patients with fecal incontinence must be prioritized for isolation in private rooms [65,260], and if this is not possible, cohorting of CDI patients is needed [65]. Each patient should use their own individual bedpan [167], ideally managed by designated staff [169,258].

Cohorting of patients, compared with non-cohorting, was associated with risks of severe CDI (OR, 1.95; 95% CI, 1.10–3.46, P = 0.022) and recurrence (OR, 3.94; 95% CI, 1.23–12.65; P = 0.021) [261], indicating that management of patient movements is necessary.

Hand contamination with *C. difficile* was reported among healthcare professionals involved in the care of CDI patients [81], so practising strict hand hygiene is one of the most important anti-infection measures. *C. difficile* spores are highly resistant to alcohol and therefore using alcohol-based hand rubs (ABHRs) will not achieve adequate *C. difficile* removal—hand hygiene with soap and water is considered more effective [262]. On the other hand, increased use of ABHRs was found not to be associated with increased incidence of CDI [263]. An education program on the use of protective gloves markedly decreased the incidence of CDI from 7.7 cases/1,000 patient discharges to 1.5 cases/1,000 patient discharges [264], indicating that appropriate use of protective gloves is an important major anti-infection measure.

2.1.7.11.11. Duration of contact precautions

Executive summary

Contact precautions should be implemented while CDI patients have diarrhea or are passing semisolid soft stools (Bristol Stool Scale ≥5). It is recommended that contact precautions be continued for at least 48 h after resolution of diarrhea, whenever possible.

Literature review

CDI prevention measures must include contact precautions in addition to standard measures until diarrhea resolves [73,167]. Some guidelines recommend that contact precautions be continued for at least 48 h until diarrhea resolves [169,257,258].

A prospective study including 27 CDI patients revealed that several

Table 16
Summary of the characteristics of NAAT, as reported in systematic reviews and meta-analyses.

Authors	Number of studies	Sensitivity[a]	Specificity[a]
Crobach et al. [281]	4	91 (86–100)	96 (95–100)
Deshpande et al. [282]	19	90 (88–91)	96 (96–97)
O'Horo et al. [283]	25	92 (91–94)	94 (94–95)

[a] Values in parentheses indicate range.

Table 15
Summary of the characteristics of tests used for CDI, as reported by studies in Japan.

Test	Authors	Number of specimens	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
GDH test	Kawada et al. [288]	60	80.0–100	93.3–100	93.8–100	83.3–100
	Morinaga et al. [290]	231	92.5	94.4	83.1	97.7
Toxin assay	Kawada et al. [288]	60	71.4–78.6	93.8–96.9	90.9–95.7	78.9–83.8
	Kosai et al. [289]	118	45.5	94.1	75.0	81.6
	Morinaga et al. [290]	231	52.8	100	100	87.7

Table 17
Summary of characteristics of NAAT, reported by studies in Japan.

Authors	Number of specimens	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Tojo et al. [291]	69	96.7	97.4	ND	ND
Kosai et al. [289]	118	93.9	96.5	91.2	97.6
Morinaga et al. [290]	231	98.1	98.9	96.3	99.4

Table 18
Association between test results and clinical course.

	Toxin (+)/NAAT (+)	Toxin (−)/NAAT (+)	Toxin (−)/NAAT (−)	P value
CDI-associated complications	7.6%	0.0%	0.3%	<0.001
CDI-associated 30-day mortality	8.4%	0.6%	0.3%	<0.001

skin sites (e.g., groin, chest, abdomen, forearms, and hands) were frequently contaminated with *C. difficile* and that skin contamination in the chest and abdomen persisted after diarrhea resolved, with a median time from resolution to detection of negative skin cultures of 7 days (95% CI, 3–9 days) [265].

A prospective study including 52 patients showed that *C. difficile* became undetectable in stool specimens by the time the diarrhea resolved (mean, 4.2 days), but the frequency of skin contamination and environmental shedding at the time of resolution was 60% and 37%, respectively. In total, 56% of patients had become asymptomatic carriers, and the frequency of skin contamination and environmental shedding, which had dropped at the time of therapy completion, reverted to high levels (≥50%) at 1–4 weeks after therapy completion [266].

Some patients may continue to excrete *C. difficile* even after diarrhea resolves, thus continuing contamination of the environment, and these patients are at high risk of recurrent CDI. However, a study showed that asymptomatic *C. difficile* carriers who had never developed CDI could produce spores, although the number of excreted spores and the intensity of contamination were not similar between such asymptomatic patients and symptomatic patients [267]. There is no evidence to support screening and isolation of such asymptomatic patients. There is also no evidence at present that extended isolation decreases the frequency of CDI, so extending contact precautions for all CDI patients until discharge is not a standard measure. Additionally, repeated stool testing to determine the timing to discontinue isolation is not recommended [260]. However, given that the incidence of CDI remained high despite implementation of standard infection control measures in healthcare facilities, contact precautions continue to be recommended until discharge even after CDI symptoms have resolved [65,260].

Recommendations in related clinical practice guidelines

Contact precautions until diarrhea resolves is recommended in the 2010 IDSA/SHEA guidelines [167] and the 2013 ACG guidelines [73]. However, contact precautions until at least 48 h after the resolution of diarrhea is recommended in the 2011 ASID/AICA guidelines [257], the 2008 ESCMID guidelines [258], the 2015 WSES guidelines [169], and the 2017 IDSA/SHEA guidelines [65].

2.1.7.11.12. Disinfection in CDI-contaminated areas

Executive summary

Cleaning agents containing chlorine (≥1,000 ppm available chlorine) or other sporicidal agents should be used for routine disinfection of rooms used by CDI patients. After discharge, the rooms should be cleaned immediately with stringent disinfection measures followed.

Literature review

C. difficile spores contaminate the environment in which CDI patients were accommodated and the equipment used for care for them, and the contaminated area and items become a reservoir for *C. difficile* transmission. Use of chloride-containing cleaning agents was found to reduce environmental contamination and thereby reduced the incidence rate of CDI in wards with a high CDI transmission rate [268,269].

The available chlorine concentration in the cleaning agent used to disinfect the environment at each healthcare facility should be determined based on the balance between the disinfectant effect and the disadvantages of its use (e.g., corrosiveness, odor, and hypersensitivity). Nevertheless, use of cleaning agents with an available chlorine concentration ≥1,000 ppm is recommended for disinfection of environmental surfaces [167,257,258]. Use of cleaning agents with an available chlorine concentration ≥5,000 ppm for at least 10 min is recommended depending on the guidelines in use [73]. It is also important to remove organic materials from environmental surfaces before using diluted sodium hypochlorite [260]. Table 12 shows the concentrations of sodium hypochlorite for specific targets for disinfection.

Gastrointestinal endoscopes should be disinfected using high-level disinfectants such as peracetic acid, glutaral (glutaraldehyde), and phtharal. Among them, 2% Glutaral is relatively inexpensive and can be used for hand disinfection. However, 15-min treatment did not achieve the expected sporicidal effect [270], so at least 30-min treatment is required for disinfecting gastrointestinal endoscopes. The use of automated systems is advisable to achieve high cleaning and disinfecting efficiency and to avoid the risk of inhalation and skin contact causing respiratory disturbance and dermatopathy, respectively. Thorough cleaning is required after disinfection to remove residual disinfectants from surfaces.

Use of high-concentration sodium hypochlorite over a large area is not advisable because of the effect on humans and degradation of materials, and its use for hand disinfection or routine environmental disinfection should be avoided. A recently introduced complex-type chlorine-based disinfectant, RUBISTA® (RST), generates hypochlorite upon oxidization of sodium chloride by the main component, potassium peroxymonosulfate, and it is easy to use because it has less chlorine odor and minimal effects on metal and plastic materials. A reduced incidence of infection was reported on changing from an agent with an available chlorine concentration of 1,000 ppm to RST [271], but RST is easily affected by temperature and expires within 1 month because the available chlorine concentration decreases gradually when stored at room temperature [272]. Also, it should be noted that RST is a disinfecting and cleaning agent—it is not an alternative to sodium hypochlorite for sterilizing equipment [273]. The use of RST needs to be examined further in clinical studies.

