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Guideline

Japanese Society for infection prevention and control guide to *Clostridioides difficile* infection prevention and control☆

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1. Principles for preparation

Clostridioides difficile is an anaerobic bacterium that is most commonly responsible for healthcare-associated infections. This bacterium is known to spread within an institution in the form of spores. This guide was prepared to improve infection control measures against *C. difficile*.

This guide was prepared based on the current body of evidence and includes general theory and clinical questions. Given that domestic and international evidence related to *C. difficile*, such as hand hygiene and other cross-infection control measures, is insufficient, the recommendations in this guide were written based on expert opinions while respecting the current state of *C. difficile* infection (CDI) control in Japan. We hope this guide serves as a starting point for the further development of *C. difficile* research in Japan, and revisions, including the dissemination of evidence from Japan, are made to the CDI control guide as needed (Fig. 1)

2. Precautions for use

This guide is intended to be used only as reference material that describes guidelines for CDI prevention and control. In addition to the fact that evidence related to CDI in Japan remains insufficient, the selection of medical treatment and care procedures for each patient should be made in cooperation between the medical staff and patient, considering each medical institution's situation. This guide does not impose clinical research or medical procedures or limit the discretion of medical

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Abbreviations

AS	antimicrobial stewardship
CDI	*Clostridioides difficile* infection
NAAT	nucleic acid amplification test
PS	performance status
ICT	Infection Control Team
AST	Antimicrobial Stewardship Team
PPE	personal protective equipment
PFGE	pulsed-field gel electrophoresis
slpA	surface-layer protein A
GDH	glutamate dehydrogenase
CCMA	cycloserine-cefoxitin mannitol agar
CCFA	cycloserine-cefoxitin fructose agar

professionals.

3. Funding

All expenditure in the development of this guideline was provided by the Japanese Society for Infection Prevention and Control.

4. Prepared by

Japanese Society for Infection Prevention and Control.

5. Drafting committee for the guidelines for *Clostridioides difficile* Infection prevention and control

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(Japanese syllabary order).

6. ● Progress of committee activities

The Board of Directors of the Japanese Society for Infection

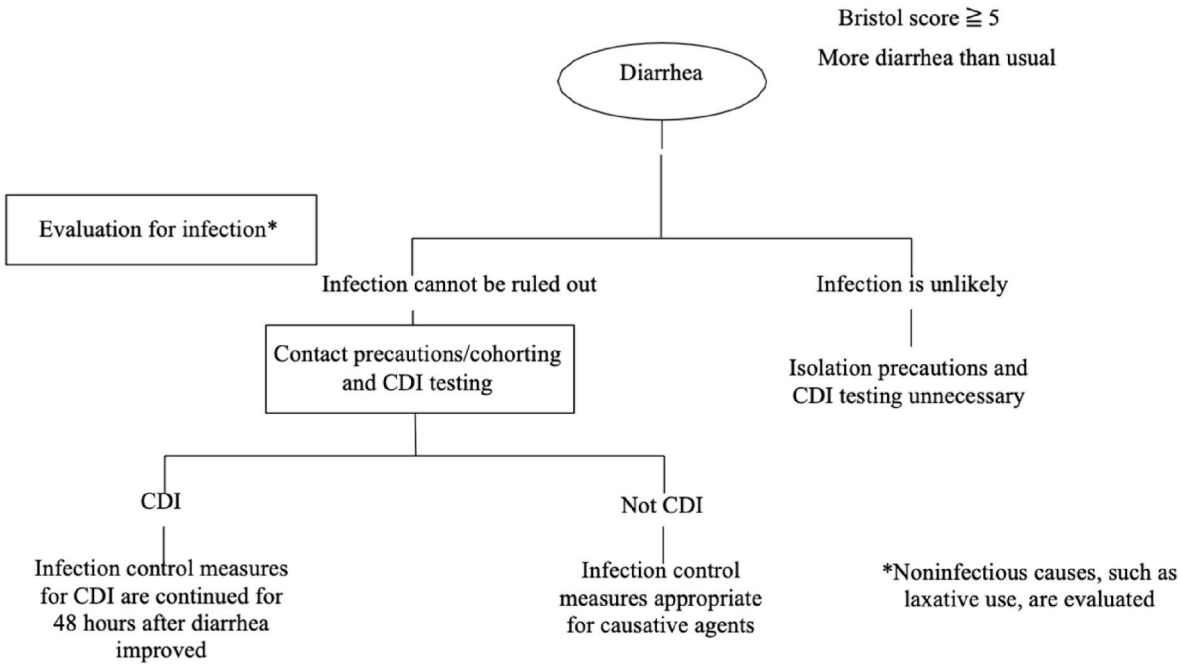

Fig. 1. Infection control flow chart for infectious diarrhea suspected of *Clostridium difficile* infection (CDI)
CDI, *C. difficile* infection.
When diarrhea with a Bristol score of ≥5 (defecation frequency of three or more times within 24 h or more than usual) is noted, check possible causes, including iatrogenic causes such as laxative use, to determine if diarrhea is infectious. When infection cannot be ruled out, active infection control measures, as well as CDI testing, are recommended. Once CDI is diagnosed, infection control measures for CDI should be continued for 48 h after the diarrhea improves.

Prevention and Control decided to prepare guidelines for *Clostridioides difficile* infection prevention and control, and Minako Mori and Hiroyuki Kunishima were appointed as the director and chairperson of the drafting committee, respectively.

7. ● Preparation process

Title: Japanese Society for Infection Prevention and Control Guide to *Clostridioides difficile* Infection Prevention and Control.

8. Evidence search

(1) Evidence types

Existing clinical practice guidelines, systematic review (SR) and meta-analysis (MA) articles, and individual research articles were searched in this order of priority. For individual research articles, those reporting randomized controlled studies, non-randomized controlled studies, and observational studies were searched.

(2) Databases
- o Medline and Ichushi for individual research articles
- o Medline, Ichushi, and the Cochrane Library for SR/MA articles
- o International Guideline Library of the Guideline International Network and National Guideline Clearinghouse of the AHRQ in the United States for existing clinical practice guidelines

(3) Basic search policy

The PICO format was used to search for interventions.

(4) Search period

Up to the end of March 2022.

Basic policy for making recommendations: Recommendations were made based on the deliberations of the guideline drafting committee.

Recommendations and their strength levels were decided based on considerations of "diversity in patients' values" and "economic perspective" as well as "evidence strength" and "risk–benefit balance," as required in the evaluation and integration of evidence.

Finalization: The draft guidelines were presented at an annual meeting and academic meetings of the Japanese Society for Infection Prevention and Control to solicit comments from participants; public comments were also solicited. Comments from the participants of the annual meeting and academic meetings of the Japanese Society for Infection Prevention and Control as well as public comments were discussed by the guideline drafting committee to decide whether revisions to the clinical practice guidelines were necessary.

9. Bacteriology and pathology

9.1. Basic bacteriological properties of Clostridioides difficile

9.1.1. Bacteriological classification

C. difficile is an obligately anaerobic, spore-forming, gram-positive bacillus measuring 0.5–1.9 × 3.0–16.9 μm [1]. In a favorable habitat, *C. difficile* proliferates as vegetative cells, while in a harsh environment, it transforms into spores while maintaining minimal vital activities.

Taxonomically, *C. difficile* belongs to the phylum Firmicutes, the class Clostridia, the order Eubacteriales, and the family Peptostreptococcaceae. This species was called *Clostridium difficile* until recently, and the current name was given based on genetic analysis data [1]. This bacterium can colonize the human intestinal tract; toxin-producing strains (bacteriotoxins) can cause diarrhea as a symptom of *C. difficile* infection (CDI).

9.1.2. Life cycle

C. difficile has a characteristic life cycle and can switch between a proliferation-competent active state and a dormant state. It can live in the intestines of humans and animals and is active in the form of proliferation-competent vegetative cells in anaerobic habitats suitable for vital bacterial activities, such as the host's intestinal tract. When *C. difficile* cells are eliminated from the host's body, they detect environmental factors unfavorable for vegetative cells, such as oxygen and dryness, and transform into spores, which are dormant cells.

C. difficile in the spore form can survive for a long period of time because spores are resistant to unfavorable conditions such as oxygen, heat, radiation, dryness, high pressure, and drugs. When the environment around the spores becomes suitable for bacterial growth, *C. difficile* spores transform into vegetative cells and start proliferating again. This phenomenon of switching from the spore state to the vegetative cell state is referred to as germination. Spore germination requires bile acids and glycine; when spores detect these substances, the membrane changes its structure and allows water to flow into spores before they become vegetative cells and vigorously initiate vital activities [2].

Autoclaving (for at least 15 min at 121 °C), dry heat sterilization (for at least 30 min at 180 °C or for at least 1 h at 160 °C), and gamma irradiation sterilization effectively inactivating spores. As disinfectants, ethanol and benzalkonium chloride are ineffective, whereas sodium hypochlorite, glutaraldehyde, and peracetic acid are effective [3,4]. Ultraviolet irradiation devices and hydrogen peroxide vapor generators are also used as environmental-friendly disinfection techniques developed for healthcare environments [5,6].

9.1.3. Bacterial culture conditions

Special media and anaerobic culture conditions are required to culture *C. difficile* because this bacterium does not grow in commonly used media. When fecal samples are used for culturing, the growth of other bacteria should be inhibited. In microorganism tests, media supplemented with cycloserine and cefoxitin as antibiotics are used to inhibit the growth of other bacteria; commonly used media include cycloserine-cefoxitin fructose agar (CCFA medium) and cycloserine-cefoxitin mannitol agar (CCMA medium) [7]. It takes 2–3 days of incubation under anaerobic conditions before colonies can be observed on the culture medium.

9.1.4. C. difficile virulence factors

9.1.4.1. Toxins A and B. Some *C. difficile* strains produce toxins, whereas others do not (Table 1). Toxins A and B are of particular importance as both are enterotoxic and involved in the onset of diarrhea, which is the leading symptom of CDI. Both toxins are included among the test items for CDI in clinical practice; antigen testing using immunochromatography detects toxins A and B, while genetic testing detects the toxin B gene. Among *C. difficile* strains, some produce both toxins (toxin A^+B^+ strains), some produce only toxin B (toxin A^-B^+ strains), and some produce neither (toxin A^-B^- strains). Strains producing neither of the two toxins do not cause CDI. Strains producing toxin A only have been found [8], but they are not clinically problematic.

Traditionally, toxin A was referred to as enterotoxins, characterized by diarrhea induction, and toxin B as cytotoxins, characterized by cytotoxicity. Currently, the two toxins are known to have similar structures and impair cell functions that disrupt cell structures via their

Table 1
Relationship between toxigenicity and clinical presentations.

	Toxin combination	Virulent	Intestinal colonization
Toxigenic strain	Toxin A^-B^+	Yes	Yes
	Toxin A^+B^+	Yes	Yes
Nontoxigenic strain	Toxin A^-B^-	No	Yes

Toxin A^+B^- strain is not found in daily clinical practice.

enzymatic glucosyltransferase activity in intestinal epithelial cells [9,10].

Glutamate dehydrogenase (GDH), which is tested along with toxins in immunochromatography, is not a virulence factor; however, all *C. difficile* strains have this enzyme [11].

9.1.4.2. Regulatory mechanism for toxin production. *C. difficile* has a mechanism to regulate the production levels of toxins A and B. When *C. difficile* has grown sufficiently, the expression of the tcdC gene encoding the regulatory mechanism is enhanced and toxin production is suppressed [12]. However, some strains have mutations in the tcdC gene (tcdC gene aberrant strains), and these strains produce both toxins excessively as they cannot control toxin production [13,14]. Strains responsible for outbreaks in Europe and the United States commonly have such gene mutations [15].

9.1.4.3. Binary toxin. Strains producing a third toxin known as binary toxin (*C. difficile* transferase) are also well known. This toxin alters the intestinal epithelium structurally to facilitate the cellular adhesion of bacteria [16,17]. While it is unclear how this toxin modifies CDI pathology, cases of CDI caused by strains producing this toxin, which have been recorded mainly overseas, are prone to aggravation and are characterized by high mortality rates [15]. In Japan, CDI caused by the binary toxin-producing strains has been reported to be aggravated and severe in some cases [18] but was treated as usual CDI in other cases [19]; thus, its relationship with severity remains unclear. Moreover, among isolates in Japan, no relationships were observed between the production of this toxin and the production of toxins A and B [20].

9.1.4.4. Examples of toxin production in virulent strains. In North America and Europe, many clones have been derived from community-acquired cases that have shown high mortality rates, and these clones have spread rapidly in the 2000s [21,22]. The ribotype of such clones is 027 (027/BI/NAP1 strain). This strain exhibits mutations in the tcdC gene, which is crucial for regulating toxin production. As a result, it is characterized by increased production of toxins A and B as well as binary toxin [23]. Additionally, a high propensity for spore formation and fluoroquinolone resistance is speculated to play a role in the spread of these strains [23]. Ribotype 078 has similar characteristics [24] and has caused similar outbreaks, mainly in Europe [25].

In Japan, such strains are rarely found [26], but there is a report describing isolation from patients with CDI who traveled frequently [27].

9.1.4.5. Methods for strain identification. In some cases, *C. difficile* strain typing is performed for epidemiological investigations and outbreak background inspections. Various methods of analyzing the *C. difficile* genome structure are used for typing to evaluate the gene diversity and evolution level (Table 2).

As analytical techniques based on bacterial whole-genome DNA, pulsed-field gel electrophoresis (PFGE method) and restriction endonuclease analysis (REA method) are used. In both methods, DNA fragmentation products are analyzed by electrophoresis and bacterial strains are identified based on the pattern of detected bands. On the contrary, PCR ribotyping and the surface-layer protein A (slpA) method focus on regions in which *C. difficile* strain differences are likely to be detected. In these methods, regions specific to the respective methods are amplified or restriction enzyme treated for typing. Toxinotyping is a technique used to determine toxinotypes by analyzing toxin gene regions.

Because typing requires special techniques and instruments, it is necessary in most cases to find facilities with analysis experience and equipment and perform analysis on a collaborative or contract basis. The recently developed PCR-based open reading frame typing (POT) method can be used wherever PCR and electrophoresis are available. However, the method is mainly used in Japan; thus, the results are difficult to compare with overseas reports. Further accumulation of data is awaited.

Each typing method uses a different site for analysis; nevertheless, some show a certain level of correlation (Table 3). Moreover, typing results are reflected in some strain names; for example, in the 027/BI/NAP1 strain, 027, BI, and NAP1 denote the ribotype, the REA group, and classification by pulsed-field gel electrophoresis, respectively.

Table 2
Major *C. difficile* typing methods.

Typing	Region analyzed	Method	Characteristics
PFGE method	Whole genome	Fragmentation by restriction enzymes, followed by pulsed-field gel electrophoresis	Frequently used in investigations in North America
REA method	Whole genome	Fragmentation by restriction enzymes, followed by electrophoresis	Requires skill in terms of reproducibility and judgment
PCR ribotyping	16S–23S rRNA ITS region	PCR using specific primers, followed by checking amplification product sizes against databases to determine 3-digit ribotypes	Widely used
slpA method	slpA gene	Electrophoresis pattern of typing sequence amplification products	Good correlation with serotypes
MLST method	Seven housekeeping genes	Sequence of each gene is checked against databases to determine sequence type	Evolutionary proximity is shown
POT method	Multiple specific genes	Multiplex PCR	Mainly used in Japan
Toxinotyping	Toxin genes	Restriction enzyme treatment, followed by PCR	Correlates with ribotypes

PFGE; Pulsed-field gel electrophoresis, REA; Restriction endonuclease analysis, ITS; internal transcribed spacers, MLST; multilocus sequence typing, POT; PCR-based open reading frame typing.

Table 3
Relationship between typing findings and toxin production.