In a randomized prospective study examining 8 disinfection methods— hydrogen peroxide vapor, dry ozone, a chlorine-producing agent (1,000 ppm), microfiber cloths, microfiber cloths in combination with a chlorine-producing agent, high temperature over heated dry atomized steam in combination with a disinfectant, steam, and peracetic wipes—3 methods were effective: using hydrogen peroxide vapor, a chlorine-producing agent (1,000 ppm), or peracetic wipes [274]. According to Rutala et al., UV-C irradiation for 15–50 min was effective in reducing the *C. difficile* contamination level on directly exposed surfaces and surfaces behind object in hospital rooms, which was shorter than the time for hydrogen peroxide vapor treatment (2–5 h), and UV-C irradiation in combination with UV-reflective wall coating further reduced the time required for hospital room decontamination to 5–10 min [275,276].

Given the high turnover of environmental cleaning personnel, it is necessary to provide frequent education programs to ensure cleaning

and disinfection techniques are properly carried out [260].

2.2. Clinical questions

2.2.1. CQ: is use of the nucleic acid amplification test (NAAT) recommended for glutamate dehydrogenase (GDH)-positive toxin-negative patients?

Recommendation: It is weakly recommended that NAAT be performed when GDH test results are positive and toxin assay results are negative.

Level of recommendation: Weak recommendation for use.

Comments: NAAT is expected to be covered by health insurance.

2.2.1.1. Background and significance of this CQ. Positive GDH test results with negative toxin assay results indicate the possibility that the toxin assay is not sensitive enough to detect toxin produced by the *C. difficile* strains in the patient. Physicians should determine CDI comprehensively by taking the clinical course into consideration and then treat the patient accordingly.

2.2.1.2. PICO. P (patient): Patients with suspected CDI who are GDH-positive and toxin-negative (irrespective of age and sex).

I (intervention): Perform additional test (i.e., NAAT) to confirm CDI.

C (comparison): No confirmation with NAAT (use GDH test results and toxin assay results only).

O (outcome): Sensitivity and rate of *C. difficile* detection.

2.2.1.3. Summary of evidence. GDH and toxin A/B are assayed separately overseas, and one study has examined diagnostic algorithms comprising these tests and NAAT (Table 13). A large-scale multicenter study by Planche et al. evaluated a 2-step algorithm comprising the first method for screening followed by the second method for confirmation of the positive results of the first test. The authors reported better performance when the GDH test was used for screening and NAAT for confirmation (sensitivity 91%–98%; specificity 96%–98%) compared with the GDH test for screening and toxin assay for confirmation (sensitivity 58%–84%; specificity >99%) and the toxin assay for screening and NAAT for confirmation (sensitivity 59%–85%; specificity >99%) [277]. Walkty et al. showed that a 3-step algorithm comprising, in order, the GDH test, toxin assay, and NAAT showed better sensitivity (70%) and specificity (100%) than the following 2-step algorithms: GDH test followed by toxin assay (sensitivity, 41%; specificity, 100%) and GDH test followed by NAAT (sensitivity, 68%; specificity, 100%) [278].

A systematic review of 13 studies including the 2 studies mentioned above showed that algorithms using NAAT for confirmation had higher sensitivity (sensitivity, 68%–100%; specificity, 92%–100%) than those that did not use NAAT for confirmation (sensitivity, 40%–93%; specificity, 97%–100%) [279].

In Japan, enzyme immunoassays (EIA) that simultaneously detect GDH and toxin are frequently used. A study examining algorithms including EIA examined 150 specimens collected from 150 patients aged ≥65 years and found 72.7% of patients who had contradictory results GDH and toxin results were NAAT-positive, and the addition of NAAT increased the final CDI diagnosis rate from 7.3% to 12.7% [280].

Table 19
Differences in CDI recurrence rate and percent decrease in relative risk in subgroups.

	Difference in CDI recurrence rate (%):placebo group – bezlotoxumab (anti-toxin B antibody) group	Rate of decrease in relative risk (%)
Presence of history of CDI	−16.1%	−39.2%
Older age ≥65 years	−16.0%	−50.9%
Immunocompromised patients	−12.8%	−46.8%
Patients with severe CDI	−11.7%	−52.4%
Virulent strains (ribotype 027, 078, or 244)	−10.4%	−30.6%

2.2.1.4. Quality of evidence for overall outcome. A.

2.2.1.5. Summary of benefits. Use of NAAT increased the detection rate and detection sensitivity.

2.2.1.6. Summary of harms (adverse reactions). Nothing particular.

2.2.1.7. Summary of harms (burden). Additional costs are required for NAAT.

2.2.1.8. Benefits-harms balance. Benefits exceed harms.

2.2.1.9. Healthcare costs necessary for the intervention. Additional costs are required for NAAT.

2.2.1.10. Feasibility of intervention. It is feasible once the system to perform NAAT is established.

2.2.1.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.1.12. Recommendations in related clinical practice guidelines. IDSA/SHEA guidelines (2017): Weakly recommended as one of the options.

IDSA guidelines for the diagnosis and management of infectious diarrhea (2017): No mention of recommendation (mentioned in a table as one of the options).

ESCMID guidelines update (2016): Recommended.

American College of Gastroenterology guidelines (2013): Strongly recommended.

2.2.2. CQ: is it recommended that the possibility of CDI is ruled out based solely on antigen test results?

Recommendation: It is strongly recommended not to rule out the possibility of CDI based solely on GDH-positive and toxin-negative results.

Level of recommendation: Strong recommendation.

Comments: When GDH test results are negative despite the presence of diarrhea, CDI is unlikely. When GDH test results are positive and toxin assay results are positive, CDI is diagnosed. However, when GDH test results are positive and toxin assay results are negative, it is possible that the test could not detect the presence of toxigenic strains, so clinical assessment results should be taken into account to make a comprehensive judgement.

2.2.2.1. Background and significance of this CQ. In Japan, antibody testing that simultaneously detects GDH and toxin is widely used. When GDH test results are positive and toxin assay results are negative, it is possible that the toxin assay is not sensitive enough to detect the presence of toxigenic strains.

2.2.2.2. PICO. P (patient): Patients with suspected CDI with diarrhea (irrespective of age and sex).

I (intervention): Perform antigen test (GDH test and toxin assay).

C (comparison): Gene detection, or toxigenic culture and cell cytotoxicity neutralization assay (CCNA) using isolated strains.

O (outcome): Sensitivity and rate of *C. difficile* detection.

2.2.2.3. Summary of evidence. *C. difficile* may colonize the intestine, so patients to be tested must have diarrhea. Common reference methods include toxigenic culture that detects toxins produced by isolated

strains, CCNA that confirms toxicity in cultured cells, and gene detection.

Systematic reviews and meta-analyses showed that the GDH test had a sensitivity of 88%–94% and specificity of 89%–94%, while toxin assay had a varying sensitivity of 73%–87% depending on the study and specificity of 97%–98% (Table 14) [6,281–285]. The negative predictive value was high (97%–100%) for the GDH test but varied for toxin assay (79%–100%) [6,285].

With respect to performance of the antigen test, slightly low sensitivity of GDH was reported when testing non 097 ribotype strains [286], with decreased detection rates seen in mild cases [287]. In Japan, strains that are associated with severe disease overseas (e.g., ribotype 027) are rare, but the results of studies conducted in Japan are similar to those from studies conducted overseas (Table 15). More precisely, the GDH test had higher sensitivity than the toxin assay (80%–100% vs 53%–79%), both the GDH test and toxin assay had high specificity (93%–100% vs 94%–100%), and the GDH test had higher negative predictive value than toxin assay (83%–100% vs 79%–88%) [288] [–] [291].

2.2.2.4. Quality of evidence for overall outcome. A.

2.2.2.5. Summary of benefits. GDH test offers high sensitivity and high negative predictive value.

Toxin assay is versatile because of its affordability and simplicity.

2.2.2.6. Summary of harms (adverse reactions). Sensitivity and negative predictive value of toxin assay are not high.

2.2.2.7. Summary of harms (burden). Healthcare expenditure for inappropriate treatment due to misdiagnosis of CDI may increase.

2.2.2.8. Benefits-harms balance. Benefits exceed harms.

Table 20
Efficacy of fidaxomicin shown in a Japanese phase III study.

Study population	Endpoints	Fidaxomicin group n/N (%)	Vancomycin group n/N (%)	Difference (95% confidence interval)
FAS	Cure rate	87/104 (83.7)	95/108 (88.0)	−4.4 (−13.8,5.0)
	Recurrence rate	17/87 (19.5)	24/95 (25.3)	−4.9 (−16.7,7.0)
	Sustained cure rate	70/104 (67.3)	71/108 (65.7)	1.2 (−11.3,13.7)
PPS	Cure rate	81/91 (89.0)	88/96 (91.7)	−2.6 (−11.3, 6.0)
	Recurrence rate	12/75 (16.0)	21/87 (24.1)	−6.6 (−18.6, 5.4)
	Sustained cure rate	63/85 (74.1)	66/95 (69.5)	3.9 (−9.1, 16.8)

Table 21
Efficacy of fidaxomicin shown in 2 overseas phase III studies.

Study population	Endpoints	Fidaxomicin group n/N (%)	Vancomycin group n/N (%)	P value
003 study				
mITT	Cure rate	253/287 (88.2)	265/309 (85.8)	–
	Recurrence rate	39/253 (15.4)	67/265 (25.3)	0.005
	Sustained cure rate	214/287 (74.6)	198/309 (64.1)	0.006
004試験				
mITT	Cure rate	221/252 (87.7)	223/257 (86.8)	–
	Recurrence rate	28/221 (12.7)	60/223 (26.9)	0.0002
	Sustained cure rate	193/252 (76.6)	163/257 (63.4)	0.001

2.2.2.9. Healthcare costs necessary for the intervention. Unchanged.

2.2.2.10. Feasibility of the intervention. NAAT, which picks up false-negative cases on antigen tests, is expected to be covered by health insurance.

2.2.2.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.2.12. Recommendations in related clinical practice guidelines. IDSA/SHEA guidelines (2017): Recommended.

IDSA guidelines for the diagnosis and management of infectious diarrhea (2017): No description regarding the recommendation (mentioned in a table as one of the options).

ESCMID guidelines update (2016): Recommended.

American College of Gastroenterology guidelines (2013): Strongly recommended.

2.2.3. CQ: is performing NAAT in suspected CDI before any tests are done recommended?

Recommendation: It is weakly recommended against performing NAAT before any tests are done. However, it is weakly recommended to perform NAAT before any tests during outbreaks or similar situations.

Level of recommendation: Weak recommendation.

Comments: The influence on healthcare costs of performing NAAT before any other tests are done is unclear in Japan. It should be noted that NAAT may detect *C. difficile* in patients with impaired immunity who have developed non-CDI diarrhea.

2.2.3.1. Background and significance of this CQ. GDH test cannot distinguish toxigenic strains from non-toxigenic strains, and the toxin assay has low sensitivity. Gene detection tests can detect toxin genes with high sensitivity, but the detection efficiency of NAAT without a preceding GDH test or toxin assay needs to be investigated.

Use of NAAT also has negative implications (overdiagnosis and cost).

2.2.3.2. PICO. P (patient): Patients with suspected CDI with diarrhea (irrespective of age and sex).

I (intervention): Perform NAAT in all patients.

C (comparison): Results of GDH test and toxin assay.

O (outcome): Sensitivity and rate of *C. difficile* detection.

2.2.3.3. Summary of evidence. According to systematic reviews and meta-analyses that examined the characteristics of NAAT, the sensitivity and specificity of NAAT were similar among the studies included, at 87%–91% and 94%–96%, respectively (Table 16) [281–283]. The

Table 22
Rate of CDI recurrence in patients with a previous history of CDI: fidaxomicin group vs vancomycin group (analysis of combined data from 2 studies).

	Fidaxomicin group n/N (%)	Vancomycin group n/N (%)	P value
With previous history of CDI	13/66 (19.7)	22/62 (35.5)	0.045

Table 23
Cure rate and recurrence rate in CDI patients with concomitant antimicrobials: fidaxomicin group vs vancomycin group (analysis of combined data from 2 studies).

	Fidaxomicin group n/N (%)	Vancomycin group n/N (%)	P value
Cure rate	81/90 (90.00)	81/102 (79.41)	0.04
Recurrence rate	15/89 (16.85)	28/96 (29.17)	0.048

Table 24
Comparison of CDI recurrence rates among fidaxomicin, vancomycin, and metronidazole, as shown in a systematic review (odds ratios).

	Odds ratio	95% confidence interval
Fidaxomicin vs Vancomycin	0.47	0.34, 0.65
Fidaxomicin vs Metronidazole	0.42	0.18, 0.96

results of studies conducted in Japan [289–291] were similar to those from overseas, with a sensitivity of 94%–98% and specificity of 97%–99% (Table 17). These results are better than those for the GDH test and toxin assay [6,281–285]. Also, when using the clinical diagnosis as reference, both the sensitivity and specificity of NAAT (99.1% and 98.9%, respectively) were better than those of the GDH test (83.8% and 94.5%, respectively) [292].

In a clinical study in which toxin assay and NAAT were performed and only the toxin assay results were reported clinically, the median duration of diarrhea was significantly shorter in toxin (−)/NAAT (+) patients than in toxin (+)/NAAT (+) patients (2 days vs 3 days, respectively), but was not different from that in toxin (−)/NAAT (−) patients. Also, toxin (−)/NAAT (+) patients had a significantly lower rate of CDI-associated complications than toxin (+)/NAAT (+) patients (0% vs 7.6%) and significantly lower 30-day CDI-associated mortality (0.6% vs 8.4%; Table 18) [293].

There are only a limited number of studies on the diagnosis of CDI in immunocompromised patients. High-dose corticosteroids and leukocytopenia were associated with false-positive toxin assay results [287], and use of NAAT increased the rate of CDI diagnosis by 2-fold in patients with malignancy [294]. However, the proportion of patients with diarrhea was higher in those with prolonged hospitalization due to ICU admission, transplantation, and chemotherapy than in those with short hospitalization (15%–80% vs < 5%), and also, in those with prolonged hospitalization, non-CDI diarrhea was more commonly observed than CDI diarrhea (70%–90% for non-infectious diarrhea associated with treatment of underlying conditions and 5%–25% for CDI diarrhea) [295]. The rate of *C. difficile* colonization was also high in such patients [93]. Thus, when NAAT results are positive in patients with *C. difficile* colonization, it is important to distinguish CDI diarrhea from non-CDI diarrhea [296–299].

No meta-analyses or systematic reviews have examined the usefulness of NAAT during outbreaks. However, simulated use of toxin assay results to determine and control CDI outbreaks that had determined and controlled based on NAAT results showed that toxin assay might have missed some CDI cases [300].

2.2.3.4. Quality of evidence for overall outcome. B.

2.2.3.5. Summary of benefit. NAAT offers good sensitivity and specificity in reference to other standard tests and to clinical diagnosis as well.

The sensitivity of NAAT increases in immunocompromised patients.

The sensitivity of NAAT also increases during outbreaks in immunocompromised patients. Performing NAAT before any other tests may facilitate early detection of CDI leading to swift implementation of requisite measures.

Table 25
Number of *C. difficile* spores in stool specimens collected 2 weeks after treatment from CDI patients; fidaxomicin group vs vancomycin group.

	Fidaxomicin group (%)	Vancomycin group (%)	P value
Proportion of patients achieving at least 2 log10 CFU/g reduction in spore numbers	67	14	0.02

Table 26
C. difficile positive detection rate in CDI patients' rooms.

	Fidaxomicin group (%)	Metronidazole/ Vancomycin group (%)	P value
Positive detection rate (rooms)	36.8	57.6	0.02
Positive detection rate (sampling sites)	17.3	25.8	0.02

2.2.3.6. Summary of harms (adverse reactions). NAAT-positive and toxin-negative patients may have a clinical course similar to that of non-CDI patients; in other words, overdiagnosis is possible if decided solely based on NAAT results.

The positive predictive value of NAA may be reduced in immunocompromised patients due to a high *C. difficile* colonization rate and complication by non-CDI diarrhea.

2.2.3.7. Summary of harms (burden). Use of NAAT increases healthcare expenditure.

2.2.3.8. Benefits-harms balance. Benefits and harms weigh similarly, or harms exceed benefits (insufficient evidence to infer harms).

However, during outbreaks, benefits and harms weigh similarly, or benefits exceed harms.

2.2.3.9. Healthcare costs necessary for the intervention. Healthcare costs increase.

2.2.3.10. Feasibility of intervention. It is feasible once the system to perform NAAT is established.

2.2.3.11. Is intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.3.12. Recommendations in related clinical practice guidelines. IDSA/SHEA guidelines (2017): NATT is weakly recommended as a test or as a part of multi-step algorithms. There is no description regarding use of NAAT during outbreaks.