Clade	Ribotype	Representative sequence type (ST)	Toxin production[a]	Note
1	001	ST3	A^+B^+	Common in Japan
	002	ST8	A^+B^+	Common in Japan
	012	ST54	A^+B^+	
	014/020	ST2	A^+B^+	Common in Japan
	018	ST17	A^+B^+	Common in Japan
	046	ST35	A^+B^+	
	106	ST42	A^+B^+	
2	027	ST1	$A^+B^+CDT^+$	Outbreak strains in North America and Europe
	244	ST41	$A^+B^+CDT^+$	
3	023	ST5	A^+B^+	
4	017	ST37	A^-B^+	Found widely in Asia
	369	ST81	A^-B^+	Common in Japan
5	033	ST11	$A^-B^-CDT^+$	Rare
	078	ST11	$A^+B^+CDT^+$	Outbreak strains in Europe
	126	ST11	$A^+B^+CDT^+$	Strains closely related to ribotype 078
	127	ST11	$A^+B^+CDT^+$	Strains closely related to ribotype 078

[a], Binary toxin (CDT) is indicated only if it is produced.

9.2. Epidemiology

9.2.1. Characteristics of isolates from Japan

In Japan, ribotype 018 is the major strain [28,29] and toxin A^+B^+ strains, such as 001, 014, 002, and 052, are relatively common [20, 28–31]. Ribotypes 369 and 017, which are found sporadically, are toxin A^-B^+ strains [28–30]. During outbreaks, ribotypes 014 [28] and 018 [28], which are toxin A^+B^+ strains, are common; however, toxin A^-B^+ strains, such as 369 [28,32,33], are responsible for some outbreaks [34].

In Japan, ribotypes 027 and 078, which are common in Europe and the United States, are rarely isolated, with an isolation frequency of 0%–1% [27], and binary toxin-positive strains are isolated at 0%–6.8 % [28, 35–40]. There is a paucity of molecular epidemiological information on isolates from community-acquired infections. Binary toxin-positive ribotype 019 (toxin A^+B^+ strain) has also been reported [41].

9.2.2. Characteristics of Asian isolates

In South Korea, China, and other East Asian and Southeast Asian countries, ribotype 017 is found relatively frequently and has caused outbreaks [42]. In South Korea, in addition to ribotype 017, ribotype 018 has increased recently and ribotypes 001 and 014/020 have also been found [43,44]. In China, ribotypes 012, 014/020, 046, and 017 are common [45–47], and ribotype 369 has caused recent outbreaks [42]. Ribotype 002 has been reported to be common in Hong Kong [48].

Ribotype 027 has been identified in South Korea [49] and China [50, 51], causing outbreaks in China [50]. Many ribotype 027 strains isolated in Asia are believed to belong to a lineage different from that of the 027 strains that are epidemic in Europe and the United States [52]. Ribotype 078 and its closely related strains (ribotypes 126 and 127) have been isolated relatively frequently in some areas in Taiwan [53,54] and have also been found in China [51,55].

9.2.3. Characteristics of isolates from regions other than Asia

In North America and Europe, ribotype 027 (027/BI/NAP1 strain) has caused outbreaks since 2003, at times constituting the majority of isolates. Despite its gradually decreasing percentage [56–59], there are still some countries and regions where this ribotype is quite common [56,60,61]. In Europe, ribotype 027 is still found most commonly and ribotypes 001, 002, 014/020, 078, and 126 are major ribotypes [60,62]. In the United States and Canada, the percentages of ribotypes 027,

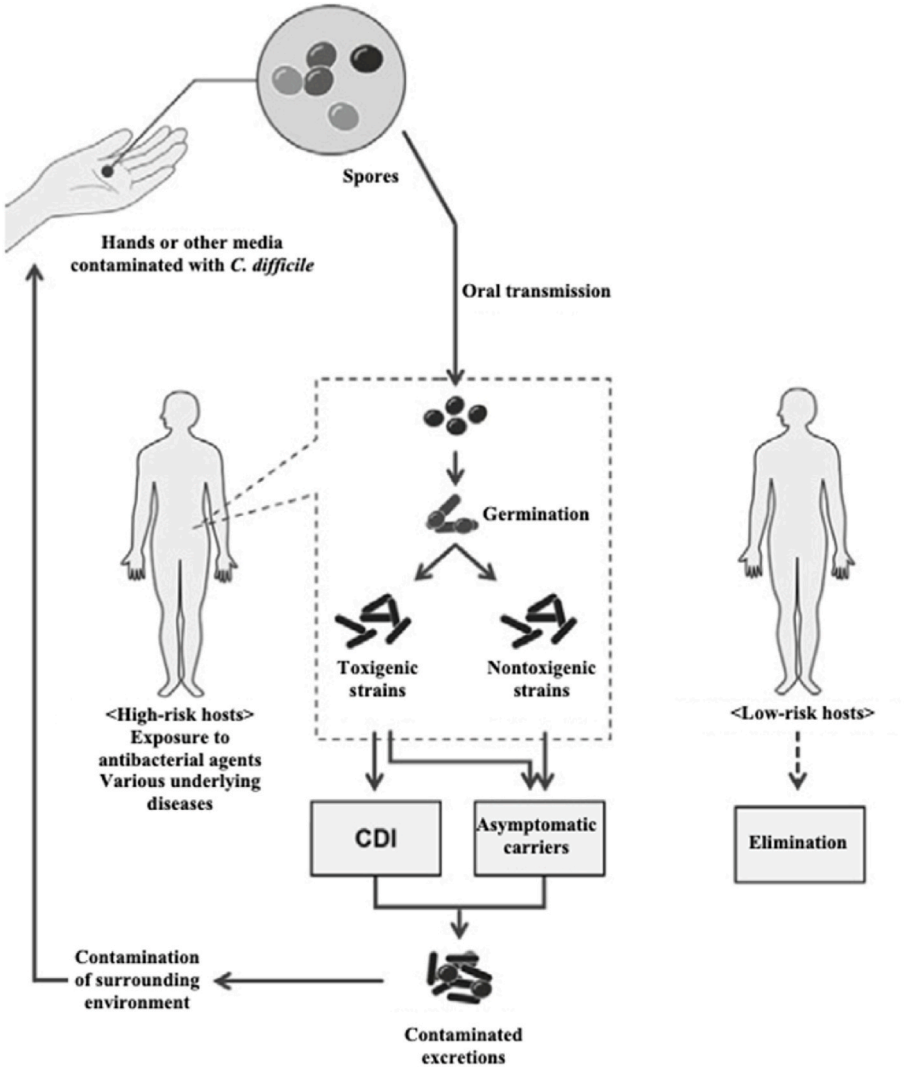

Fig. 2. Transmission routes of *Clostridium difficile* and *C. difficile* infection (CDI)
CDI, *C. difficile* infection.
C. difficile spores that have entered the intestinal environment via hands or other contaminated media germinate to form vegetative cells when the host's intestinal bacterial flora is disturbed. Toxigenic strains can cause CDI. Both toxigenic and nontoxigenic strains can colonize the intestinal tract and make hosts asymptomatic carriers. *C. difficile* present in excretions can survive in the environment as spores, which can contaminate hands or any objects they come into contact with. When the host's intestinal bacterial flora is undisturbed, *C. difficile* cannot enter the intestinal environment or is eliminated from the body.

014/020, and 106 are high [56,63,64]. Ribotypes 014/020 and 002 [65] are common in Australia, and ribotypes 012, 014/020, 027, and 046 are found in Chile [66].

Common binary toxin-producing strains are ribotype 027 in North America [22,52], ribotypes 027 and 078 in Europe [60,67], and ribotype 244 in Australia [65].

9.3. Pathology of CDI

9.3.1. Transmission routes of C. difficile

A prerequisite for the onset of CDI is the entry of toxigenic *C. difficile* into the intestinal environment. *C. difficile* outside the body cannot enter the intestinal environment easily in the presence of stable intestinal bacterial flora. Therefore, the establishment of *C. difficile* colonization and infection in the intestinal environment requires the surrounding environment to be contaminated with *C. difficile*, along with unstable host intestinal bacterial flora, allowing for the easy introduction of *C. difficile* bacteria (Fig. 2) .

The instability of the intestinal bacterial flora occurs for various reasons, including treatments such as antibiotic use and chemotherapy for malignant tumors, as well as underlying diseases and changes in the immune status of the host. An important transmission route is contact with a patient with CDI or an asymptomatic carrier, which can even be an infant [68]. Spores found in patients'/carriers' excretions contaminate the room and equipment and are then ingested orally through hands and other media that have come into contact with such an environment. Besides humans, intestinal colonization by *C. difficile* has been confirmed in pets and livestock animals [68–70], and *C. difficile* has also been found in environments such as rivers, seawater, and soil [23]. Some hosts have a low susceptibility to CDI, and even if they ingest *C. difficile* orally, the bacterium is either eliminated or only colonizes the intestinal tract asymptomatically [59].

9.3.2. Colonization

Intestinal colonization by *C. difficile*, whether toxigenic or nontoxigenic, is observed in <2%–15 % of adults, and *C. difficile* colonies are identified within this range [71–73]. The colonization rates in hospitalized patients and residents of long-term care facilities have been reported to be as high as ~30 % and ~50 %, respectively [72]. The colonization rate in hospitalized patients increases with the duration of hospital stay [74].

The intestinal colonization rates among infants aged less than 2 years from different surveys range from 20 % to 90 % but are generally very high [71–73,75–77]. In Japan, the rate is 0%–2.5 % in early neonates and as high as 30%–84 % in infants under 2 years of age, while it decreases gradually to 20%–30 % in children aged 2–5 years [77,78]. Rates of colonization by both nontoxigenic and toxigenic strains are high in children with underlying diseases [78]. In infants, the rate of colonization by toxigenic strains is high, but CDI occurs very rarely. A possible explanation for this finding is the immaturity of host factors required for toxin function [79]. Different strains can be isolated at different times in the life of the same child [71,80].

9.3.3. Clinical features of CDI

CDI is mostly characterized by enteritis. Diarrhea is the main symptom and is sometimes accompanied by abdominal pain and fever. In the symptomatic phase, pseudomembranes and hemorrhage may be observed in the intestinal tract. Intestinal perforation, megacolon, and ileus also occur, albeit rarely.

The incidence of CDI is 0.8–7.4 per 10,000 patient-days in Japan [27,29], 5.5–18.1 on average in European countries [60,61], 7.4 on average in the United States [71], and 5.3 in Asian countries [81]. The prevalence rate is 0.3–5.5 per 1000 hospital admissions in Japan and 6.9 in the United States [27].

The prevalence rate and incidence in Japan are somewhat low, most likely due to differences in testing methods and epidemic strains [27,81]. There are many cases of recurrent CDI, occurring in 20%–30 % of cases even after appropriate treatment [82,83]. The incidence of CDI increases with age, and most patients have a history of visiting healthcare institutions, including inpatient and outpatient facilities, and nursing homes.

C. difficile can also cause extraintestinal infections, along with bacteremia, intra-abdominal infections, perianal abscesses, post-traumatic wound infections, and catheter-associated urinary tract infections [84–86]. However, extraintestinal CDIs occur very rarely, accounting for 0.17 % of all CDI cases [86]. Patients with extraintestinal CDI are hospitalized and have underlying diseases, these patients then develop diarrhea. Moreover, multiple bacteria, including *C. difficile*, are often isolated from samples collected from patients with extraintestinal CDI [84–86].

CDI mainly occurs during admission to healthcare facilities or in the community after being discharged therefrom; CDI can also be acquired in the community [87]. In Japan, there is a paucity of data on community-acquired cases; nevertheless, there are reports showing that the incidence per 10,000 patient-days is 0.2 and the incidence per 100,000 patient-years is 1.4 [38] for community-acquired CDI compared to 3.11 for healthcare-associated CDI [88]. These data suggest that community-acquired CDI is less common in Japan than in Europe and the United States.

9.3.4. Contamination of healthcare environments

Healthcare professionals and indoor environments contaminated with *C. difficile* can mediate new colonization and infection. Hospitalized patients often have diarrhea. When such patients are tested for suspected CDI, the hands of healthcare professionals are at a high risk for contamination, unless appropriate measures are in place before the definitive diagnosis is made [89]. The hands of healthcare professionals involved in the care of patients with CDI are prone to contamination with *C. difficile* [90]. The skin and surroundings of patients with CDI may still be contaminated even when treatment is completed and the patients no longer have diarrhea [91].

Patients sharing a room with a patient with CDI are known to be at an elevated risk of contracting CDI, and the risk increases with the duration of their stay in the same room [92].

Environmental transmission can also occur, as a hospital room used by a patient with CDI or a patient with a history of antibiotic treatment poses an increased risk of infection to the next user [90,93].

9.3.5. Health economic effects

Health economic effects associated with clinical practice for CDI are substantial. In terms of effects per patient, CDI results in a 1.3–1.8-fold higher total hospitalization cost and a 1.4–1.5-fold longer duration of hospital stay than other diseases [82,94–97] (Table 4).

Medical costs for cases of recurrent CDI are even higher [82,98,99] (Table 5). Based on a survey in Japan, patients with CDI pay an estimated ~¥2,440,000–3,720,000 as the total hospitalization cost [99]. Patients with recurrent CDI pay ¥1,280,000 more for total hospitalization costs and require 20.3-day longer hospitalization than nonrecurrent cases [99].

In terms of effects at the healthcare institution level, there are extra cost burdens, such as those for infection control measures in case of outbreaks and bed closures [100]. During an outbreak, there is an increase in expenses for microbiological tests, therapeutic agents, personal protective equipment (PPE), environmental cleaning, personnel, and other factors. Moreover, there is a reduction in income due to a decreased bed occupancy rate resulting from prolonged hospitalization and ward closures [100,101]. However, only a few reports have dealt with the cost estimates in the event of an outbreak. According to a report on a 027/BI/NAP1 strain outbreak in a tertiary care institution in the Netherlands, an income decrease due to bed closures and the combined cost of activities of infection control staff and bacteriological surveillance accounted for 36 % and 25 %, respectively, of the total economic

Table 4
Hospitalization expenses required for patients with CDI.

Author	Survey period	Region	Design	CDI		Control	
				Expense of hospitalization	Duration of hospitalization	Expense of hospitalization	Duration of hospitalization
Vonberg et al. [96]	January to December 2006	Germany	CDAD vs. non-CDAD	€33,840 (median)	27 days (median)	€18,981 (median)	20 days (median)
Dubberke et al. [94]	January to December 2003	USA	CDAD vs. non-CDAD	$8394 (estimate)	–	$5940 (estimate)	–
Kyne et al. [95]	January to December 1998	USA	CDAD vs. non-CDAD	$10,489 (estimate)	10.2 days (estimate)	$6820 (estimate)	6.6 days (estimate)
Yasunaga et al. [97]	January 2007 to December 2010	Japan	CDAD vs. non-CDAD (after gastrointestinal surgery)	$32,376 (estimate)	28 days after surgery (estimate)	$25,652 (estimate)	19 days after surgery (estimate)

CDAD, *C. difficile*-associated diarrhea.

Table 5
Hospitalization expenses required for first-time CDI and recurrent CDI.

Author	Year of publication	Region	First-time CDI		Duration of hospitalization	
			Expense of hospitalization	Duration of hospitalization	Expense of hospitalization	Duration of hospitalization
Wilcox et al. [98]	September 2013 to September 2014	UK	£6294 (median)	15.5 days (median)	£7539 (median)	21 days (median)
Kunishima et al. [99]	January 2012 to September 2016	Japan	2,436,019 yen (estimate)	57.8 days (estimate)	3,720,538 yen (estimate)	78.1 days (estimate)

CDI, *C. difficile* infection.

loss [100].

10. Specimen collection

The detection of toxigenic *C. difficile* in fecal specimens is important for diagnosing CDI. However, some patients are carriers of the pathogen and remain asymptomatic, and CDI may not be diagnosed appropriately using specimens that were collected without evaluating the quality of the feces.