IDSA guidelines for the diagnosis and management of infectious diarrhea (2017): Recommended as one of the options. There is no description regarding use of NAAT during outbreaks. (Note that multiplex nucleic acid testing to detect causative bacteria is recommended during outbreaks of infectious diarrhea.)

ESCMID guidelines update (2016): Recommended as one of the options (although NAAT-positive status needs to be accompanied by toxin-positive status determined by EIA, or, if toxin assay results are negative, to be accompanied by adequate clinical findings for diagnosis). For use during outbreaks, the only description available is that of molecular typing of strains.

American College of Gastroenterology guidelines (2013): Strongly recommended as a standard test. There is no description regarding use of NAAT during outbreaks.

2.2.4. CQ: is treatment with bezlotoxumab (anti-toxin B antibody) recommended for preventing recurrence of CDI?

Recommendations: Bezlotoxumab, an anti-toxin B monoclonal antibody, has proven efficacy for preventing recurrence of CDI, but its use is strongly recommended against in patients at low risk of CDI recurrence. In patients at high risk of CDI recurrence, its use for prevention is weakly recommended.

Addition of bezlotoxumab as an adjuvant to standard therapy for CDI is weakly recommended for patients at high risk of CDI recurrence, bearing in mind the important considerations associated with the partial revision of the national health insurance drug price standards.

Level of recommendation: Weak recommendation.

Comments: Bezlotoxumab can prevent CDI recurrence, but its use is weakly recommended in CDI patients at high risk of recurrence, specifically patients with a previous history of CDI, aged ≥65 years, and with immunodeficiency and/or severe CDI. Use of bezlotoxumab is not recommended in a wide range of patients, including those with no risk of CDI recurrence. When bezlotoxumab is used for prevention of CDI recurrence, it is necessary to bear in mind the important considerations associated with partial revision of the national health insurance drug price standards (see below).

Reference: Important considerations associated with the partial revision of the national health insurance drug price standard.

This drug is indicated for patients with CDI who are at high risk of developing aggravation or recurrence. Reasons for using this drug should be chosen from the following options (A-E) and should be recorded in the remarks column on the receipt. If option E is chosen, reasons should be recorded for why the case was judged to be at high risk of aggravation or recurrence. Age ≥65 years or previous history of ≤2 episodes are not considered a sole reason for high-risk status.

A. Immunocompromised state
B. Severe CDI
C. Infection with virulent strains (ribotype 027, 078, or 244)
D. Previous history of ≥3 CDI episodes
E. Other reasons why the case was judged to be at high risk of aggravation or recurrence

2.2.4.1. Background and significance of this CQ. CDI recurrence may worsen prognosis or disturb treatment of underlying conditions in the clinical setting. Recurrence occurs at a certain percentage after treatment of CDI with vancomycin and metronidazole, although little evidence is available on the effects of these agents on preventing recurrence. Thus, whether bezlotoxumab (anti-toxin B antibody) can be used for prevention of CDI recurrence needs to be investigated.

2.2.4.2. PICO. P (patient): Patients with CDI.

I (intervention): Administration of bezlotoxumab in addition to standard anti-CDI agents.

C (comparison): Administration of standard anti-CDI agents only.

O (outcome): CDI recurrence rate by risk factor (the recurrence preventing effect).

2.2.4.3. Summary of evidence. Toxin B is likely to be play a more important role in disease than toxin A, and it alone causes damage to the intestine and systematic organopathy [301]. A study examining the virulence of toxins and the role of antibodies in the prevention and treatment of CDI showed that bezlotoxumab was effective in preventing systemic symptoms and intestinal damage, whereas actoxumab (anti--toxin A antibody) alone was not effective [302].

With respect to the clinical evidence, a placebo-controlled phase II study of bezlotoxumab showed that this antibody to toxin B is an independent factor preventing CDI recurrence [156]. Also, the multinational randomized phase III trials MODIFY I and MODIFY II showed that bezlotoxumab in combination with the standard therapies was effective in preventing CDI recurrence; more precisely, the recurrence rate was significantly lower in the treated group than in the placebo group in both MODIFY I (17% vs 28%) and MODIFY II (16% vs 26%) [157]. Further, MODIFY I showed that actoxumab alone was not effective in preventing CDI recurrence (recurrence rate, actoxumab alone vs placebo, 26% vs 28%), and MODIFY I and MODIFY II showed that the recurrence preventing effect was comparable between bezlotoxumab alone and the combination of bezlotoxumab with actoxumab (recurrence rate, bezlotoxumab alone vs combination: 17% vs 16% in MODIFY I and 16% vs 15% in MODIFY II). This indicates that recurrent CDI can be prevented by bezlotoxumab alone.

In terms of treatment-related evidence, there have been reports of low therapeutic effect in patients with a history of CDI and in older patients, and of the influence of older age on CDI treatment [143,303,304].

Regarding CDI recurrence, a phase III study analyzing the effect of bezlotoxumab in high-risk subgroups found decreases in the CDI recurrence rate in all of the high-risk subgroups tested: patients with a history of CDI, patients aged ≥65 years, immunocompromised patients, patients with severe CDI determined by Zar score, and patients infected with virulent *C. difficile* strains (Table 19) [157].

Ninety-five patients from 35 facilities in Japan were enrolled in MODIFY II [157], and the subgroup analysis showed that bezlotoxumab can be a new option for prevention of recurrent CDI in Japanese CDI patients [305]. Also, this multicenter randomized double-blinded placebo-controlled trial compared the CDI recurrence rates in 3 groups (placebo, 10 mg/kg bezlotoxumab, and 10 mg/kg bezlotoxumab plus actoxumab 10 mg/kg), and showed that bezlotoxumab decreased the CDI recurrence rate at 12 weeks after the baseline episode resolved (recurrence rate, 21% in the bezlotoxumab group vs 46% in the placebo group; P = 0.0393).

2.2.4.4. Quality of evidence for overall outcome. A.

2.2.4.5. Summary of benefits. Bezlotoxumab significantly reduced the rate of CDI recurrence.

2.2.4.6. Summary of harms (adverse reactions). Major adverse reactions of bezlotoxumab were nausea in 8 patients (1.0%), headache in 6 patients (0.8%), and fatigue in 5 patients (0.6%).

2.2.4.7. Summary of harms (burden). Bezlotoxumab is administered as a single infusion, causing little burden in relation to QOL. On the other hand, it is an expensive therapy, so medical-economic studies are necessary in future.

2.2.4.8. Benefits-harms balance. Benefits exceeds harms in patients at high risk of repeated recurrent episodes.

2.2.4.9. Healthcare costs necessary for the intervention. Use of bezlotoxumab in addition to standard anti-CDI agents increases medication costs.

2.2.4.10. Feasibility of the intervention. Feasible.

2.2.4.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.4.12. Recommendations in related clinical practice guidelines. None given as of August 2018.

2.2.5. CQ: Should fidaxomicin be used as primary treatment for the initial episode of CDI?

Recommendation: A phase III study including Japanese CDI patients did not examine the non-inferiority of fidaxomicin to vancomycin in relation to the rate of sustained cure (primary endpoint) in the full analysis set, and therefore there is a weak recommendation against using fidaxomicin. However, fidaxomicin had favorable effects for preventing CDI recurrence and achieving sustained cure in overseas patients, and compared to vancomycin, showed a lower recurrence rate and a higher sustained cure rate in Japanese CDI patients. Taken together, fidaxomicin can be recommended as the primary treatment for patients at high risk of recurrence.

Level of recommendation: Weak recommendation against using fidaxomicin as primary treatment for CDI, but it can be considered for patients at high risk of recurrence.

Comments: Two overseas phase III studies and systematic reviews

confirmed that fidaxomicin prevented CDI recurrence and achieved sustained cure significantly more than metronidazole and vancomycin in overseas patients.

2.2.5.1. Background and significance of this CQ. It is known that a certain proportion of patients have CDI recurrence after a prior CDI episode is treated with vancomycin and metronidazole. Also, CDI recurrence sometimes worsens prognosis or disturbs treatment of underlying conditions in the clinical setting. Given the high cure rate as well as the favorable effects of preventing recurrence and achieving sustained cure, whether fidaxomicin can be used as primary treatment for the initial episode of CDI, needs to be investigated.

2.2.5.2. PICO. P (patient): Patients with CDI.
I (intervention): Administration of fidaxomicin.
C (comparison): Administration of metronidazole or vancomycin.
O (outcome): CDI recurrence rate.

2.2.5.3. Summary of evidence. Fidaxomicin was evaluated in a Japanese phase III study and 2 overseas phase III studies (003 and 004). In the Japanese phase III study, the non-inferiority of fidaxomicin to vancomycin in relation to the sustained cure rate was not tested in the full analysis set, but fidaxomicin showed a lower recurrence rate and a higher sustained cure rate than vancomycin (Table 20) [306]. Two overseas phase III studies demonstrated the non-inferiority of fidaxomicin to vancomycin in relation to the cure rate, as well as a significantly lower recurrence rate and a higher sustained cure rate in fidaxomicin-treated patients compared with vancomycin-treated patients (Table 21) [159,210].

In particular, analysis of the combined data from these 2 overseas phase III studies showed that fidaxomicin significantly prevented CDI recurrence in patients with a previous history of CDI (a previous CDI episode within 3 months; Table 22) [207]. The cure rate in patients who received concomitant antimicrobials during treatment with the investigational agent was significantly higher in the fidaxomicin group than in the vancomycin group, and the recurrence rate was significantly lower in patients who received an antimicrobial sometime during the study period than in the vancomycin group (Table 23) [307]. Comparison of fidaxomicin, vancomycin, and metronidazole in a systematic review showed a significantly lower recurrence rate for fidaxomicin compared with the other agents (Table 24) [308].

2.2.5.4. Quality of evidence for overall outcome. A.

2.2.5.5. Summary of benefits. Two overseas phase III studies demonstrated the non-inferiority of fidaxomicin to vancomycin in relation to the cure rate and a significantly lower recurrence rate and higher sustained cure rate for fidaxomicin. Also, a Japanese phase III study showed a higher sustained cure rate and lower recurrence rate for fidaxomicin compared with vancomycin, although non-inferiority of fidaxomicin to vancomycin was not tested.

2.2.5.6. *Summary of harms (adverse reactions).* In 2 overseas phase III studies, the major fidaxomicin-associated adverse reactions were nausea, vomiting, and constipation and they occurred in ≥1% patients [309]. In a Japanese phase III study, the adverse reactions were vomiting, delusion, and ventricular fibrillation, and they occurred in 1% of patients and resulted in cessation of fidaxomicin [309].

2.2.5.7. Summary of harms (burden). Fidaxomicin is an expensive medicine overseas, and medical-economic studies are necessary in the future.

2.2.5.8. Benefits-harms balance. Benefits exceed harms in patients at high risk of recurrence.

2.2.5.9. Healthcare costs necessary for the intervention. None.

2.2.5.10. Feasibility of the intervention. Feasible.

2.2.5.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.5.12. Recommendations in related clinical practice guidelines. IDSA/SHEA guidelines recommended fidaxomicin, as well as vancomycin, for treating the initial CDI episode and the initial recurrent episode [65].

ESCMID guidelines (2014) recommend fidaxomicin for treating the initial CDI episode and the initial recurrent episode (or in patients at risk of recurrence), at the recommendation grade of B-1 [135].

2.2.6. CQ: is fidaxomicin effective in reducing nosocomial transmission during CDI outbreaks?

Recommendation: It is weakly recommended from the perspective of anti-nosocomial infection measures.

Level of recommendation: Weak recommendation for use.

Comments: It was reported that the number of spores in stool specimens collected from CDI patients at the end of treatment was markedly smaller in the fidaxomicin group than in the vancomycin group, and that fidaxomicin prevented *C. difficile* contamination of healthcare facilities.

2.2.6.1. Background and significance of this CQ. *C. difficile* forms spores, and many inpatients are asymptomatic carriers. Spores can survive for lengthy periods in healthcare facilities (e.g., patients' rooms). The main symptom of CDI is diarrhea, so once a patient develops CDI, contact precautions should be instituted to avoid the spread of infection. Fidaxomicin was shown to reduce the number of spores in stool specimens collected after CDI treatment as well as the number of bacteria in patients' room. Thus, the patient's condition and situation in the healthcare facility must be considered in fidaxomicin administration.

2.2.6.2. PICO. P (patient): Patients with CDI.
I (intervention): Administration of fidaxomicin.
C (comparison): Administration of metronidazole or vancomycin.
O (outcome): Decreased number of *C. difficile* spores in stool specimens of CDI patients, and decreased positive detection rate of *C. difficile* in patients' rooms.

2.2.6.3. Summary of evidence. A prospective single-center open-label randomized study found that more patients in the fidaxomicin group than in the vancomycin group achieved a reduction in *C. difficile* spores in stool specimens 2 weeks after completing CDI treatment compared with baseline (67% vs 14%, P = 0.02; Table 25) [310].

Also, the rate of *C. difficile* contamination was significantly lower in the rooms of 68 patients who received fidaxomicin from October 2012 to June 2014 than in the rooms of 66 patients who received metronidazole or vancomycin from April 2012 to September 2012 (36.8% vs 57.6%, P = 0.02; Table 26) [311].

2.2.6.4. Quality of evidence for overall outcome. C.

2.2.6.5. Summary of benefits. Fidaxomicin reduced the number of spores in stool specimens significantly more than vancomycin. Also, the *C. difficile* detection rate was lower in the rooms of fidaxomicin-treated patients than in those of metronidazole- or vancomycin-treated patients.

2.2.6.6. Summary of harms (adverse reactions). Fidaxomicin-associated adverse reactions were nausea, vomiting, and constipation and occurred in ≥1% of patients [309].

2.2.6.7. Summary of harms (burden). Fidaxomicin is an expensive medicine overseas, and medical-economic studies are necessary in the

Table 27
Pooled analysis of the preventive effect of FMT on CDI recurrence.

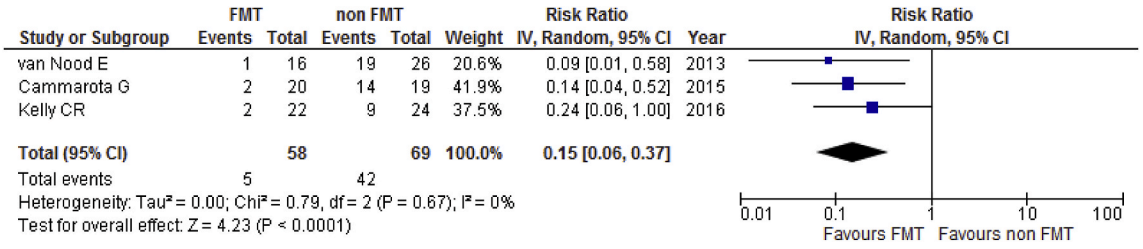
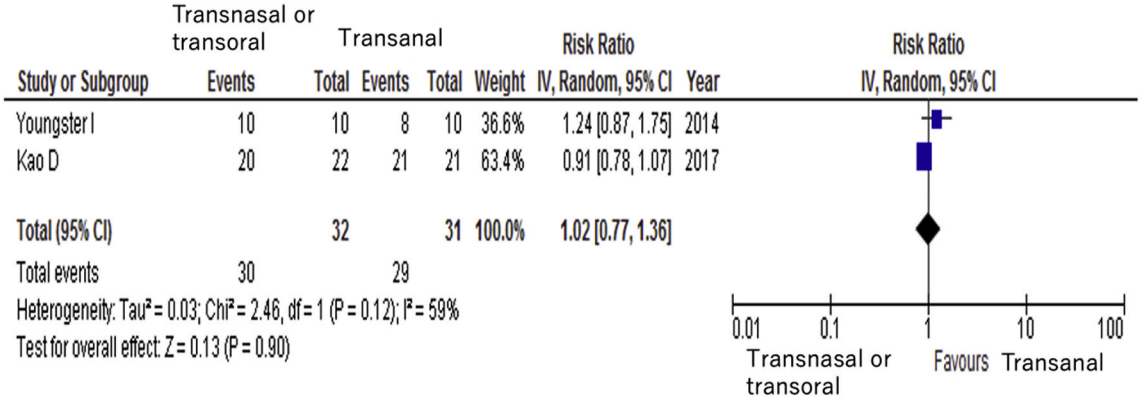


Table 28
Pooled analysis of preventive effect on recurrence depending on the FMT delivery route.



future.

2.2.6.8. Benefits-harms balance. Benefits exceed harms from the perspective of anti-nosocomial infection measures.

2.2.6.9. Healthcare costs necessary for the intervention. None.

2.2.6.10. Feasibility of the intervention. Feasible.

2.2.6.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.6.12. Recommendations in related clinical practice guidelines. None given as of March 2018.