As a general rule, specimens collected from patients who have diarrhea should be tested. However, many patients with CDI are elderly; some of them may not be able to defecate independently and may face practical difficulties in measuring the accurate frequency of defecation. Thus, for diarrhea, either of the following can be used as a guide: a defecation frequency of three times or more within 24 h or a defecation frequency higher than usual, both with a Bristol Stool Scale score of 5 or higher [102]. However, confirmation of diarrhea in some severe cases may not be possible due to a dynamic ileus or toxic megacolon.

Differentiation between CDI and the carriage state is also important when specimens for testing are collected from children. The rate of intestinal carriage is very high for the first 2 years after birth; thus, CDI testing is not recommended for children under 2 years of age unless other infectious and noninfectious causes of diarrhea are ruled out [102].

Evaluators perceive and describe the form of diarrhea stools differently. To objectively standardize the macroscopic appearance, the Bristol Stool Scale is recommended for evaluation (Table 6) [103].

When CDI is suspected, the specimens used for testing should have a score of 5 or higher so that the CDI diagnosis flowchart that assumes that the patient has diarrhea can be used appropriately.

Table 6
Bristol stool scale.

Score	Stool form
1	Separate hard, lumpy stools, like nuts
2	Sausage-shaped but hard stools
3	Sausage-shaped stools with cracks on the surface
4	Soft, sausage-shaped stools with a smooth surface
5	Semi-solid, soft stools
6	Irregularly shaped mushy stools without a clear-cut edge
7	Liquid stools with no solid pieces

11. Diagnosis and treatment flowcharts

The basic algorithms for diagnosing and treating CDI, described in the Japanese Clinical Practice Guidelines for Management of *Clostridioides difficile* Infections [102], are outlined here.

11.1. Diagnosis flowchart

The algorithm shown in the flow chart is not designed to prescribe the characteristics or line of thinking in individual institutions, and testing methods should be selected based on the current situation of the region and institution. As any test method can produce false positive and negative results, it is important to make a careful diagnosis based on an adequate understanding of the characteristics of the test methods.

11.2. C. difficile testing algorithm in routine clinical practice

First, GDH/toxin tests via immunochromatography should be performed using a fecal sample with a Bristol Stool Scale score $\geq$5. The sensitivity of the GDH test, indicating the presence of *C. difficile* in feces upon a positive result, is known to be high on some level, while the sensitivity of the toxin test, which evaluates toxigenicity, is known to be low [102]. When the results of both tests are negative, CDI can be ruled out. When the results of both tests are positive, the patient can be diagnosed with CDI. However, when the GDH test is positive and the toxin test is negative, it cannot be determined whether the patient has toxigenic or nontoxigenic *C. difficile* because the toxin test result might be a false negative.

For samples where the GDH test result is positive and the toxin test result is negative, the nucleic acid amplification test (NAAT) can be used to evaluate the toxigenicity genetically. The NAAT detects the presence of the toxin B gene and has high sensitivity. When the NAAT result is negative, CDI can be ruled out and other causes of diarrhea should be sought. When the NAAT yields a positive result, the patient may have CDI or be a carrier; therefore, the clinical appropriateness should be re-evaluated before CDI is diagnosed.

11.3. C. difficile testing algorithm during outbreaks

During outbreaks, broader surveillance of carriers and patients as well as evaluation using molecular epidemiological techniques may be required.

Moreover, samples from certain patients, such as neutropenic patients and transplant recipients, may produce false-negative GDH test results [104]. Thus, the more sensitive NAAT and culture tests should be used proactively. Culture tests are time-consuming but can be used for detailed analysis of strains to determine the outbreak status. The decision of whether NAAT should be used at the beginning or after GDH/toxin testing should be made depending on the availability of NAAT in individual medical institutions.

11.4. Treatment flowchart

In the flowchart for *C. difficile* treatment, risk factors are identified and reduced before different treatment strategies are chosen for nonsevere, severe, recurrent, and intractable cases. Metronidazole, vancomycin, and fidaxomicin are used as therapeutic agents; bezlotoxumab (an antitoxin B antibody) is used to prevent recurrence; and probiotics are used as prophylactic agents.

Metronidazole is available in oral and injectable dosage forms that are available at low prices. A dose of 500 mg is given orally or intravenously thrice a day for 10 days. Neurotoxicity is a potential adverse effect commonly occurring when used at a high dose or for a long duration. Moreover, caution should be exercised when it is administered to patients with severe hepatic or renal impairment (e.g., use of a lower dose or a longer dosing interval) because its metabolites may be neurotoxic.

Vancomycin is available in an oral dosage form. It is poorly absorbed by the body and is thus found in feces at very high concentrations. A dose of 125 mg is given orally four times a day for 10 days. If a higher dose is necessary, 500 mg may be given orally four times a day for 10 days. It is also administered through an enteral route in some cases. Pulsed/tapered vancomycin regimens (gradually tapered doses of vancomycin are administered) may be used for recurrent or intractable cases.

Fidaxomicin is an oral drug; a dose of 200 mg is given twice daily for 10 days. It is used for treating recurrent and intractable cases as it is highly effective in preventing recurrence and maintaining remission.

For nonsevere cases, metronidazole and vancomycin are used as the first- and second-line agents, respectively. For severe cases, vancomycin is used as the first-line drug, and fidaxomicin, vancomycin plus metronidazole, or high-dose vancomycin are used as second-line treatments. For recurrent cases, vancomycin or fidaxomicin are used as first-line therapeutic agents, and a second-line treatment is either high-dose vancomycin or a pulsed/tapered vancomycin regimen. For intractable cases, fidaxomicin is used as the first-line agent, and vancomycin plus metronidazole, high-dose vancomycin, or pulsed/tapered vancomycin are used as second-line treatments.

Bezlotoxumab (an antitoxin B antibody) should be considered for the prevention of recurrence in immunocompromised patients; patients with severe CDI, patients infected by virulent strains (ribotype 027, 078, or 244); patients who have contracted CDI three or more times previously; or patients with other special characteristics. It is not recommended to be used widely among non-risk patients [102].

The prophylactic use of probiotic preparations is considered for individuals at risk of developing CDI.

12. Risk factors for CDI transmission

12.1. Introduction

Before we discuss transmission, it is important to understand that *C. difficile* survives in various environments (e.g., nature, various goods, clothes, and patients' surroundings) and that *C. difficile* spores can survive for several months. Patients and healthcare professionals can readily acquire *C. difficile* in the spore or vegetative state from contaminated environments, and transmission occurs primarily through the fecal–oral route.

12.2. Microbiological properties

C. difficile is found in both the vegetative and spore forms. It exists primarily as vegetative cells in the intestinal tract, and vegetative cells outside the intestine die within ~24 h [105,106]. However, *C. difficile* in the spore state survives for several months in the extraintestinal environment. Moreover, the spores are resistant to many disinfectants/antiseptics [105,106]. *C. difficile* spores transmitted to humans pass through the stomach and reach the intestinal tract because the spores are resistant to gastric acid. In the intestinal tract, spores germinate, produce toxins, and cause infections. The ability to form spores contributes to the high transmission risk of *C. difficile* compared to other bacteria.

C. difficile in its vegetative form can survive on dry surfaces in indoor air for only 15 min and on wet surfaces for ~6 h [107]. On the contrary, the spores are highly resistant to dryness, heat, and chemical/physical agents. A report in 1981 documented its survival on hospital floors for 5 months [105]. Regarding the effects of temperature changes, refrigeration, freezing, and thawing stimuli have been shown to affect both vegetative cells and spores [108].

While the primary transmission route is fecal–oral, *C. difficile* spores have also been isolated from the air. Best et al. have shown that spores were found in 6 (12 %) of 50 ambient air samples collected around patients with *C. difficile* for 1 h, but no controls were included in the study. In a follow-up study, ambient air samples from around 10 patients with *C. difficile* were collected for 10 h, and airborne spores were detected in samples from ~70 % of the patients; they also detected spores on the surfaces in the vicinity of ~90 % of the patients [109]. These results suggest that *C. difficile* spores are diffused into the environment in the form of an aerosol, which can be a mechanism by which extensive environmental contamination occurs [107].

12.3. Transmission routes

There are three possible modes of *C. difficile* transmission: environment-mediated, patient-mediated, and healthcare worker-mediated [108]. In healthcare settings, there are two possible sources of transmission: patients with CDI (symptomatic and asymptomatic) and nonhuman sources.

Durovic et al. reviewed 24 reports published between 2007 and 2017 to investigate sources of CD transmission [68]. They found that transmission within medical care facilities accounted for 67 %, while community transmission accounted for 37 % [68]. Among cases of transmission within medical care facilities, *C. difficile* was transmitted via contact with symptomatic carriers in 53.5 %, from the hospital environment in 40.0 %, and from asymptomatic carriers in 20.0 % [68]. Among cases of community transmission, *C. difficile* was transmitted from children in 30.0 % of cases, from humans in medical care facilities in 30.0 %, from outpatient care facilities in 20.0 %, and from livestock animals and farms in 20.0 % [68]. Moreover, infectious sources in medical facilities were hospital rooms in 25 % of cases, beds in hospital rooms in 13 %, hoppers in 13 %, janitor's equipment rooms in 12 %, bathrooms in 12 %, and toilets in 12 % [68].

12.4. Transmission from patients (carriers and infected individuals)

In non-CDI patients who shared hospital rooms with patients with CDI, the length of stay in the same room and the length of exposure have been shown to be possible risks for developing CDI along with other factors [92]. In particular, symptomatic patients are considered a major

group of reservoirs [110]. Regarding the level of environmental contamination with *C. difficile* spores, it has been reported that the contamination level increases with the severity of CDI in patients [95].

Asymptomatic carriers are considered potential reservoirs of environmental contamination [111]. *C. difficile* is also found in the normal intestinal bacterial flora, and reported rates of carriage are ~3 % in healthy adults, 20%–30 % in hospitalized adults [112], and up to ~50 % in medical institutions with many reports [113]. A certain percentage of *C. difficile* carriers are also found in the community [114], and transmission from them can occur at any time.

12.5. Environmental contamination around patients (carriers and infected individuals)

Studies on the extent of environmental surface contamination in patient rooms are scarce. According to one report, 49 % of the environment around patients is contaminated in the hospital rooms of patients with symptomatic CDI, whereas 2 % of the area is contaminated in the hospital rooms of asymptomatic patients [90]. Other studies have reported a wide range of percentages, from 2.9 % to 75 % [105]. Furthermore, *C. difficile* can be detected in hospital rooms of noncarriers or noninfected individuals; however, the detection frequency is very low.

C. difficile has also been detected on care products around patients [107]. For example, electronic thermometers used by patients with *C. difficile* and contaminated patients' belongings serve as reservoirs for *C. difficile* transmission [115]. Some medical devices, such as portable toilets and electronic rectal thermometers, have also been implicated in *C. difficile* transmission [107]. Moreover, contaminated mobile phones and portable electronic devices have also been reported to mediate transmission [116]. In one study, the hands of 30 of 32 clinicians who used an alcohol-based hand sanitizer for hand hygiene were found to be contaminated with *C. difficile* after they used mobile phones [116].

Bedclothes, clothes, and footwear can also be *C. difficile* reservoirs. Tarrant et al. showed that washing with an inappropriate cleaning solution resulted in incomplete spore removal, causing their dispersal. This suggests that spores scattered due to such inappropriate washing may contribute to sporadic outbreaks [117]. Other possible reservoirs include shoes, slippers [118], and wheelchairs used to access and leave medical institutions [119].

As for environmental and hand contamination, *C. difficile* has been detected on the hands of patients with CDI [107] and on the hands of staff engaged in patient care. The frequency of detection of hand contamination reflects the contamination level of the environment around patients [120]. In particular, frequencies of hand contamination were 8 % and 36 % when 26%–50 % and ≥50 % of the environment were contaminated respectively, and the frequency of hand contamination was 0 % when the percentage of environmental contamination was <25 % [120].

Therefore, environmental contamination plays an important role in the nosocomial transmission of *C. difficile*. For example, the frequency of CDI is correlated with the level of environmental contamination [121]. Moreover, a patient who uses a room previously used by a patient with CDI is at an increased risk of acquiring *C. difficile* [122]. A study has shown that CDI can be reduced by improving the disinfection of rooms [123].

12.6. Inadequate environmental management

Places to be checked in patients' surroundings include frequently touched surfaces in patients' rooms, such as bed rails, overhead tables, door handles, and portable toilets near the bed; for these places, routine cleaning and disinfection with sodium hypochlorite at least once daily are recommended [124]. Environmental management requires appropriate cleaning and disinfection procedures, and it is important to have a good understanding of *C. difficile* properties, such as spore formation, strong resistance to heat, dryness, and disinfectants, and the ability of long-term survival on dry environmental surfaces.

A study on *C. difficile* contamination of the hospital room environment immediately after patients with CDI left the rooms, after inappropriate cleaning/disinfection, and after proper cleaning/disinfection has demonstrated that inappropriate cleaning is not at all effective for disinfection, even when the disinfectant used is the same as that used in appropriate cleaning [125], indicating the importance of education for the cleaning staff.

12.7. Transmission from community sources

There are various reports on routes of *C. difficile* transmission from community sources to hospitals.

Many reports have described the detection of *C. difficile* in meat and vegetables for human consumption and in livestock and pet animals [126].

Regarding studies on *C. difficile* carriage by animals, many studies have focused on its distribution among pigs, indicating that the rate of isolation from adult pigs was as low as 0.8 % [127], whereas the rate of isolation from piglets was as high as 57.5 % [128]. The study showed that 26 % of the piglet-derived strains had all toxin genes and 35 % had any of the toxin genes. In Japan, no ribotypes found in pigs were identical to clinical isolates from humans; however, ribotype 078 was common between human- and animal-derived isolates overseas, suggesting entry to Japan via pigs. Similarly, *C. difficile* was not isolated from adult cattle but was isolated from 17 % of calves. Furthermore, CD was isolated from 5 of 14 samples (36 %) of matured manure from pigs, with a high rate of *C. difficile* isolation [129]. In terms of vegetables and meat, *C. difficile* was isolated from 8 samples (3 %) of vegetables with soil on the surface (taro, onion, and burdock root) among 242 samples of vegetables purchased from grocery stores and 7 samples (2.4 %) of ground chicken and chicken liver among 286 samples of commercially available meat [129]. An overseas survey on meat has reported the detection of ribotypes 027 and 078 from meat, such as beef, pork, and turkey (e.g., ground meat and sausages), from retailers in the United States and Canada [70]; however, it remains unclear whether consumption of *C. difficile*-containing meat is directly associated with CDI development.

In terms of companion animals (pet animals), an epidemiological study on dogs that are frequently used as companion animals has reported that *C. difficile* was isolated from 62 of 204 dog samples (30.4 %), with no associations between isolation rate and dog age [130]. Furthermore, the whole-genome analysis of isolates determined to be the same strains by PFGE identified dog- and human-derived strains that were closely related to each other, suggesting dog–human transmission [130].

Loo et al. compared the transmission rates from humans and pet animals and reported 1 case (1.5 %) of probable transmission and 5 cases (7.5 %) of possible transmission among 15 human contacts. Additionally, there were three cases (20 %) of probable transmission and one case (6.7 %) of possible transmission among 15 pet animal contacts [131]. It has also been reported that ribotype 027 was isolated from a dog that visited patients in medical institutions and residents of nursing homes. The authors of this report inferred that the dog was infected during visits to a medical institution where ribotype 027 infection was occurring frequently [132].