2.2.7. CQ: are probiotics useful in preventing CDI in patients on antimicrobials?

Recommendation: Probiotics are recommended to prevent CDI in patients at risk of CDI.

Level of recommendation: Weak recommendation for use.

Comments: Routine use of probiotics for patients at high risk of CDI (e.g., those on antimicrobials) is not recommended, but it is recommended that administration of probiotics be considered for individual patients based on comprehensive assessment.

2.2.7.1. Background and significance of this CQ. Probiotics are defined as live microorganisms that confer benefit to the host. The gut microbiota is reduced in antibiotics-associated diarrhea (AAD) such as in CDI diarrhea due to use of antimicrobials, and probiotics were shown to be effective for such conditions by improving the gut microbiota (e.g., maintaining diversity). Whether probiotics can be used for the prevention of CDI needs to be investigated.

2.2.7.2. PICO. P (patient): Patients at risk of CDI.
I (intervention): Administration of probiotics.
C (comparison): No administration of probiotics.
O (outcome): Prevention of CDI onset.

2.2.7.3. Summary of evidence. There is clinical evidence associated with this CQ. A Cochrane review of 31 RCTs showed a lower incidence rate of CDI in the probiotics-treated group than in the placebo group (1.5% vs 4.0%; RR 0.40; 95% CI 0.30–0.52) [312]. Also, in 13 of the RCTs that showed a CDI incidence rate of >5% in the control group, the decrease in the CDI incidence rate by probiotics was even greater (3.1% in the probiotics group vs. 11.6% in the control group; RR, 0.30; 95% CI, 0.21–0.42).

However, it should be noted that these studies do not use a single definition of CDI and the probiotics used vary in terms of species (e.g., *Saccharomyces boulardii*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Clostridium butyricum*, and *Bifidobacterium bifidum*), strains, and microorganism amounts. Thus, there is insufficient evidence to make an unconditional recommendation.

S. boulardii has been tested for its effect in many CDI-related studies. It was shown to cause, albeit infrequently, fungemia such as intravascular catheter-associated infection [313]. So, caution should be exercised when administering probiotics to patients with severe CDI or with immunocompromised status.

Probiotics have also been examined in non-CDI studies, such as probiotics studies in relation to AAD and improvement of the gut microbiota. *C. butyricum* was shown to inhibit spore germination and growth of *C. difficile* [314]. Also, a study of *Helicobacter pylori* eradication therapy showed that the group administered *C. butyricum* maintained a better level of anaerobes and had less frequent abdominal symptoms including diarrhea compared with the control group [315].

2.2.7.4. Quality of evidence for overall outcome. B.

2.2.7.5. Summary of benefits. Administration of probiotics can reduce CDI incidence.

2.2.7.6. Summary of harms (adverse reactions). The level of safety of probiotics is generally high. It should be noted that bacteremia/fungemia, although rare, may occur in immunocompromised patients. A study examining 6 types of probiotic organisms (e.g., *L. acidophilus*) showed that probiotic prophylaxis significantly increased the incidence of bowel ischemia and mortality in patients with acute pancreatitis [316].

2.2.7.7. Summary of harms (burden). Probiotics are inexpensive, and the burden on patients is small.

2.2.7.8. Benefits-harms balance. Benefits exceed harms in patients at risk of CDI onset.

2.2.7.9. Healthcare costs necessary for the intervention. Formulation generates additional costs, but probiotics are still inexpensive even after formulation.

2.2.7.10. Feasibility of the intervention. Feasible.

2.2.7.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.7.12. Recommendations in related clinical practice guidelines. Japanese guidelines state that probiotics help restore the gut microbiota in CDI patients [317]. Overseas guidelines do not necessarily recommend probiotic prophylaxis due to insufficient evidence.

2.2.8. CQ: are probiotics useful in combination with other anti-C. difficile agents?

Recommendation: There is insufficient evidence that probiotics are effective in the treatment of CDI.

Level of recommendation: Weak recommendation against use.

Comments: It is not recommended to use probiotics alone in the treatment of CDI. This does not rule out the use of probiotics in combination with standard anti-*C. difficile* agents.

2.2.8.1. Background and significance of this CQ. Probiotics are defined as live microorganisms that confer benefit to the host. The gut microbiota is reduced in antibiotics-associated diarrhea (AAD) and CDI due to the use of antimicrobials, and probiotics have been shown to be effective in the treatment of such conditions by improving the gut microbiota (e.g., maintaining diversity). Probiotics are sometimes administered on CDI onset in clinical practice, and whether probiotics are effective therapy for patients with CDI needs to be investigated.

2.2.8.2. PICO. P (patient): Patients with CDI.

I (intervention): Administration of probiotics.

C (comparison): No administration of probiotics.

O (outcome): Relief of CDI symptoms.

2.2.8.3. Summary of evidence. With respect to the clinical evidence associated with this CQ, an RCT showed that *S. boulardii* in combination with vancomycin or metronidazole was effective in the treatment of CDI in patients with relapse (RR 0.43; 95% CI, 0.20–0.97), but currently there are few studies indicating the effectiveness of probiotics in the treatment of initial CDI [318].

With respect to studies related to AAD, including CDI, a meta-analysis of 31 studies showed that probiotic administration was associated with a smaller number of patients who developed severe diarrhea (RR, 0.52; 95% CI, 0.36–0.75) [319]. A smaller RCT, showed that treatment of CDI with probiotics significantly reduced CDI [320].

A meta-analysis of 19 studies showed the RR for CDI was 0.32 (95% CI, 0.22–0.48) when probiotics were administered within 1–2 days of the first antimicrobial dose but was 0.70 (95%, CI 0.40–1.23) when probiotics were administered within 3–7 days [321]. Therefore, probiotics should be initiated as early as possible.

As described in the section of the previous QC "Are probiotics useful in preventing CDI in patients on antimicrobials?", it should be noted that studies have varied in the definition of CDI used as well as in the species, strains, and amounts of microorganisms in the probiotics used.

2.2.8.4. Quality of evidence for overall outcome. C.

2.2.8.5. Summary of benefits. Probiotics are expected to relieve CDI symptoms, but there is insufficient evidence available.

2.2.8.6. Summary of harms (adverse reactions). The level of safety of probiotics is generally high. It should be noted that bacteremia/fungemia, although rare, may occur in immunocompromised patients. A study examining 6 types of probiotic organisms (e.g., *L. acidophilus*) showed that probiotic prophylaxis significantly increased the incidence of bowel ischemia and mortality in patients with acute pancreatitis [316].

2.2.8.7. Summary of harms (burden). Probiotics are inexpensive, and the burden on patients is small.

2.2.8.8. Benefits-harms balance. Benefits exceed harms in patients with CDI.

2.2.8.9. Healthcare costs necessary for the intervention. Formulation generates additional costs, but probiotics are still inexpensive even after formulation.

2.2.8.10. Feasibility of the intervention. Feasible.

2.2.8.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.8.12. Recommendations in related clinical practice guidelines. Japanese guidelines state that probiotics help restore the gut microbiota in CDI patients [317]. Overseas guidelines do not necessarily recommend probiotic prophylaxis due to insufficient evidence.

2.2.9. CQ: Do probiotics prevent recurrence after treatment of CDI?

Recommendation: There is insufficient evidence to recommend probiotics for the prevention of recurrent CDI.

Level of recommendation: Weak recommendation against use.

Comments: Use of probiotics to prevent recurrent CDI is not recommended. However, because options for prevention are limited, administration of probiotics can be considered.

2.2.9.1. Background and significance of this CQ. Approximately 20% of CDI patients have recurrence that reduces their QOL and increases healthcare costs. Although fecal microbiota transplantation and anti-toxin B monoclonal antibodies are effective for preventing recurrent CDI, it is difficult to use these therapies for a broad range of patients, such as those with mild CDI. Thus, whether probiotics can be used for the prevention of recurrent CDI needs to be investigated.

2.2.9.2. PICO. P (patient): Patients at a risk of CDI.

I (intervention): Administration of probiotics.

C (comparison): No administration of probiotics.

O (outcome): Prevention of relapse of CDI.