Environmental transmission risks include transmission from sandboxes. Obata et al. isolated *C. difficile* from 47.5 % of 40 sandboxes and reported that most isolates were closely related, from a molecular epidemiological perspective, to clinical isolates or strains derived from certain strains via a series of mutations. These sandboxes could serve as sources of transmission for children who play in them [133]. Perumalsamy et al. collected 159 samples of soil, mulch, lawn, and sand from surrounding areas or rooftops of four healthcare institutions over a period of 6 months or longer and reported that *C. difficile* was isolated from 96 (60.4 %) of the 159 samples [134] (Fig. 3).

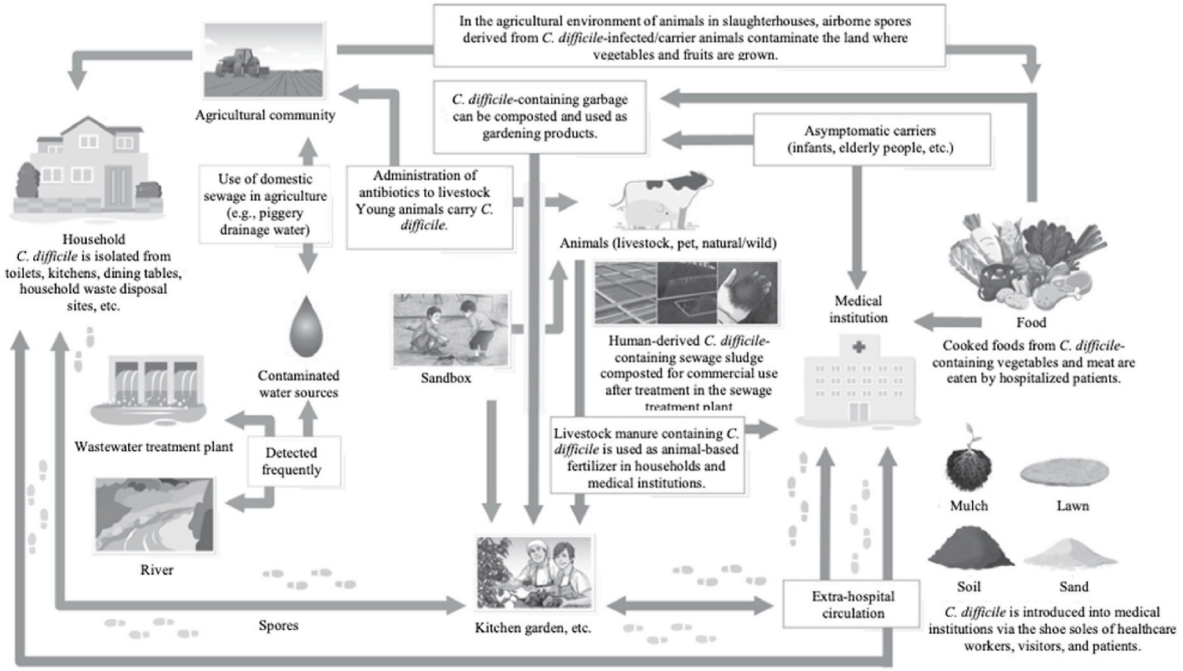

Fig. 3. Reference drawing to summarize routes of *Clostridium difficile* transmission (adapted from Perumalsamy et al. [140] with modifications).

12.8. Transmission from patients

Patients treated for *C. difficile* for insufficient lengths of time are at risk for recurrence and represent a possible source of CDI transmission. Patients who are discharged from hospitals, particularly after treatment in the ICU, should be suspected of having recurrent CDI [135]. Patients suspected of having CDI should be treated as having CDI, even if the test result is negative. Patients who wander around and are incapable of adequate hand hygiene due to dementia or any other reason are at risk of CDI transmission.

Conflicting opinions exist regarding the appropriate timing for discontinuing measures against contact transmission. Weber et al. argued that measures should be taken for at least 48–72 h after the patient becomes asymptomatic [108]; however, the rates of *C. difficile* isolation from patients' skin and the environmental surfaces around them, including asymptomatic carriers, are high [125]. It is considered beneficial to adhere to contact precautions even after patients no longer have symptoms and until they are discharged, at least during outbreaks [113].

12.9. Transmission from healthcare workers

Inadequate hand hygiene is a risk factor for transmission. Disinfectants commonly used for hand hygiene, such as alcohol, chlorhexidine, hexachlorophene, iodophors, and triclosan, are not effective against spore-forming bacteria because they are not sporicidal.

Regarding transmission from healthcare workers, the rate of *C. difficile* detection in the hands of healthcare workers providing care for patients with CDI was significantly higher than that in the hands of healthcare workers who were not involved in such care. Furthermore, the transmission risk was reported to be 6.26 among those who had at least one patient contact without wearing gloves (1.27–30.78) ($p = 0.02$) [136]. This report, among others, supports the notion that healthcare workers should wear gloves during care procedures and perform hand hygiene before and after the routine care of patients with CDI.

It has also been reported that the use of gloves reduced the incidence of CDI [137]. Transmission risks associated with healthcare workers' medical care activities for patients with *C. difficile* (symptomatic and asymptomatic) include sharing electronic rectal thermometers (the handle may be contaminated even when a probe cover is used); oral care and oral suctioning with contaminated hands; meal assistance and drug administration; emergency procedures, such as intratracheal intubation; inadequate hand hygiene; sharing patient care items; and inadequate environmental management [124].

13. Infection control for CDI

The two wheels of infection control measures against CDI are to reduce patients' risks for the onset or prevention of CDI development and to block routes of *C. difficile* transmission. To prevent the development of CDI, it is important to promote the proper use of antibiotics (such as broad-spectrum antibacterial agents and antibacterial agents effective against anaerobic bacteria) in patients with a high risk of CDI onset and to reduce host risk factors. Drugs should be chosen particularly carefully for patients with a history of CDI because they are prone to recurrence. It is also important to implement appropriate infection control measures, excrement disposal, and environmental cleaning for the prevention of horizontal transmission from a patient with CDI to other patients. The Antimicrobial Stewardship Team (AST) activities to reduce the risks of occurrence and the Infection Control Team (ICT) activities to deter intrahospital transmission are both critical for protecting hospitals from healthcare-associated infection (Table 7).

13.1. Reduction of host risks of developing CDI

Most patients who develop CDI have undergone treatment with antibacterial agents before the onset. Certain antibacterial agents, such as cephalosporins, quinolones, and clindamycin, have been regarded to be associated with a high likelihood of subsequent onset of CDI; however, all antibacterial agents, including vancomycin and metronidazole, carry such a risk [138]. Efforts should be made to minimize the frequency and duration of administering antibacterial agents because the CDI risk increases with the number of antibacterial agents, amounts administered, and duration of administration. Particular caution in drug selection is required for patients with a history of CDI because they are prone to recurrence. A meta-analysis on AS activities to reduce the occurrence of CDI has reported a 32 % reduction, showing the

Table 7
Summary of infection control for CDI.

Reduction of patient risks for CDI	
Antibacterial control	Appropriate use of high-risk antibacterial agents and minimization of frequency and duration
Antacid control	Appropriate use of proton pump inhibitors and H_2 receptor antagonists
AST activities	Providing physicians with education, recommendations, and interventions for the appropriate use of antibacterial and antacid agents
Prevention of horizontal transmission from infected individuals	
Patient placement	Private-room isolation or cohorting
Infection prevention measures	Hand hygiene with S/W and contact precautions using gloves and gowns
Environmental cleaning	Cleaning with sodium hypochlorite solution or complex-type chlorine-based disinfectant cleaner
Environmental disinfection	Use of no-touch cleaning techniques, such as UV irradiation and hydrogen peroxide vapor
ICT activities	Educating healthcare workers and patients/families/visitors on infection prevention measures

AST, Antimicrobial Stewardship Team; CDI, *Clostridium difficile* infection; ICT, information and communications technology; S/W, soap and water; UV, ultraviolet.

effectiveness of AS activities [139].

Certain risks for CDI, such as aging; history of hospitalization and gastrointestinal surgery; and underlying diseases, including inflammatory bowel disease and chronic kidney disease, cannot be reversed. However, as other risk factors besides antibacterial agents where AST can intervene, discontinuation of antacids, such as proton pump inhibitors and H_2 receptor blockers, can reduce the risk for CDI.

Broadly, AS activities encompass more than just restricting the use of antibacterial agents. They also involve aiding in infectious disease management, including initiatives to promote early testing and treatment for patients suspected of having CDI.

13.2. Infection prevention measures

As *C. difficile* is found abundantly in feces, the primary route of transmission is contact transmission, including fecal–oral transmission. Therefore, patients with CDI and patients suspected of having CDI should be isolated in private rooms in principle, and staff should exercise contact precautions in addition to standard precautions, including thorough hand hygiene and PPE such as gloves and gowns or aprons. Excrement should be handled with special care. Cohort isolation of patients with CDI may be chosen when isolation in private rooms is not an option. It should be ensured that visitors, as well as healthcare workers, perform proper hand hygiene and wear PPE when they enter a patient's room. These infection control measures against CDI should be considered separately for normal times and outbreaks [140].

13.3. Patient placement

It has been reported that the incidence of CDI in two-bed room units is higher than that in one-bed room units and that the risk of infection increased after exposure to a *C. difficile* culture-positive roommate [141]; thus, various guidelines widely recommend that patients with CDI or patients suspected of having CDI are placed in private rooms whenever possible, ideally in those equipped with special facilities, such as dedicated toilets and washbasins. When a sufficient number of one-bed room units are not available, patients with fecal incontinence are preferentially placed in private rooms. When there are too many patients and placement of them in private rooms is impossible, patients with CDI can be cohorted in the same room [71]. However, it has been reported that patients who were cohorted developed more severe CDI and had a higher recurrence rate than patients who were not [142]. Thus, when cohort isolation is chosen, thorough management of patient flow is necessary. A prospective study of patients suspected of having CDI has shown that it takes 2 days before the patients are diagnosed with CDI, and 69 % of healthcare workers who had contact with the patients during these 2 days acquired *C. difficile* on their hands [89].

Therefore, patients suspected of having CDI should be isolated, and contact precautions should be exercised until their test results are obtained.

13.4. Hand hygiene and gloves

It has long been known that the hands of healthcare workers engaged in care for patients with CDI are contaminated with *C. difficile* [90], and strict adherence to hand hygiene is one of the most important infection control measures. Because *C. difficile* in the spore state is highly resistant to alcohol, the use of soap and water (S/W) is a more effective means of hand hygiene to remove *C. difficile* than the use of alcohol-based hand sanitizers [143]. However, there is also a report showing that an increase in the use of alcohol-based hand sanitizers was not necessarily linked with an increase in CDI [144]. In some medical institutions, it is difficult to require staff engaged in care for patients with CDI in normal times to use S/W for hand hygiene strictly. Healthcare workers should perform hand hygiene with S/W after contact with a patient for care or any other purposes regardless, at least when the rate of CDI is elevated or during outbreaks.

In facilities where the rates of CDI were increased, training on and thorough implementation of proper glove use resulted in a clear decrease in the CDI incidence from 7.7 cases/1000 patient discharges before the intervention to 1.5 cases/1000 patient discharges after the intervention [115]. Thus, the use of appropriate gloves is an important infection control measure.

13.5. Discontinuation of isolation/contact precautions

Isolation/contact precautions should be continued as long as a patient with CDI has diarrhea or muddy stools. If the patient's stool remains *C. difficile*-positive after the resolution of diarrhea and possible sources of environmental contamination are present, such patients face an increased risk for recurrence post-treatment. Therefore, it is advisable to continue implementing contact precautions for at least 48 h after diarrhea has resolved, if possible.

There is no evidence that extended isolation reduces the frequency of CDI, and it is not practical to continue isolation precautions until all patients with CDI are discharged. However, once diarrhea is resolved, skin and environmental contamination are found in 60 % and 37 % of patients with CDI, respectively, while *C. difficile* is no longer detectable, mostly in their stools; moreover, the skin and environmental contamination rates increased again 1.4 weeks after treatment completion [91].

Thus, it is recommended to continue implementing isolation and contact precautions until all patients with CDI are discharged, even after CDI symptoms have resolved, if the incidence of CDI remains high while infection control measures are implemented.

13.6. Environmental management

13.6.1. Environmental cleaning

The surrounding environment of *C. difficile*-contaminated patients and the equipment used for their care act as *C. difficile* reservoirs, facilitating horizontal transmission. The use of chlorine-based detergents to reduce the environmental contamination of hospital wards where CDI rates were high has been reported to have reduced the incidence of CDI [141]. Various guidelines recommend wiping the environmental surfaces in hospital rooms using a sodium hypochlorite solution at a concentration higher than 1000 ppm after patients with CDI are discharged and have left. Some guidelines recommend the use of detergents containing at least 5000 ppm chlorine for at least 10 min in places that are likely to be contaminated with *C. difficile* [73]. However,

the use of sodium hypochlorite over a wide area or at a high concentration is undesirable due to its effects on human health and damage to materials and should be avoided for hand disinfection and daily environmental disinfection purposes. It is also important to clean the environmental surfaces and remove organic matter before a diluted sodium hypochlorite solution is used [140]. Newly available complex-type chlorine-based disinfectant cleaners are user-friendly because they have little chlorine odor and cause little damage to metal and plastic materials. These cleaners have been reported to reduce the infection rate of CDI [145].

13.6.2. Environmental disinfection

Hospital rooms should be cleaned and thoroughly disinfected immediately after patients have been discharged. The following three disinfection procedures have been reported to be effective for the environmental disinfection of hospital rooms: hydrogen peroxide vapor, 1000 ppm chlorine generators, and peracetic acid wipes [146]. For the disinfection of hospital rooms, Rutala et al. reported that ultraviolet (UV-C) irradiation could eradicate *C. difficile* in a shorter time than hydrogen peroxide vapor [147]. When the incidence of CDI was high in the Mayo Clinic, pulsed xenon ultraviolet irradiation was introduced for terminal cleaning on a trial basis for 6 months. As a result, the incidence of CDI was reduced to half of that of the control group and remained reduced for 2 years thereafter [148]. Furthermore, a systematic review by Kato et al. revealed that hydrogen peroxide reduced the frequency of environmental contamination with *C. difficile* far more effectively than hypochlorite salts and reduced the incidence of hospital-acquired CDI to a higher degree than other disinfection methods.

Ultraviolet irradiation also reduces the incidence of hospital-acquired CDI substantially more effectively than hypochlorite salts [149]. These no-touch cleaning techniques are expected to be effective means of environmental disinfection during CDI outbreaks.

A study in the United States has shown that the application of an environmental service model that successfully reduced CDI incidence in a medical institution to other medical institutions reduced the CDI incidence from 0.49 to 0.00 per 1000 patient-days ($p = 0.02$), reporting that it was beneficial for the reduction of CDI incidence and that the company engaged in environmental cleaning understood their role and educated the staff to implement proper environmental cleaning procedures [150]. However, a high turnover of cleaning staff in the company in charge of environmental cleaning required the company to offer frequent opportunities for education on proper cleaning and disinfection techniques [140].

13.6.3. Linen management

C. difficile-contaminated linen, such as sheets, should be treated as infectious linen; they should be placed gently in a plastic bag, and the bag should then be sealed to prevent the dirt on the surface from scattering.

14. CQ: Is education of healthcare workers and patients/families/visitors useful in reducing CDI?

Recommendation: The education of healthcare workers and patients/families/visitors is useful in reducing CDI.

Strength level: Providing education is weakly recommended.

Comment: It is important to start education on infectious diseases, including *C. difficile,* with student education and to continue providing healthcare workers with education tailored to their specific needs in clinical settings, depending on their professions, years of experience, and prior education frequency. During outbreaks, education and awareness on *C. difficile* transmission prevention should be provided to strengthen countermeasures. Educating CDI patients/families/visitors is important for their understanding of and cooperation in infection control during hospitalization and for the prevention of transmission via patients/families/visitors. Additionally, discharge education is necessary to provide patients/families with guidance in their daily lives.