2.2.9.3. Summary of evidence. In terms of the clinical evidence associated with this CQ, one study reported a CDI relapse rate of 17% in patients who received *Saccharomyces boulardii* in addition to vancomycin and a CDI relapse rate of 50% in those who received placebo in addition to vancomycin (P = 0.05) [322]. Another study showed a CDI relapse rate of 36.3% in the group that received *Lactobacillus plantarum* 299v, compared with 67% in the placebo group (P = 0.37) [323]. A meta-analysis of 6 studies of probiotics showed lower CDI recurrence rates in 2 studies that examined *S. boulardii* but not in the remaining 4 studies [324].

2.2.9.4. Quality of evidence for overall outcome. B.

2.2.9.5. Summary of benefits. Some probiotics are associated with a lower rate of CDI relapse.

2.2.9.6. Summary of harms (adverse reactions). The level of safety of probiotics is generally high. It should be noted that bacteremia/fungemia, although rare, may occur in immunocompromised patients. A study examining 6 types of probiotic organisms (e.g., *L. acidophilus*) showed that probiotic prophylaxis significantly increased the incidence of bowel ischemia and mortality in patients with acute pancreatitis [316].

2.2.9.7. Summary of harms (burden). Probiotics are inexpensive, and the burden on patients is small.

2.2.9.8. Benefits-harms balance. Benefits exceed harms in patients with recurrent CDI.

2.2.9.9. Healthcare costs necessary for the intervention. Formulation generates additional costs, but probiotics are still inexpensive even after formulation.

2.2.9.10. Feasibility of the intervention. Feasible.

2.2.9.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.9.12. Recommendations in related clinical practice guidelines. Japanese guidelines state that probiotics help restore the gut microbiota in CDI patients [317]. Overseas guidelines do not necessarily recommend probiotic prophylaxis due to inadequate evidence. The WSES guidelines recommend considering probiotics as adjuvant therapy for recurrent CDI in immunocompromised patients (2B, Weak recommendation, moderate-quality evidence) [169].

2.2.10. CQ: is fecal microbiota transplantation (FMT) recommended to reduce recurrence?

Recommendation: FMT has a considerable preventive effect on recurrent CDI. The effect was not different between FMT delivery via the upper gastrointestinal route and that via the lower gastrointestinal route. However, all RCTs conducted to date have been small. Also, while serious adverse events were reported in several studies, the frequency of these events is not clear. Furthermore, long-term safety should be examined. At present, this therapy cannot be recommended solely based on its efficacy.

Level of recommendation: Weak recommendation against use.

2.2.10.1. Background and significance of this CQ. Recurrence of CDI negatively affects prognosis, prolongs hospital stay, and increases the healthcare costs, and it is therefore is an important issue to address in Japan as well as in other countries [104]. FMT is used as an anti-recurrence measure overseas and is recommended in the UK guidelines. Expectation for FMT is high in counties where deaths due to severe CDI have been reported, but FMT is rarely performed in Japan. It is necessary to assess the significance of this therapy in Japan.

2.2.10.2. PICO. P (patient): Patients with recurrent CDI.
I (intervention): FMT.
C (comparison): No FMT.
O (outcome): Prevention of recurrent CDI.

2.2.10.3. Summary of evidence. Seven RCTs examining FMT, published in 2013 or later, were identified, 3 of which compared FMT with non FMT [325–327]. One of these 327 studies had a double-blind design and compared FMT with donor stool and FMT with the patient's own stool: this study's level of evidence is regarded as high. Also, differences in the effectiveness between delivery routes have been reported [328,329], as have differences between FMT using fresh stools and frozen stools [330].

Pooled analysis of 3 RCTs showed that FMT was significantly more effective in preventing recurrent CDI (P < 0.0001, Table 27). Pooled analysis of 2 RCTs showed no difference in the preventive effect on recurrence between the different delivery routes (Table 28).

With respect to safety, serious adverse events attributed to FMT were not reported in any of the RCTs. Adverse events that have been reported previously are listed under 6. below.

2.2.10.4. Quality of evidence for overall outcome. The level of evidence for efficacy is high, but that for safety cannot be assessed due to a small number of cases.

2.2.10.5. Summary of benefits. FMT has a preventive effect on recurrence in patients with a history of recurrent CDI. Also, it is reported to be effective in children [331], immunocompromised patients [332], and patients with complications [333].

2.2.10.6. Summary of harms (adverse reactions). The following are previously reported serious adverse events associated with FMT.

- Death from septic shock [334].
- Death from suffocation due to aspiration [332].
- Death from aspiration pneumonitis [333,335,336].
- Lower gastrointestinal perforation [337].
- Norovirus infection [338].

Non-serious adverse events were also reported.

- Vomiting, diarrhea, and abdominal discomfort [325,336,339–342].

2.2.10.7. Summary of harms (burden). Nothing particular.

2.2.10.8. Benefits-harms balance. It is difficult to assess safety of FMT due to a small number of cases in RCTs. Several serious adverse events were reported but frequency is unknown. This makes discussion of the balance between the preventive effect on recurrence and safety difficult. Also, concern was raised that long-term observation has not yet been reported [343].

2.2.10.9. Healthcare costs necessary for the intervention. FMT is reportedly less costly than pharmacotherapies [344,345].

2.2.10.10. Feasibility of the intervention. Not feasible, given that securing stool donors, safety assessment, and establishing a delivery protocol have not yet been achieved.

2.2.10.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. Medical professionals are aware of the effect of FMT, while patients and their families are likely to have a great deal of psychological resistance and anxiety

toward FMT.

2.2.10.12. Recommendations in related clinical practice guidelines. NICE guidance (https://www.nice.org.uk/guidance/ipg485) states that FMT should be considered only when antimicrobials and other therapies are not effective in patients with recurrent CDI. Also, the 2017 IDSA/SHEA guidelines strongly recommend FMT when adequate antimicrobials are not effective in patients with multiple recurrent CDI episodes.

2.2.11. CQ: Should antimicrobial stewardship be promoted to reduce CDI?

Recommendation: Implementation of antimicrobial stewardship (AS) interventions in a broad sense is reportedly effective in reducing CDI at healthcare facilities.

Level of recommendation: Strong recommendation for use.

Comments: AS is recommended for patients at risk of CDI, including those on antimicrobials.

2.2.11.1. Background and significance of this CQ. AS aims to improve prognosis and to minimize antimicrobial-associated adverse events in patients, including those with CDI, through the provision of appropriate antimicrobial therapies and supportive interventions by infection disease specialists across multiple professions [346]. In Japan, more active implementation of AS is expected [347]. The efficacy of AS interventions in the context of anti-CDI measures needs to be investigated.

2.2.11.2. PICO. P (patient): Patients at a risk of CDI.

I (intervention): Implementation of AS interventions.

C (comparison): No implementation of AS interventions.

O (outcome): Decreases in CDI.

2.2.11.3. Summary of evidence. In terms of the clinical evidence associated with this CQ, a meta-analysis of 11 studies showed that implementation of AS reduced the incidence of CDI by 32%; IR, 0.78; 95% CI, 0.53–0.88; P = 0.0029) [348]. AS interventions against CDI include reduction in the use of broad-spectrum of antimicrobials [349], and AS interventions in a broad sense include cessation of acid suppressing agents, provision of consultations about infectious diseases, and early initiation of appropriate vancomycin [350]. It was reported that AS interventions reduced the CDI incidence at a chronic-phase medical facility from 3.6/10,000 patient days to 1.2/10,000 patient days (P = 0.001) [351].

Implementation of AS interventions, including those for CDI patients, is essential. Accumulation of evidence, including that for individual interventions, is awaited.

2.2.11.4. Quality of evidence for overall outcome. A.

2.2.11.5. Summary of benefits. Implementation of AS activities reduces CDI.

2.2.11.6. Summary of harms (adverse reactions). Adverse events due to discontinuation of antimicrobials, anti-cancer agents, and acid suppressing agents may occur.

2.2.11.7. Summary of harms (burden). There are no harms (burden) for patients from implementing AS interventions.

2.2.11.8. Benefits-harms balance. Benefits exceeds harms in patients at risk of CDI.

2.2.11.9. Healthcare costs necessary for the intervention. It is necessary to develop and secure personnel specializing in infectious diseases.

2.2.11.10. Feasibility of the intervention. Feasible.

2.2.11.11. Is the intervention perceived differently by patients, family members, allied health professionals, and doctors?. No.

2.2.11.12. Recommendations in related clinical practice guidelines. Implementation of AS interventions for CDI is strongly recommended by IDSA (recommendation level, A-II), ACG (strong recommendation, high-quality evidence), ESCMID (recommendation level, IB), and WSES (recommendation level, IB).