14.1. Background and importance of the clinical question (CQ)

The *C. difficile* section was established in Guidelines for Infection Control in University Hospitals, 4th Edition, edited by the Japan Infection Prevention and Control Conference for National and Public University Hospitals in 2014 and revised in 2018 (5th edition) [151]. In 2018, the Japanese Clinical Practice Guidelines for Management of *Clostridioides (Clostridium) difficile* Infections by the Japanese Society of Chemotherapy and the Japanese Association for Infectious Diseases were published [102] and have clarified the directions for diagnosis, treatment, and management of *C. difficile* in Japanese clinical practice. *C. difficile* education for healthcare workers and patients/families/visitors based on these guidelines is important because it may reduce *C. difficile* transmission as well as interinstitutional differences in diagnosis, treatment, and management.

14.2. PICO

P (healthcare worker, patient, family member, and visitor): Healthcare workers engaged in CDI patient care, patients with CDI, their families, and visitors.

I (intervention): Providing education on CDI
C (comparison): No education provided.
O (outcome): Reduced *C. difficile* transmission within medical institutions and households.

14.3. Summary of evidence

In Europe and the United States, as the number of patients with CDI increases, so does the outbreak in medical institutions [69,152,153] and the number of patients with CDI in the community, such as those in nursing homes. The role of carriers as reservoirs is concerning [113, 154–156]. Because CDI is not suspected, misdiagnosis and delayed diagnosis can lead to delayed responses. Therefore, it is crucial to educate healthcare workers, patients, families, and visitors on *C. difficile*, which is why education-related items are included in various guidelines [157].

In Japan, a nationwide survey of 80 medical schools of universities or medical universities, 235 nursing schools of universities or nursing universities, and 74 schools of pharmacy of universities or universities of pharmacy on student education about *C. difficile* in 2013 showed that 76 % of medical schools/universities, 36 % of nursing schools/universities, and 62 % of schools/universities of pharmacy had lectures on "*C. difficile* infection control" [158]. A questionnaire survey of 2537 hospitals across Japan in 2013 on "recent epidemiology of *C. difficile* infection in Japan" revealed large differences among hospitals in terms of the number of CDI cases, timing of testing, and treatment strategies [159]. In Japan, it is crucial to educate and enlighten healthcare workers in accordance with the guidelines, as this will result in correct diagnosis, treatment, and management and may contribute to the reduction of *C. difficile* transmission.

Education for healthcare workers should cover basic knowledge, including an understanding of *C. difficile* and CDI, the tests necessary for its diagnosis (when to test, test flowchart, and interpretation of results), mode of transmission (such as fecal–oral transmission, survival for several months or longer in the environment, risk of transmission from environmental surfaces and hands), hand hygiene (ineffectiveness of alcohol for disinfection, importance of water and liquid soap), contact precautions (such as private-room isolation, appropriate wearing/removal of PPE), environmental cleaning, the importance of proper use of antibacterial agents, and CDI treatment [160–162]. Different healthcare professionals should receive education separately.

Education should be provided to not only medical doctors/dentists,

nurses, pharmacists, medical technologists, and radiology technologists but also workers in any job category related to medical institutions. The education of staff in charge of environmental cleaning is particularly important [163–165]. Ramphal et al. have reported that education of cleaning staff and enhanced cleaning decreased the incidence from 0.27 to 0.21 per 1000 patient-days [165]. Moreover, Eisler et al. reported that the education of workers in multiple professions, including environmental service staff; combined improvements in patient care; appropriate antibacterial use; and environmental cleaning resulted in a decrease in the incidence from 2.53 to 0.31 per 1000 patient-days within 2 years after the initiation of these measures [165].

Bundled interventions to reinforce all possible measures simultaneously, in addition to routine measures, have been reported to be effective during outbreaks [161,163,164,166,167]. Muto et al., Weiss et al., and Bommiasamy et al. have reported that the incidence per 1000 patient-days decreased from 4.8 to 3.0 [168], from 37.28 to 14.48 [169], and from 11.2 to 4.8 [170], respectively, after the introduction of the bundles. While the bundle components differed from one report to another, those that are commonly reinforced in reports include hand hygiene, environmental cleaning, patient isolation, contact precautions, appropriate use of antibacterial agents, education of healthcare workers, early detection of patients, and rapid diagnosis [167].

14.4. Healthcare workers should undergo education and awareness-building during non-outbreak times and outbreaks on a continuous basis

Patients and their families should receive education at the onset of an outbreak (during hospitalization) and discharge. The objectives of education at the outbreak onset are to develop their understanding of CDI and prevent transmission within healthcare institutions. Specifically, they receive explanations about the nature of CDI as an infectious disease, particularly highlighting the transmission via hands contaminated through direct patient contact (e.g., disposal of excrement, such as diapers/absorbent pads) and indirect contact with patient surroundings (e.g., items around the bed and toilet) [161,162,171]. To ensure their cooperation in transmission prevention, education contents should be designed to help them understand that hand disinfection with water and liquid soap should be used strictly because alcohol-based disinfectants are ineffective [160,172–174]; private-room isolation is required; patients' family members and visitors must wear PPE, such as gloves and disposable aprons, upon entering the patient's room, similar to healthcare professionals [161,171,173,174]; and the toilet in the private room used by the patient should be dedicated to patient use [171,174]. Patients' families should receive instructions about specific hygiene behaviors, such as disinfecting laundry with hypochlorous acid and disposing of diapers/absorbent pads [175,176]. It is particularly important to educate attending family members on diaper/absorbent pad handling because a report on a case of transmission via diapers used by children with CDI has shown that *C. difficile* was repeatedly detected in a sanitary room where attending family members disposed of patients' diapers/absorbent pads [177]. In addition to staff education, patient/family education should be strengthened when the number of patients in the medical institution is elevated (outbreak).

The objectives of education at the time of discharge are to prevent transmission at home (including transmission from carriers) and recurrence. Wearing PPE, such as gloves and disposable aprons, akin to healthcare workers, is advisable while the patient is experiencing diarrhea or loose stools. The patient's family members are encouraged to adopt these precautions to the greatest extent possible. Education at discharge should also include the following: the toilet door handle, flushing lever, and toilet seat should be wiped and disinfected with hypochlorous acid after they are used by the patient; precautions related to laundry and diaper/absorbent pad handling; other than those prescribed, antibacterial agents should not be used at the patient's discretion because antibacterial use may facilitate recurrence [171]; and when the patient visits a medical institution, to avoid recurrence, he/she should inform the attending physician that he/she had CDI [178]. Among these points, education on hand hygiene with S/W is of utmost importance; a study has reported an increased rate of implementation of hand hygiene by patients and a decrease in the incidence of CDI after staff and patient education over 6 months [179] (Table 8).

14.5. Quality of evidence for the overall outcome

C.

14.6. Summary of benefits

Education can be expected to decrease the incidence of CDI.

14.7. Summary of risks (adverse effects)

Unremarkable.

14.8. Summary of risks (burdens)

Time spent on education.

14.9. Benefit–risk balance

The benefits outweigh the risks because a decreased incidence can be expected.

14.10. Healthcare costs necessary for the intervention

Additional costs, including labor costs and educational material costs.

14.11. Feasibility of the intervention

Feasible.

14.12. Is the intervention perceived differently by patients/families/visitors and doctors/nurses/other medical staff?

Education for patients/families/visitors is different from education

Table 8
Recommendations in related clinical practice guidelines and other guidelines.

Guidelines	Education for	Recommendation level
ESCMID 2018 Guidance [163]	Healthcare workers, patients, families, and visitors	Strongly recommended
Japanese Society of Chemotherapy/Japanese Association for Infectious Diseases 2018 Clinical Practice Guidelines [102]	Families and visitors	NA
Scottish Health Protection Network 2017 Guidance [180]	Healthcare workers and visitors	Strongly recommended
APIC 2013 Guide [124]	Healthcare workers, patients, families, and visitors	NA
Public Health Agency of Canada 2013 Guidance [173]	Healthcare workers, patients, families, and visitors	NA
ASID/AICA 2011 Guidelines [174]	Healthcare workers, patients, families, and visitors	NA

NA, Not applicable; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; APIC, Association for Professionals in Infection Control and Epidemiology; ASID, Australasian Society for Infectious Diseases; AICA, Australian Infection Control Association.

for medical professionals, such as doctors/nurses/other medical staff. Education for medical professionals should be adjusted to the specific needs of their respective professions.

15. CQ: Is handwashing with soap and water only acceptable for healthcare workers to use for hygiene after CDI patient care?

Recommendation: Hand hygiene using soap and water(S/W), followed by a alcohol-based hand rub, is weakly recommended by healthcare workers after CDI patient care.

Strength level: Implementation is weakly recommended.

15.1. Comment

The skin of patients with CDI, the environment around their beds, and the hands of healthcare workers engaged in care and clinical practice for patients with CDI have been reported to be contaminated with *C. difficile*. *C. difficile* spores are highly resistant to alcohol. Hand hygiene with an alcohol-based hand rub (ABHR) is not very effective for the removal of *C. difficile*, whereas hand hygiene with S/W effectively removes *C. difficile*. Therefore, it is recommended that healthcare workers perform hand hygiene with S/W after removing their gloves following CDI patient care. Furthermore, hand hygiene with S/W, followed by ABHR, is recommended to reduce the risk of transmission of resistant bacteria. These recommendations also apply to asymptomatic CD carriers.

Healthcare workers are recommended to observe hand hygiene with S/W after CDI patient care, and this recommendation is consistent with multiple guidelines. However, opinions on ABHR differ from one guideline to another [157]. The SHEA/IDSA guidelines 2) and the APIC guidelines 3) recommend that healthcare workers should perform hand hygiene with S/W followed by ABHR after CDI patient care during outbreaks and hand hygiene with S/W only in non-outbreak times. However, this society has made a common recommendation for outbreak and non-outbreak times because each medical institution defines an outbreak differently and spread of resistant bacteria is also an issue to be considered when hand hygiene methods are compared.

15.2. Background and importance of the CQ

Hand hygiene is an important infection control measure to prevent the transmission of pathogens via human hands. Hand-hygiene methods to be used after CDI patient care should be selected based on the mode of transmission of resistant bacteria as well as the effectiveness of removing *C. difficile*. ABHR is not effective for the removal of *C. difficile*; however, it is highly effective for the removal of pathogens, including resistant bacteria, when no visible contamination can be found on the hands. The recommendation that after CDI patient care, healthcare workers should perform hand hygiene with S/W after gloves have been removed, followed by ABHR, is reasonable in order to reduce the transmission risk for both *C. difficile* and resistant bacteria.

15.3. PICO

P (Healthcare workers): Healthcare workers after CDI patient care and tests/examinations
I (intervention): S/W after gloves are removed, followed by ABHR
C (comparison): S/W after gloves are removed
O (outcome): Risk for transmission of resistant bacteria

15.4. Summary of evidence

C. difficile is highly resistant to disinfectants because it can form spores. Studies comparing the removal effectiveness between ABHR and S/W have reported that ABHR is not very effective in removing *C. difficile,* and S/W is more effective in removing *C. difficile* than ABHR [143,182,183]. A randomized, controlled crossover study on hand hygiene in volunteers by Oughton et al. has shown that hand hygiene with plain soap and lukewarm water most effectively removed *C. difficile*; the next most effective methods were hand hygiene with plain soap and water, hand hygiene with antibacterial soap and lukewarm water, and the use of alcohol-based wipes. Concurrently, ABHR was less effective in removing *C. difficile* [143]. Moreover, a study conducted by Jabbar et al. on volunteers reported that a person with *C. difficile* remaining on his/her hands after ABHR can easily transmit the bacterium to other people's hands by shaking their hands [182].

CDI patients' skin and bedside environment and asymptomatic CD carriers are contaminated with *C. difficile* [90,105,106,120,183,184]. Before hand hygiene was performed, *C. difficile* was detected in the hands of 9 of 28 (32 %) patients with CDI and 6 of 16 (38 %) asymptomatic CD carriers [183]. In addition to the hands, the skin of the forearms, thoracoabdominal area, and genital area of patients with CDI are contaminated with *C. difficile*, and *C. difficile* can easily adhere to gloves that contact the skin of these contaminated areas [184]. The environments around the beds of patients with CDI and asymptomatic CD carriers are contaminated with *C. difficile*, and the bedside environment of patients with CDI is more contaminated with *C. difficile* than that of asymptomatic CD carriers [90,105,184].

As a predictable result of contamination of the skin and bedside environment of patients with CDI and asymptomatic CD carriers with *C. difficile*, the hands of healthcare workers engaged in CDI patient care are contaminated with *C. difficile* [90,120,136]. It has been reported that the *C. difficile* contamination level in the hands of healthcare workers engaged with CDI patients rises as the frequency of their contact with the surroundings of patients increases [120]. Among 35 healthcare workers engaged in CDI patient care, *C. difficile* was detected in the hands of one healthcare worker before care and in the hands of an additional 20 healthcare workers after care. In this study, *C. difficile* was detected in the hands of 14/16 healthcare workers who did not wear gloves during patient contact, despite performing hand hygiene with S/W after care, while *C. difficile* was not detected in the hands of healthcare workers who wore gloves during patient contact [90]. Non-use of gloves is an important risk factor for *C. difficile* contamination of healthcare workers' hands; however, *C. difficile* contamination of the hands of healthcare workers who wore gloves has been reported to occur when they make frequent contact with patients with CDI [136].

Accordingly, healthcare workers are recommended to perform hand hygiene with S/W after they remove their gloves, which is highly effective in removing *C. difficile*, after they have completed care services for patients with CDI and asymptomatic CD carriers. However, there is a concern that adherence to hand hygiene with S/W may be reduced due to problems with sink access and the time required. The rate of implementing S/W after CDI patient care was 14.2 %, and multivariate analysis showed an association between the S/W implementation rate and the distance between the patient zone and sink (adjusted odds ratio [OR], 0.90; 95 % confidence interval [CI], 0.84–0.97; $p = 0.01$) [185]. Hand hygiene with S/W requires implementation monitoring as there is a risk of a decrease in hand-hygiene adherence.

Furthermore, hand-hygiene methods after caring for patients with CDI and asymptomatic CD carriers should be selected based on the transmission of resistant bacteria as well as the effectiveness of removing *C. difficile*.

As a major resistant bacterium, co-infection of *C. difficile* with vancomycin-resistant enterococci (VRE) has been reported [186–189]. Of 158 toxigenic CD isolates, 88 (55.7 %) were from cases of co-infection with VRE. Moreover, the 88 patients with *C. difficile*-VRE co-infection were significantly more commonly co-infected with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter* spp. than CDI patients without VRE co-infection ($p = 0.002$ and $p = 0.006$, respectively) [187]. In a study investigating the co-infection rates of toxigenic and nontoxigenic CD strains with VRE, co-infection was found in 19/158 overall cases (12.1 %), 15/88 cases of toxigenic *C. difficile* strains (17.0

%), and 4/70 cases of nontoxigenic *C. difficile* strains (5.7 %); thus, the rate of co-infection with VRE differed significantly between toxigenic *C. difficile* strains and nontoxigenic *C. difficile* strains ($p < 0.05$) [189]. It has been reported that the rate of MRSA carriers among healthcare workers was around 5 %, and the rates of MRSA carriers among nurses and nursing assistants, who have contact more frequently with patients among healthcare workers, were higher than those among other healthcare workers [190–192]. If the hands are not visibly soiled, ABHR is effective for preventing the transmission of pathogens, including resistant bacteria [193–197], and the introduction of ABHR has been reported to significantly reduce the rates of MRSA and VRE infections [193,194,196]. Therefore, to reduce the risk of resistant bacteria transmission, hand hygiene with S/W, followed by ABRH, is recommended to be performed after CDI patient care.

S/W is more likely to cause skin irritation on the hands than ABHR, and the simultaneous use of S/W and ABHR is generally not recommended [198,199]. Because S/W removes sebum, it often causes skin irritation and dryness. Healthcare workers engaged in CDI patient care are prone to rough hands due to more frequent S/W than usual. Thus, they should perform skin care in parallel with hand hygiene.

Recently, patients undergoing medical treatment have resided in a wider variety of places. It is preferable for family members providing CDI patients with home care to perform hand hygiene and wear PPE, akin to healthcare workers, and thus receive such education.

15.5. Quality of evidence for the overall outcome

C (recommended by experts).

15.6. Summary of benefits

Reduction of risk for transmission of *C. difficile* and resistant bacteria.

15.7. Summary of harms (adverse effects)

The recommended S/W easily causes skin irritation on hands.

15.8. Summary of harms (burden)

S/W requires time and sink access for hand hygiene.

15.9. Benefit–harm balance

The benefits outweigh the harms because transmission of *C. difficile* and resistant bacteria is prevented.

15.10. Healthcare costs necessary for the intervention

Same as the costs required for routine infection control.

15.11. Feasibility of the intervention

Feasible.

15.12. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

15.13. Recommendations in related clinical practice guidelines

See the Table 9.

Table 9
Recommendations in related other clinical practice guidelines.

	Hand hygiene	Recommendation level
WSES 2019 Guidelines [200]	Hand hygiene with soap and water is the cornerstone of the prevention of *C. difficile* infection. Hand hygiene, contact precautions, and good cleaning and disinfection of patient care equipment and the environment should be used by all health-care workers in contact with any patient with known or suspected CDI.	1B
IDSA/SHEA 2017 Guidelines [71]	In routine or endemic settings, perform hand hygiene before and after contact with a patient with CDI and after removing gloves with either soap and water or an alcohol-based hand-hygiene product.	Strongly recommended
	In a CDI outbreak or hyperendemic setting, perform hand hygiene with soap and water preferentially instead of alcohol-based hand-hygiene products for a patient with CDI.	Weakly recommended
APIC 2013 Guide [181]	The use of soap and water for hand hygiene over the use of ABHRs after caring for a patient with CDI is not recommended in a non-outbreak setting.	NA

WSES, World Society of Emergency Surgery; IB, strong recommendation, moderate-quality evidence, IDSA/SHEA, Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; APIC, Association for Professionals in Infection Control and Epidemiology; NA, Not applicable.

16. CQ: Is washing hands with soap and water only acceptable for CDI patients to use?

Recommendation: Hand hygiene with soap and water(S/W) is weakly recommended to be used by patients with CDI. Patients who have difficulty performing hand hygiene with S/W routinely may use alternatives to S/W, such as single-use wipes, to wipe their hands.

Strength level: Implementation is weakly recommended.

16.1. Comment

The hands of patients with CDI have been reported to be contaminated with *C. difficile*. Patients with CDI have a risk of transmitting *C. difficile* to the environment, healthcare workers, and other patients via their hands. Hand hygiene with an ABHR is not effective for removing *C. difficile*, whereas hand hygiene with S/W effectively removes *C. difficile*. Therefore, it is recommended that patients with CDI perform hand hygiene with S/W. Furthermore, hand hygiene with S/W, followed by ABHR, should be considered to reduce the risk of transmitting resistant bacteria because it has been reported that hospitalized patients are susceptible to colonization by resistant bacteria and that some patients are colonized simultaneously by resistant bacteria and *C. difficile*.

For patients who have difficulty performing hand hygiene with S/W because they have a low-performance status (PS), it is recommended to wipe their hands with an alternative to S/W, such as premoistened wipes.

These recommendations also apply to asymptomatic CD carriers.

16.2. Background and importance of the CQ

It has been reported that the hands of hospitalized patients are often contaminated with pathogens that can cause healthcare-associated infections. If the hands of a patient with CDI are contaminated with *C. difficile*, *C. difficile* can be transmitted to the environment, healthcare workers, and other patients via the hands of that patient. Thus, it is

important to promote hand hygiene in patients with CDI.

C. difficile is highly resistant to alcohol and is effectively removed by S/W. Thus, it is significant in the prevention of *C. difficile* transmission to recommend that patients with CDI perform hand hygiene with S/W. If a patient's PS limits routine hand hygiene using S/W, such patients must remove contaminations physically by wiping their hands with an alternative to S/W, such as premoistened wipes, as recommended.

16.3. PICO

P (patient, population, problm): Patients with CDI
I (intervention): Hand hygiene using S/W; alternatively, hand wiping with premoistened wipes or similar methods for patients with a low PS
C (comparison): Non-implementation of hand hygiene using S/W or hand wiping with premoistened wipes or similar methods for patients with a low PS
O (outcome): Risk of *C. difficile* transmission

16.4. Summary of evidence

It has been reported that pathogens causing healthcare-associated infections, such as MRSA, VRE, *Acinetobacter* spp., and gram-negative bacteria, are detected in the skin of patients' hands, arms, abdominal area, and genital areas [201–205]. Pathogens colonizing the skin of patients are also detected in the surroundings of their beds [203–205]. Similarly, the skin and bedside environment of patients with CDI and asymptomatic CD carriers are contaminated with *C. difficile* [90,91,105,106,120,183,184,202,206]. A study using the glove juice method to detect bacteria on the hands of 100 patients hospitalized for at least 48 h has shown that one or more pathogens were detected on the hands of 39 patients and that *C. difficile* was detected on the hands of 14 patients [202]. Prior to the implementation of hand-hygiene measures, *C. difficile* was detected on the hands of 9/28 (32 %) patients with CDI and 6/16 (38 %) asymptomatic CD carriers [183].

Patients' hand hygiene is important to prevent pathogen transmission because pathogens are detected on the hands of some patients. However, in reality, hand hygiene is not adequately performed by patients.

Hospitalized patients exhibit a reduced frequency of performing hand hygiene during their hospitalization in comparison to their routine practices at home, despite being cognizant of the importance of hand hygiene during hospitalization [202]. It has been reported that only half of the nurses explained to patients the importance of hand hygiene while being aware of the importance of patients' hand hygiene [207].

Therefore, efforts to promote hand hygiene among patients and their families have been initiated, which have resulted in reduced rates of MRSA, VRE, and CDIs [179,208,209]. Promotion of patient hand hygiene before meals, care unit efforts for improved patient hand hygiene, and hand hygiene reminders to visitors, which were conducted as a bundle to promote patient hand hygiene, significantly reduced the rate of CDI after the intervention compared to that before the intervention ($p = 0.0009$) [208]. After healthcare workers were educated on the promotion of patient hand hygiene, the frequency of patient hand hygiene increased significantly ($p < 0.0001$) and the standardized incidence of CDI decreased significantly ($p < 0.05$) compared to that before the intervention [179]. In both interventions, patients used the hand-hygiene method consisting of S/W, followed by hand wiping with alcohol-based premoistened wipes at the bedside. Although these were single-center studies, these reports highlight the importance of promoting patient hand hygiene to prevent *C. difficile* transmission.

Hand hygiene with S/W is recommended for patients with CDI and asymptomatic CD carriers. A study comparing ABHR and S/W has reported that ABHR minimally removes *C. difficile* and that S/W removes *C. difficile* more effectively than ABHR [143,182,183]. If patients' PS conditions preclude hand hygiene with S/W, they are recommended to wipe their hands with S/W alternatives, such as premoistened wipes, at the bedside.

Furthermore, hand-hygiene methods for patients with CDI and asymptomatic CD carriers should be selected based on the transmission of resistant bacteria as well as the effectiveness of removing *C. difficile*. As a major resistant bacterium, the co-infection of *C. difficile* with VRE has been reported [186–189]. Moreover, patients co-infected with MRSA or *Acinetobacter* spp. were found to be significantly more common among patients with *C. difficile*-VRE co-infection than those among CDI patients without VRE co-infection [208]. Therefore, patients with CDI may be able to reduce the risk of transmitting resistant bacteria by performing hand hygiene with S/W, followed by ABHR.

Four distinct instances of patient hand hygiene (before and after touching wounds or devices, before meals, after excretion, and before and after entering hospital rooms) have been proposed [210]. In addition to the aforementioned four instances, five more instances of patient hand hygiene have been explored, including one when healthcare personnel enter hospital rooms [211].

16.5. Quality of evidence for the overall outcome

C (recommended by experts).

16.6. Summary of benefits

Promotion of patient hand hygiene with S/W and hand wiping with premoistened wipes by patients with low PS can reduce the risk of *C. difficile* transmission.

16.7. Summary of harms (adverse effects)

There are no particular harms.

16.8. Summary of harms (burden)

There are no particular harms.

16.9. Benefit–harm balance

The benefits outweigh the harms.

16.10. Healthcare costs necessary for the intervention

Same as the costs required for routine infection control.

16.11. Feasibility of the intervention

Feasible.

16.12. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

16.13. Recommendations in related clinical practice guidelines

See the Table 10.

17. CQ: Should long-sleeved gowns be worn during CDI patient care?

Recommendation: It is recommended to wear PPE while being in contact with patients diagnosed with or suspected of having CDI; however, there are no clear indications as to which of the long-sleeved or sleeveless gowns should be selected. Wearing long-sleeved gowns is weakly recommended during CDI patient care.

Table 10
Recommendations in related other clinical practice guidelines.

	Hand hygiene	Recommendation level
IDSA/SHEA2017 Guidelines[26)]	Encourage patients to wash hands and shower to reduce the burden of spores on the skin.	Good Practice Recommendation
APIC2013 Guide[27)]	To promote patients' understanding of feasible preventive measures, including hand hygiene, in order to reduce CDI transmission	NA

IDSA/SHEA; Infectious Diseases Society of America/Society for Healthcare Epidemiology of America APIC; Association for Professionals in Infection Control and EpidemiologyNA; Not applicable.

Strength level: Weakly recommended.

Comment: Gloves were worn alone or in combination with long-sleeved gowns in many reports showing the effectiveness of PPE as a CDI control measure. However, evidence-based discussion on the differences in the protection effectiveness between use versus non-use of PPE or among different types of PPE is difficult (e.g., long-sleeved versus sleeveless, different materials), as few studies have evaluated CDI transmission with a sole focus on PPE use. Large numbers of *C. difficile* are found on the skin of patients with CDI and on environmental surfaces around them, which can contaminate the hands and white coats of medical professionals upon contact. PPE is advised for healthcare workers who will come into contact with CDI patients and their surroundings because it theoretically prevents direct contact with patients or environmental surfaces and may reduce the risk of infection with *C. difficile*. In terms of PPE to protect the trunk, it is unclear whether and how the effectiveness of long-sleeved gowns and sleeveless aprons vary. The decision should be based on the patient's contact conditions and associated risks.

17.1. Background and importance of the CQ

CDI is transmitted primarily by oral ingestion of *C. difficile* spores via direct contact with patients and their surroundings or indirectly mediated by hands and items contaminated with *C. difficile*. Therefore, CDI transmission may be prevented by wearing PPE to prevent healthcare workers' hands and white coats from being contaminated with *C. difficile*.

In Japan, contact precautions include both long-sleeved gowns and sleeveless aprons used as PPE to protect the trunk. Long-sleeved gowns can protect most parts of the body, including the arms and collar, but not the face; however, they have some disadvantages, such as the fact that the process of donning and doffing takes some time, users may feel hot, and they are expensive. On the contrary, sleeveless aprons are easier to don and doff and are less expensive than long-sleeved gowns; however, they expose the shoulders and arms. The impact of the use/non-use of PPE and the different types of PPE on the prevention of CDI transmission remains unknown and warrants further investigation.

17.2. PICO

P (facility requirements): CDI patient rooms
I (intervention): Healthcare workers wear gloves and sleeveless aprons before they enter the patient rooms.
C (comparison): Healthcare workers wear gloves and long-sleeved gowns before they enter the patient rooms.
O (outcome): The infection rate or prebention of CDI and the count of remnant *C. difficile*

17.3. Summary of evidence

Large numbers of *C. difficile* are found on CDI patients' skin, the devices used by these patients, and their surroundings [90,91,105,108,212,213]. They have also been detected on devices used for patients and on white coats of medical professionals [214]. Moreover, the hands of healthcare workers engaged in CDI patient care were *C. difficile*-positive at a higher rate than the hands of healthcare workers engaged in non-CDI patient care [136,215]. A study on hand contamination with *C. difficile* has identified feces contact (odds ratio: 2.78, 95 % confidence interval: 1.42–5.45, $p = 0.003$) and contact without gloves (OR: 6.26, 95 % CI: 1.27–30.78, $p = 0.02$) as independent risk factors [136]. Strict adherence to glove use when bodily fluids and excretions from all patients are handled has also been reported to have significantly reduced the incidence of CDI from 7.7 to 1.5 cases per 1000 patient discharges [115]. Therefore, healthcare workers are strongly recommended to wear gloves during contact with CDI patients because gloves prevent their hands from being contaminated with *C. difficile*, and this may reduce CDI transmission.

Long-sleeved gowns have been studied in many reports on the effectiveness of PPE other than gloves; however, these studies have reported the results from multifaceted interventions, including hand hygiene, environmental disinfection, isolation and/or cohorting, and appropriate antibacterial use [163]. Very few studies have focused exclusively on the effectiveness of PPE during contact with CDI patients, making it difficult to determine which intervention is the most effective. Furthermore, no studies have compared long-sleeve gowns and sleeveless aprons in terms of CDI transmission. Meanwhile, a study has shown that long-sleeved gowns may be more effective than sleeveless aprons as PPE for the protection of healthcare workers from contamination with pathogens of highly infectious diseases, such as Ebola hemorrhagic fever, severe acute respiratory syndrome, and coronavirus disease 2019 [216].

In a review of the adherence to and effectiveness of *C. difficile* prevention bundles, the incidence of CDI after intervention was lower than that before intervention in 26 studies [167]. Hand hygiene and environmental cleaning were the most common components of these bundles, followed by isolation and/or cohorting. Other components included staff education, appropriate use of antibacterial agents, and system changes. Contact precautions, including PPE use, were implemented in 73 % (19/26) of the studies.

Therefore, although there is no high-quality evidence evaluating the effectiveness of wearing PPE, such as gloves and long-sleeved gowns/sleeveless aprons, for preventing CDI, healthcare workers may be able to reduce the chance of infection through direct or indirect contact with CDI patients and their surroundings by wearing PPE. Furthermore, healthcare workers are strongly recommended to use PPE in combination with other CDI control measures that are likely to be effective, such as hand hygiene, environmental disinfection, isolation/cohorting, and appropriate antibacterial use. However, one cannot conclude whether long-sleeved gowns or sleeveless aprons should be selected as a CDI control measure. Specific PPE should be chosen based on conditions of contact with patients and environments likely to be contaminated with feces. Long-sleeved gowns are desirable, particularly when healthcare workers are going to perform continence care or genital care, which is associated with a high likelihood of having contact with feces or areas where *C. difficile* is frequently detected (anus, genital area, and groin) [71].

17.4. Quality of evidence for overall outcome

B (recommended in various guidelines).

17.5. Summary of benefits

The use of PPE by healthcare workers prevents or reduces contamination of the hands and clothes with *C. difficile* and theoretically reduces the chance of transmission to other patients.

17.6. Summary of harms (adverse effects)

Contact precautions using PPE are associated with concerns regarding psychological effects on patients, such as anxiety, depression, and humiliation.

17.7. Summary of harms (burden)

Healthcare workers must receive instructions and undergo assessments to ensure their adherence to proper methods for donning and doffing PPE.

17.8. Benefit–harm balance

The benefits outweigh the harms because CDI transmission is prevented.

17.9. Healthcare costs necessary for the intervention

Same as the costs required for routine contact precautions.

17.10. Feasibility of the intervention

Feasible.

17.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

17.12. Recommendations in related clinical practice guidelines

SHEA/IDSA Guidelines (2017) [167]: Strongly recommended to wear gloves and gowns during CDI patient care.