2.3. Drug information

2.3.1. Metronidazole oral tablets

2.3.1.1. Indications.

1. Trichomoniasis (infectious disease caused by *Trichomonas vaginalis*)

2. Anaerobic infections

   Type of Organism:

   Microorganisms susceptible to metronidazole (i.e., *Peptostreptococcus*, *Bacteroides, Prevotella*, *Porphyromonas*, *Fusobacterium*, *Clostridium*, and *Eubacterium*).

   Indications:

- Deep seated skin infection
- Infection secondary to external wound, burn, and surgical wound
- Osteomyelitis
- Pneumonia, lung abscess
- Pelvic inflammatory disease
- Peritonitis, intraabdominal abscess
- Liver abscess
- Brain abscess

3. Infectious enteritis

   Type of Organismmicroorganisms:

   Clostridium difficile that is susceptible to metronidazole.

   Indications:

   Infectious enteritis (including pseudomembranous colitis).

4. Bacterial vaginosis

   Type of Organism:

   Microorganisms that are susceptible to metronidazole (i.e., *Peptostreptococcus*, *Bacteroides fragilis, Prevotella bivia*, *Mobiluncus*, *Gardnerella vaginalis*).

   Indications:

   Bacterial vaginosis.

5. *Helicobacter pylori* infection

   Type of Organism:

   H. pylori that is susceptible to metronidazole.

   Indications:

   Stomach ulcer, duodenal ulcer, gastric MALT lymphoma, idiopathic thrombocytopenic purpura, *H. pylori* infection in the endoscopy-treated stomach for early stomach cancer, and *H. pylori* gastritis.

6. Amebic dysentery
7. Giardiasis

2.3.1.2. Dosage and administration.

1. Trichomoniasis (infectious disease caused by *T. vaginalis*)

For adults, in general, administer a single 250-mg dose of oral metronidazole (as active ingredient) twice daily for 10 days in 1 cycle.

2. Anaerobic infections

For adults, in general, administer a single 500-mg dose of oral metronidazole (as active ingredient) 3 or 4 times daily.

3. Infectious enteritis

For adults, in general, administer a single 250-mg dose of oral metronidazole (as active ingredient) 4 times daily, or a single 500-mg dose of oral metronidazole (as active ingredient) 3 times daily, for 10–14 days.

4. Bacterial vaginosis

For adults, in general, administer a single 250-mg dose of oral metronidazole (as active ingredient) 3 times daily, or a single 500-mg dose of oral metronidazole (as active ingredient) twice daily, for 7 days.

5. *H. pylori* infection

When *H. pylori* eradiation therapy using a combination of amoxicillin hydrate, clarithromycin, and a proton pump inhibitor is not successful, for adults, in general, simultaneously administer a single 250-mg dose of oral metronidazole (as active ingredient), a single 750-mg dose of oral amoxicillin hydrate (as titer), and a proton pump inhibitor (oral) twice daily for 7 days.

6. Amebic dysentery

For adults, in general, administer a single 500-mg dose of oral metronidazole (as active ingredient) 3 times daily for 10 days.

Depending on the symptoms, administer a single 750-mg dose 3 times daily.

7. Giardiasis

For adults, in general, administer a single 250-mg dose of oral metronidazole (as active ingredient) 3 times daily for 5–7 days.

2.3.1.3. Adverse reactions. Gastrointestinal disorder, hepatobiliary disorder, peripheral neuropathy, central neuropathy, abacterial meningitis, toxic epidermal necrolysis, muco-cutaneo-ocular syndrome, acute pancreatitis, leukopenia, neutropenia, hemorrhagic colitis, etc.

2.3.1.4. Important precautions. Adverse reactions such as peripheral neuropathy and central neuropathy may occur, so patients should be monitored carefully, especially when this agent is administered for >10 days or at high dose (1,500 mg/day).

2.3.2. Metronidazole intravenous infusion

2.3.2.1. Indications.

1. Anaerobic infections

Type of Organism:
Microorganisms that are susceptible to metronidazole (i.e., *Peptostreptococcus*, *Bacteroides, Prevotella*, *Porphyromonas*, *Fusobacterium*, *Clostridium*, and *Eubacterium*).
Indications:

- Sepsis
- Deep seated skin infection
- Infection secondary to external wound, burn, and surgical wound
- Osteomyelitis
- Pneumonia, lung abscess, thoracic empyema
- Pelvic inflammatory disease
- Peritonitis, intraabdominal abscess
- Cholecystitis, liver abscess
- Purulent meningitis
- Brain abscess

2. Infectious enteritis

Type of Organism:
C. difficile that is susceptible to metronidazole.
Indications:
Infectious enteritis (including pseudomembranous colitis).

3. Amebic dysentery

2.3.2.2. Dosage and administration. For adults, in general, administer a single 500-mg dose of metronidazole (as active ingredient) over ≥20 min 3 times daily. For intractable or severe infections, a single 500-mg dose can be administered 4 times daily depending on symptoms.

2.3.2.3. Adverse reactions. Gastrointestinal disorder, hepatobiliary disorder, peripheral neuropathy, central neuropathy, abacterial meningitis, toxic epidermal necrolysis, muco-cutaneo-ocular syndrome, acute pancreatitis, leukopenia, neutropenia, etc.

2.3.2.4. Important precautions. Adverse reactions such as peripheral neuropathy and central neuropathy may occur, so patients should be monitored carefully, especially when this agent is administered for >10 days.

2.3.3. Vancomycin powder

2.3.3.1. Indications.

1. Infectious enteritis

Type of Organism:
Methicillin resistant *Staphylococcus aureus* and *C. difficile* that are susceptible to vancomycin.

2.3.3.2. Indications.

- Infectious enteritis (including pseudomembranous colitis)

2. Gastrointestinal decontamination at the time of bone marrow transplantation

2.3.3.3. Dosage and administration.

1. Infectious enteritis (including pseudomembranous colitis)

For adults, in general, dissolve as needed and orally administer a single 0.125-g to 0.5-g dose of vancomycin (titer) 4 times daily.

Increase or decrease dose depending on age, bodyweight, and symptoms.

2. Gastrointestinal decontamination at the time of bone marrow transplantation

For adults, in general, dissolve as needed and orally administer a single 0.5-g dose of vancomycin (titer) in combination with nonabsorbable antibacterial agents and antifungal agents 4–6 times daily.

Increase or decrease dose depending on age, bodyweight, and symptoms.

2.3.3.4. Adverse reactions. Gastrointestinal disorder, shock, etc.

2.3.3.5. Important precautions. Patients with kidney disorder, such as those on dialysis, and those with severe intestinal lesions (e.g., pseudomembranous colitis) should be monitored carefully because orally administered vancomycin may accumulate and cause adverse reactions, similar to those reported for vancomycin hydrochloride (intravenous injection).

2.3.4. Fidaxomicin oral tablets

2.3.4.1. Indications.

1. Infectious enteritis (including pseudomembranous colitis)

Type of Organism:
C. difficile that is susceptible to fidaxomicin.

2.3.4.2. Dosage and administration. For adults, in general, administer a single 200-mg dose of oral fidaxomicin (as active ingredient) twice daily.

2.3.4.3. Adverse reactions. Anaphylaxis, constipation, nausea, vomiting, etc.

2.3.4.4. Important precautions. The duration of administration is 10 days in principle, and administration for a longer duration should carefully determined after assessing benefits and risks.

2.3.5. Bezlotoxumab intravenous infusion

2.3.5.1. Indications. Prevention of recurrence of *C. difficile* infection.

2.3.5.2. Dosage and administration. For adults, in general, infuse 10 mg/kg bezlotoxumab (recombinant) over 60 min.

2.3.5.3. Adverse reactions. Nausea, headache, fatigue, increases in AST and ALT, etc.

2.3.5.4. Important precautions. This agent should be used for patients with *C. difficile* infection who are at a high risk of aggravation or recurrence. Reasons for using this agent should be chosen from the following options (A-E) and should be recorded in the remarks column on the receipt. If option E is chosen, reasons should be recorded for why the case was judged to be at high risk of aggravation or recurrence. Age ≥65 years or previous history of ≤2 episodes are not considered a sole reason for high-risk status.

A. Immunocompromised state
B. Severe *C. difficile* infection
C. Infection with virulent strains (ribotype 027, 078, or 244)
D. Previous history of ≥3 CDI episodes
E. Other reasons why the case was judged to be at high risk of aggravation or recurrence

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