ESCMID Guidance: Strongly recommended [163]: Strongly recommended to wear gloves and gowns during CDI patient care.

APIC guide (2013) [124]: The recommendation level is not stated.

18. CQ: Can contact precautions for patients with CDI be discontinued when diarrhea resolves?

Recommendation: The use of contact precautions for patients diagnosed with CDI or patients suspected of having CDI is strongly recommended; however, there are no clear indications to recommend the specific duration of using contact precautions. The application of contact precautions should persist for at least 48 h after the resolution of diarrhea, as a guide.

Strength level: Use of contact precautions for patients diagnosed with CDI or patients suspected of having CDI is strongly recommended.

Comment: Contact precautions for patients diagnosed with CDI or patients suspected of having CDI include isolation in single rooms, each of which has a dedicated toilet and hand-washing facility; use of dedicated devices and supplies; donning and doffing PPE when someone enters and leaves the patient room; and environmental disinfection. When a sufficient number of single rooms are not available, patients with CDI may be cohorted in groups. Use of these contact precautions for patients diagnosed with CDI or patients suspected of having CDI is recommended; however, clear recommendations for initiating and discontinuing the contact precautions have not been established because of limited relevant evidence.

18.1. Background and importance of the CQ

Hospital environments contaminated with *C. difficile* can be *C. difficile* reservoirs. Therefore, it is necessary to identify patients suspected of having CDI early and initiate contact precautions promptly. Regarding the discontinuation of precautions, some guidelines recommend their continuation until 48 h after the resolution of diarrhea. However, a definitive rationale for this 48-h period is lacking, and there is limited discussion about the duration of using contact precautions, including when to initiate and discontinue the precautions. It is important to study the duration of contact precautions.

18.2. PICO

P (patients): Symptomatic patients with CDI
I (intervention): Isolation in single rooms/cohorting
C (comparison): No isolation in single rooms/cohorting
O (outcome): Rate of CDI transmission

18.3. Summary of evidence

C. difficile has been reported to survive for long periods of time in healthcare environments and more than 5 months in dry environments because it is a spore-forming bacterium, making it highly resistant to disinfectants [105,217,218]. Hospital rooms used by patients with CDI are contaminated with *C. difficile* at higher rates than those used by asymptomatic carriers or *C. difficile*-negative patients [105,217,218], We found that healthcare personnel frequently acquired *C. difficile* on their hands when caring for patients who have recovered from CDI (<6 weeks after treatment) and were no longer under contact precautions [219]. Moreover, a study using fecal, skin, and environmental samples of 52 CD-infected patients reported that 60 % and 37 % of the skin and environmental samples, respectively, collected at the time of resolution of diarrhea were contaminated with *C. difficile*, while the mean number of days to resolution of diarrhea was 4.2 days and the bacterium was undetectable in most fecal samples by the time of resolution of diarrhea [220]. Fidaxomicin, a therapeutic agent for CDI, is sporicidal and may be associated with shorter lengths of time to resolution of diarrhea after initiation of treatment for CDI. Studies comparing hospital room contamination levels after treatment of hospitalized CDI patients with different therapeutic agents have reported that the rooms of patients treated with fidaxomicin had less environmental contamination than those of patients treated with metronidazole and/or vancomycin [168,169]. As for the effectiveness of isolation in single rooms, refurbishment of all ICUs to single rooms equipped with hand-washing facilities could reduce the incidence of CDI by 43 % (95 % CI: 7%–65 %), while other potential confounding factors, such as antibacterial agents used, were not analyzed [221]. It has also been reported that patients placed in two-bed rooms tend to acquire CDI at a higher rate than patients placed in single rooms (17 % vs. 7 %; $p = 0.08$) [217].

Isolation or cohorting is commonly used as a component of infection control bundles for CDI [71,167,222–224]. In a review of the adherence to and effectiveness of *C. difficile* prevention bundles in hospitalized patients, the incidence of CDI after intervention was lower than that before intervention in 26 studies. The most common components of the bundles were hand hygiene and environmental cleaning; other components included isolation and/or cohorting, PPE use, staff education, appropriate antibacterial use, and system changes [124]. Contact precautions were applied for various durations; for example, they were initiated at the onset of diarrhea, when CDI was suspected, or when CDI was diagnosed and discontinued at the time of resolution of diarrhea or when patients were discharged [124].

WSES, World Society of Emergency Surgery; IDSA/SHEA, Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; APIC, Association for Professionals in Infection Control and Epidemiology; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; CDC, Centers for Disease Control and Prevention

The CDC guidelines for isolation precautions [224] recommend the use of contact precautions over the duration of CDI, and the APIC guide

[124], IDSA/SHEA 2017 Guidelines [71], APIC guide [181], ESCMID/ESGCD guidance [163], and WSES guidelines [200] recommend the maintenance of contact precautions for at least 48 h after resolution of diarrhea. However, no clear recommendations on the duration of contact precautions can be made because there are no evaluation data available on the duration of contact precautions and no studies have shown a decrease in the incidence of CDI with an increase in the duration of contact precautions.

A recommended timeframe for contact precautions in patients diagnosed with CDI or patients suspected of having CDI is deemed to be a minimum of 48 h following diarrhea resolution; however, when the rate of CDI remains high despite the implementation of standard infection control measures for CDI, environmental contamination may underlie transmission and extension of contact precautions, including isolation until patient discharge, should be considered. Further evaluation on this issue is awaited.

18.4. Quality of evidence for overall outcome

B (recommended in various guidelines).

18.5. Summary of benefits

Implementation of contact precautions for patients diagnosed with CDI or suspected of having CDI can prevent transmission of CDI.

18.6. Summary of harms (adverse effects)

Because of the lack of clarity regarding the optimal timing for initiation, discontinuation, and duration of contact precautions to effectively prevent CDI transmission, potential drawbacks include increased human resource use and cost burdens due to the implementation of excessive measures. Additionally, patients may experience psychological effects, including anxiety, depression, and humiliation.

18.7. Summary of harms (burden)

Single-room costs associated with single-room isolation and PPE costs are required.

18.8. Benefit–harm balance

Benefits outweigh harms because CDI transmission is prevented.

18.9. Healthcare costs necessary for the intervention

Single-room costs associated with single-room isolation and PPE costs are required.

18.10. Feasibility of the intervention

Feasible.

18.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

18.12. Recommendations in related clinical practice guidelines

Continued implementation for the duration of the illness or for 48 h after the resolution of diarrhea is recommended.

Duration of contact precautions in various guidelines are shown in the Table 11.

Table 11
Durations of contact precautions in various guidelines.

CDC 2007 [224]	APIC 2013 [124]	IDSA/SHEA 2017 [71]	ESCMID 2018 [163]	WSES 2019 [200]
Over the duration of the illness	For 48 h after the resolution of diarrhea	For 48 h after the resolution of diarrhea	For 48 h after recovery of normal bowel movement	For 48 h after the resolution of diarrhea

WSES, World Society of Emergency Surgery; IDSA/SHEA, Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; APIC, Association for Professionals in Infection Control and Epidemiology; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; CDC, Centers for Disease Control and Prevention.

19. CQ: Is cohorting selected when isolation of patients with CDI in private rooms is not possible?

Recommendation: It is weakly recommended that patients with CDI be cohorted separately from patients positive for other resistant bacteria.

Strength level: Implementation is weakly recommended.

Comment: In principle, isolation in private rooms is recommended for patients with CDI, including patients suspected of having CDI; however, cohorting is recommended when isolation in private rooms is difficult. When patients are cohorted, it is recommended to provide each patient with a portable toilet, define the patient traffic and care flow clearly, and keep the patients separate from other patients with resistant bacteria.

19.1. Background and importance of the CQ

Isolation of patients with CDI, including patients suspected of having CDI, is recommended in various guidelines based on past evidence and is practiced in healthcare institutions in Japan and other countries [71,102,163]. The environment surrounding patients with CDI is known to be contaminated with *C. difficile* spores [90,113,120,225], and isolation in private rooms is desirable in principle; however, some institutions' building structures and available facilities may not be suited for isolation in private rooms. The practice of cohorting patients with CDI into groups is employed in such cases. Cohorting, however, is reportedly associated with higher recurrence rates [142], prompting a need to review its utility.

19.2. PICO

P (patients): Symptomatic patients with CDI
I (intervention): Patients are cohorted.
C (comparison): Patients are not cohorted.
O (outcome): Rate of CDI transmission and rate of recurrence

19.3. Summary of evidence

The environment surrounding patients with CDI is known to be contaminated with *C. difficile* spores; however, *C. difficile* is also detected in non-CDI patients and hospital rooms of non-CDI patients in some cases, and it has been reported that spores surviving in the environment for a long time are involved mechanistically in such cases [90].

Spores can survive in the environment for several weeks to months [105,226], and the hands of healthcare workers can also be contaminated depending on the level of environmental contamination [120]. Thus, the early identification of patients with CDI and the implementation of appropriate infection control measures are important to prevent transmission. The usefulness of isolation precautions has been evaluated in several cohort studies. In a prospective cohort study, McFarland et al. reported that CDI patients who were placed in two-bed rooms transmitted the bacterium to roommates at a high rate [90].

Teltsch et al. investigated changes in the rate of detection of microorganisms subject to infection control in an intensive care unit that had two 12-bed rooms and was renovated to have 24 private rooms. They found that the detection rate of *C. difficile* decreased by 43 % after the renovation [220]. Therefore, it is commonly recommended to isolate patients with CDI, including those suspected of having CDI, in private rooms whenever possible. Ideally, these rooms should be equipped with dedicated toilets and hand-washing facilities [71,102,124,200,227]. However, isolation in private rooms is not possible in some institutions owing to the building structures and available facilities. In such cases, patients with fecal incontinence are preferentially placed in private rooms [71,140], and other patients with CDI are cohorted; the infection rate may increase among cohorted patients. In a retrospective study investigating the recurrence rate among CDI patients cohorted, Islam et al. reported the results of a multivariate analysis showing that the recurrence rate among cohorted patients was significantly higher (OR: 3.94; 95 % CI: 1.23–12.65; p = 0.021) [142]. Accordingly, it is recommended that each patient cohorted is provided with a portable toilet, the patient traffic and care flow clearly determined, and that CDI patients are kept separate from patients with other resistant bacteria in principle [71,102,161].

19.4. Quality of evidence for the overall outcome

B (recommended in various guidelines).

19.5. Summary of benefits

Cohorting patients with CDI, including patients suspected of having CDI, is recommended in various guidelines and may reduce transmission of CDI.

19.6. Summary of harms (adverse effects)

Implementation of cohorting may result in an increased rate of recurrence.

19.7. Summary of harms (burden)

As patients with CDI have to be cohorted separately from patients with other resistant bacteria, cohorting may affect the bed occupancy rate.

19.8. Benefit–harm balance

Given the burden on patients and the health economic impact associated with CDI, the benefits outweigh the harms, although cohorting may affect the bed occupancy rate.

19.9. Healthcare costs necessary for the intervention

Some beds may have to be left vacant when cohorting for different bacteria for infection control.

19.10. Feasibility of the intervention

Feasible; as long as the institution can establish a cohorting system.

19.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

Each institution may have different criteria for cohorting or isolation in private rooms.

19.12. Recommendations in related clinical practice guidelines

Descriptions in related guidelines of various societies are summarized in the Table 12. Many societies recommend isolation in private rooms as a general rule and cohorting when isolation in private rooms is difficult [71,73,102,124,227].

20. CQ: If body-contacting medical devices are dedicated for CDI patient use, would it effectively reduce healthcare-associated CDI?

Recommendation: The use of dedicated or disposable medical devices, such as thermometers and stethoscopes, for patients with CDI, is weakly recommended.

Comment: High-level disinfectants, such as glutaraldehyde and phtharal, as well as potassium peroxymonosulfate, are commonly used as disinfectants for medical devices/instruments. These are sporicidal.

20.1. Background and importance of the CQ

Control of nosocomial CD infection requires the prevention of spore transmission. Caution must be exercised to prevent transmission via

Table 12
Isolation precautions for CDI in various guidelines.

	Isolation precautions	Recommendation level	Duration of isolation precautions
Japanese Society of Chemotherapy/ Japanese Association for Infectious Diseases Guidelines 2018 [102]	Isolation in private rooms or cohorting	NA	While diarrhea/ muddy stool (BSS ≥5) persists For at least 48 h after the resolution of diarrhea, if possible
IDSA/SHEA 2017 Guidelines [71]	Isolation in private rooms or cohorting	C-III	For 48 h after the resolution of diarrhea
APIC 2013 Guide [124]	Isolation in private rooms or cohorting	NA	For 48 h after the resolution of diarrhea
ACG 2013 Guidelines [73]	Isolation in private rooms or cohorting	Strongly recommended	Until the resolution of diarrhea
ASID/ACIPC 2019 Position Paper [228]	Isolation in private rooms or placement in multi-bed rooms with portable toilet use and thorough contact infection control measures	NA	For 48 h after the resolution of diarrhea
ESCMID 2018 Guidelines [163]	Isolation in private rooms or placement in multi-bed rooms with portable toilet use and thorough contact infection control measures	Strongly recommended	For 48 h after the resolution of diarrhea

ACG, American College of Gastroenterology; APIC, Association for Professionals in Infection Control and Epidemiology; IDSA/SHEA, Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ASID/ACIPC, Australasian Society for Infectious Diseases/Australasian College of Infection Prevention and Control; NA, Not applicable.

toilets (including door handles, various switches, and paper holders) used by CDI individuals and environmental contamination associated with incontinence care for individuals with fecal incontinence, including changing diapers and genital washing. Pulse oximeters, sphygmomanometer cuffs, and electrocardiographic leads are also frequently contaminated with *C. difficile* spores (75%–100 %) [229]. While patients with CDI are isolated in single rooms, it should be assumed that all environmental surfaces in the patients' rooms, as well as the patients themselves, are contaminated with *C. difficile* spores. Therefore, it is desirable to dedicate pulse oximeters, thermometers (excluding noncontact types) [213,230], sphygmomanometer cuffs [212], and stethoscopes [231], as well as urine bottles and toilets, for CDI patient use. Common disinfectants that are sporicidal against *C. difficile* spores include sodium hypochlorite, glutaraldehyde, and potassium peroxymonosulfate; however, sodium hypochlorite cannot be used for electronic medical devices containing metal components. Alternatively, the use of disposable products is desirable if they are available.

20.2. PICO

P (patients): Patients with CDI
I (intervention): Implementation of disinfection and dedicated use of medical devices/instruments
C (comparison): Non-implementation of disinfection and dedicated use of medical devices/instruments
O (outcome): Decreased incidence of nosocomial CDI

20.3. Summary of evidence

No meta-analysis studies on the reduction of CDI incidence through the use of dedicated medical devices/instruments such as pulse oximeters, electronic thermometers, and stethoscopes have been reported. However, a significant decrease in the incidence of *C. difficile*-associated diarrhea has been reported ($p < 0.05$) after thermometers were switched to disposable ones [230]. Contact precautions are required to be in place as the transmission of *C. difficile* spores in hospitals occurs via the fecal–oral route and is mediated by the hands of healthcare workers and patients with CDI as well as medical instruments [59]. Actual cases of transmission via toilets and rectal thermometers have been reported [111]. Thus, medical devices/instruments that come in contact with CDI patients should not be shared with other patients, as spores adhere to them when used by patients with CDI and are likely to continuously contaminate them. Medical devices/instruments for which disposable equivalents are not available should be dedicated for CDI patient use and should be disinfected as needed if they are used for other patients. For disinfection, 1 % potassium peroxymonosulfate, which causes minimal metal corrosion and has been reported to reduce *C. difficile* spores by 10^5 CFU/mL after exposure to the solution for 20 min at room temperature [232], is recommended.

20.4. Quality of evidence for the overall outcome

C.

20.5. Summary of benefits

Reduced transmission of *C. difficile* spores is expected.

20.6. Summary of harms (adverse effects)

High-level disinfectants that are sporicidal have strong effects on human health. Thus, caution should be exercised regarding residues on instruments after the application of such disinfectants. Adequate ventilation and skin contact precautions are also required during disinfection.

20.7. Summary of harms (burden)

High-level disinfectants and potassium peroxymonosulfate are relatively expensive.

20.8. Benefit–harm balance

Benefits exceed harms.

20.9. Healthcare costs necessary for the intervention

Costs for disinfectants and disposable thermometers are necessary.

20.10. Feasibility of the intervention

Feasible.

20.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors/nurses/other medical staff?

No.

20.12. Recommendations in related clinical practice guidelines

The IDSA/SHEA 2017 Guidelines strongly recommend the use of dedicated noncritical medical devices/instruments [71].

21. CQ: Should dedicated toilets be used for patients with CDI?

Recommendation: The use of dedicated toilets by patients with CDI is weakly recommended.

Strength level: There is weak evidence suggesting that the use of dedicated toilets by patients with CDI reduces the risk of CDI.

Comment: Multiple epidemiological studies have suggested that shared use of toilets increases the risk of CDI. A small number of experiments have also shown that *C. difficile* was recovered from the surfaces of toilet seats and water tanks after water inoculated with *C. difficile* was flushed. As these data suggest that the shared use of toilets may contribute to *C. difficile* transmission, although none of them provide high-quality evidence, the use of dedicated toilets by patients with CDI is recommended.

21.1. Background and importance of the CQ

CDI is associated with a high disease burden, and outbreaks due to hypervirulent strains, including ribotypes 027 and 078, have been reported recently in medical institutions, mainly in Europe and the United States [25,233]. Using dedicated toilets by patients with CDI may be effective in preventing *C. difficile* transmission via contaminated environmental surfaces, thereby justifying further review.

21.2. PICO

P (facility requirements): Toilets for use by patients with CDI
I (intervention): Use of dedicated toilets by patients with CDI
C (comparison): Shared use of toilets by CDI and non-CDI patients
O (outcome): Incidence of CDI

21.3. Summary of evidence

C. difficile in the vegetative form can survive for only up to 15 min in an aerobic environment and for only up to 6 h in a moist environment; however, *C. difficile* in the spore form can withstand dryness, heat, and disinfection and survive for up to 5 months on environmental surfaces [25,233,234].

C. difficile on environmental surfaces has been known to easily

adhere to hands and objects [105,235], and ingestion of spores via contaminated hands and objects can lead to CDI.

Multiple epidemiological studies have suggested that the shared use of toilets might increase the risk of CDI [50,90,120,236]. In an experiment where the toilet was flushed with the lid open after the bowl water was seeded with *C. difficile* spores, the bacteria were recovered from the toilet seat, water tank, and floor near the toilet. While the bacterial counts were as low as 1–3 CFU per settle plate, the results indicated that infectious droplets emitted during lidless flushing could lead to environmental contamination [237,238]. However, it is difficult to generalize that all toilets will cause similar levels of contamination because the amount of droplets produced may differ according to their flushing modes. Additionally, among 30 sterile sponge samples collected from toilet seats in the homes of eight patients with recurring CDI, *C. difficile* was recovered from eight samples (27 %) [239].

Therefore, the use of dedicated toilets by patients with CDI is recommended based on the findings from epidemiological studies that show toilets and their surrounding environmental surfaces that have been in contact with CDI patients are likely to be contaminated with *C. difficile* spores and may become sources of infection.

21.4. Quality of evidence for overall outcome

C (low).

21.5. Summary of benefits

The use of dedicated toilets by patients with CDI may prevent *C. difficile* transmission through contact with toilets and surrounding environmental surfaces.

21.6. Summary of harms (adverse effects)

Implementation is considered harmless.

21.7. Summary of harms (burden)

Additional portable toilets (commode chairs) for dedicated use are required.

21.8. Benefit–harm balance

Benefits are considered to outweigh harms because contact with environmental surfaces likely to be contaminated with *C. difficile* can be prevented.

21.9. Healthcare costs necessary for the intervention

Costs to purchase portable toilets (commode chairs) or install additional toilets may be needed.

21.10. Feasibility of the intervention

Feasible.

21.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

21.12. Recommendations in related clinical practice guidelines

The U.S. Centers for Disease Control and Prevention recommend placing patients with CDI in private rooms with dedicated toilets [240].

22. CQ: Is sodium hypochlorite effective in reducing CDI in the disinfection of healthcare environments of patients with CDI?

Recommendation: Environmental disinfection with sodium hypochlorite to reduce the CDI incidence is recommended.

Strength level: Weakly recommended.

Comment: Many guidelines recommend sporicidal disinfectants, such as chlorine-based disinfectants, for environmental disinfection for CDI because *C. difficile* is alcohol-resistant. Many reports have described decreases in the incidence of CDI after the introduction of environmental cleaning with sodium hypochlorite.

22.1. Background and importance of the CQ

As *C. difficile* is sporulating and survives in environments for a long time, non-implementation of adequate environmental cleaning can be a risk for horizontal transmission of CDI through the environment. While *C. difficile* is resistant to disinfectants such as ethanol and quaternary ammonium salts, the use of sporicidal agents such as sodium hypochlorite for environmental cleaning are anticipated to be effective against CDI.

22.2. PICO

P (facility requirements): Hospital rooms in which patients with CDI were placed
I (intervention): Environmental cleaning around patients with sodium hypochlorite
C (comparison): Environmental cleaning around patients with non-sporicidal disinfectants, such as ethanol and benzalkonium chloride
O (outcome): Count of remaining *C. difficile* and the infection rate or decreased rate of CDI

22.3. Summary of evidence

Even when patients with CDI no longer have diarrhea and *C. difficile* is no longer detectable in stools after treatment, patients' skin and surroundings are still contaminated with *C. difficile* [91] and patients' room environments and instruments used for patient care can be *C. difficile* reservoirs that can contribute to transmission.

Studies have reported that cleaning CDI patients' environments with sodium hypochlorite reduced the residual *C. difficile* counts [125,241] and that the CDI incidence decreased after disinfectants used to reduce environmental contamination in wards with high CDI rates were switched from neutral detergents and quaternary ammonium salts to chlorine-based detergents [141,242–244]. A systematic review of 46 studies on interventions for the occurrence of CDI in acute care hospitals revealed that interventions comprising disinfection of frequently touched surfaces once or twice daily with chlorine-based disinfectants and terminal cleaning of patient rooms most effectively reduced CDI incidence [245].

Meanwhile, according to a report [246] comparing the effectiveness of removing *C. difficile* spores among 10 different sporicidal wipes, only wipes soaked in 5000 ppm sodium hypochlorite showed high sporicidal activity, killing spores within 5 min of contact; other wipes transferred spores to other environmental surfaces. To date, international guidelines have recommended using ≥1000 ppm sodium hypochlorite solutions for environmental surface cleaning after patients with CDI vacate hospital rooms [161,174,247]. Additionally, for areas prone to *C. difficile* contamination, the use of ≥5000 ppm chlorine-based cleaners for at least 10 min is also recommended [73].

However, as for the effective chlorine concentrations of chlorine-based cleaners, it is necessary to consider the balance between the benefits expected in the institution and the harms because the use of sodium hypochlorite solutions at such high concentrations also has disadvantages, including corrosion and decoloration of metals and linen,

odor, and health risks such as hypersensitivity. The IDSA/SHEA guidelines 2017 update recommends the inclusion of environmental cleaning with sodium hypochlorite, in conjunction with other measures, in situations requiring the prevention of horizontal *C. difficile* transmission from patient environments. Such instances include CDI outbreaks, persistent high incidence, and repeated occurrences of CDI cases within the same hospital room [71]. Table 13.

Complex-type chlorine-based disinfectant cleaners, primarily encompassing potassium peroxymonosulfate (an oxidant), oxidize sodium chloride to generate hypochlorous acid in the solution. These cleaners have been shown to effectively eradicate various resistant bacteria and feline calicivirus [248–250]. They are also easy to use because they release less chlorine gas [251] and cause less damage to metal and resin materials [252]. It has been reported that the infection rate decreased after the disinfection procedures as an infection control measure for CDI were switched from wiping with 1000 ppm sodium hypochlorite solution to cleaning with a complex-type chlorine-based disinfectant cleaner [145]. However, this cleaner has a short shelf life of 1 week because it is susceptible to the effect of temperature, and the effective chlorine concentration gradually decreases while the cleaner is stored at room temperature [253]. Furthermore, this agent is an environmental disinfectant/cleaner and cannot be used at present for instrument disinfection, where sodium hypochlorite should be used instead [254].

Noncontact environmental disinfection procedures, such as hydrogen peroxide spraying and ultraviolet irradiation, or the combined use thereof with hypochlorous acid, have been reported to be effective for environmental cleaning for CDI [5,149,255], and the introduction of these environmental cleaning procedures is an option to consider during outbreaks. However, these cleaning procedures require patients and medical staff to leave the room and cannot replace routine cleaning procedures.

Table 13
Methods of environmental cleaning with sodium hypochlorite in various guidelines.

	Environmental cleaning with sodium hypochlorite	Recommendation
Japanese Society of Chemotherapy/Japanese Association for Infectious Diseases Guidelines 2018	Use cleaners containing ≥1000 ppm chlorine or other sporicidal agents for routine disinfection of hospital rooms Prompt cleaning and thorough disinfection after a patient leaves the room Clean environmental surfaces to remove organic substances before a diluted sodium hypochlorite solution is used	NA
IDSA/SHEA 2017 Guidelines	Environmental cleaning with sodium hypochlorite should be considered, in conjunction with other measures, during CDI outbreaks, when high incidence persists, and when CDI cases occur repeatedly in the same hospital room	Weakly recommended Low-evidence quality
ESCMID 2018 Guidelines	The introduction of daily environmental disinfection and terminal disinfection of CDI patients' rooms with sporicidal agents to reduce CDI transmission is recommended	During outbreaks: Strongly recommended Low-evidence quality During endemic phases: Weakly recommended Low-evidence quality
WSES 2019 Guidelines	Disinfection with sodium hypochlorite solutions for environmental cleaning of patient areas where CDI cases keep occurring is recommended	NA

WSES, World Society of Emergency Surgery; IDSA/SHEA, Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; APIC, Association for Professionals in Infection Control and Epidemiology; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; CDC, Centers for Disease Control and Prevention; NA, Not applicable.

22.4. Quality of evidence for overall outcome

C (recommended by experts).

22.5. Summary of benefits

Removal of *C. difficile* from environmental surfaces and reduced infection rates of CDI can be expected.

22.6. Summary of harms (adverse effects)

The use of high-concentration sodium hypochlorite has health-related concerns, such as odor and hypersensitivity.

22.7. Summary of harms (burden)

The use of high-concentration sodium hypochlorite may incur a cost burden due to the corrosion and decoloration of metal medical instruments and linen.

22.8. Benefit–harm balance

Benefits outweigh harms based on the prevention of environmentally mediated *C. difficile* transmission.

22.9. Healthcare costs necessary for the intervention

Within normal infection control costs and labor.

22.10. Feasibility of the intervention

Feasible.

22.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

22.12. Recommendations in related clinical practice guidelines

The Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) recommends that environmental cleaning with sodium hypochlorite be considered, in conjunction with other measures, during CDI outbreaks, when high incidence rates persist, and when CDI cases occur repeatedly in the same hospital room (weakly recommended, low-evidence quality) [73]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend the introduction of daily disinfection and terminal disinfection of CDI patients' rooms with environmental sporicidal agents to reduce CDI transmission (during outbreaks: strongly recommended, low-evidence quality; during endemic phases: weakly recommended, low-evidence quality) [163]. The World Society of Emergency Surgery (WSES) guidelines recommend disinfection with sodium hypochlorite solutions for environmental cleaning of patient areas where CDI cases keep occurring (recommendation level is not stated) [200].

23. CQ: Is it recommended to use hydrogen peroxide vaporizers (HPVs) for environmental surface disinfection of CDI patients' rooms after discharge cleaning?

Recommendation: The use of hydrogen peroxide vaporizers (HPVs) for disinfection of hospital rooms after patients with CDI are discharged is weakly recommended.

Strength level: Non-use is weakly recommended. Use may be considered when CDI cases occur frequently.

Comment: Routine and discharge cleaning of patients' rooms is performed manually; however, the compliance rates for routine and discharge cleaning are often low. It has been reported that environmental cleaning of wards using nebulizers that generate dry mist hydrogen peroxide significantly reduces contamination with *C. difficile* spores compared to that before cleaning. Although only a few studies have been conducted in Japan, the implementation of appropriate safety measures is recommended.

23.1. Background and importance of the CQ

CDI is a common causative bacterium for healthcare-associated infections. Healthcare environments should be cleaned/disinfected thoroughly, as *C. difficile* can survive for a long time in a dry environment; however, environmental cleaning by manual wiping alone may leave some surfaces uncleaned. The use of disinfection with HPVs to complement routine cleaning and disinfection may be effective for environmental cleaning and the reduction of the incidence of CDI among newly hospitalized patients. Thus, the use of HPVs is worth considering.

23.2. PICO

P (facility requirements): Hospital rooms after patients with CDI are discharged
I (intervention): Disinfection of hospital rooms with HPVs
C (comparison): Disinfection of hospital rooms by manual wiping with disinfectants
O (outcome): Count of remaining *C. difficile* and the infection rate or decreased rate of CDI

23.3. Summary of evidence

C. difficile has been reported to survive for long periods of time in healthcare environments and more than 5 months in dry environments because *C. difficile* is a spore-forming bacterium, making it highly resistant to disinfectants [218]. Because contaminated hospital environments can serve as reservoirs of *C. difficile*, which can cause healthcare-associated infection, thorough environmental cleaning is required to reduce contamination [256].

C. difficile and antimicrobial-resistant bacteria remaining in hospital environments after discharge cleaning have recently been pointed out to pose a transmission risk to newly hospitalized patients [257,258]. Shaughnessy et al. have reported that being placed in a hospital room used by a patient with CDI was an independent risk factor for newly developing CDI (HR 2.35, 95 % CI 1.21–4.54) [257]. This is because frequently touched surfaces of the hospital rooms are contaminated with *C. difficile* and some parts are left uncleaned after manual wiping during discharge cleaning.

Conventionally, routine and discharge cleaning of patient rooms has been performed manually; however, Carling reported the compliance rate of routine discharge cleaning to be as low as 30 % [259]. In a study investigating levels of *C. difficile* in hospital environments after patients with CDI were discharged, the bacterial counts on telephones, nurse call buttons, door handles, and some other surfaces before and after cleaning by housekeeping staff did not differ [125]. These findings suggest that manual cleaning and disinfection by humans can reduce contamination but are incomplete and cannot eliminate contamination completely. Moreover, manual cleaning and disinfection are also associated with concerns in equipment and material management, such as erroneous disinfectant dilution and contamination of environmental wipes.

To complement manual cleaning and disinfection that have these problems, HPVs are used in the United States and UK to kill microorganisms, including *C. difficile*, on environmental surfaces [260]. HPV is an automated system for disinfecting environmental surfaces [261] and can kill microorganisms by spraying vaporized hydrogen peroxide. Moreover, it can disinfect environments more evenly than manual disinfection and may be effective for infection control and prevention.

Hydrogen peroxide has a broad antimicrobial spectrum and is effective against gram-positive and -negative bacteria, viruses, *Mycobacterium tuberculosis*, and spores [262].

Recently, multiple reports showing that the use of HPVs reduced *C. difficile* contamination of hospital room environments and the incidence of CDI have been published [263]. The use of hydrogen peroxide dry mist generators has also been reported to significantly reduce *C. difficile* contamination in geriatric wards [264].

A study evaluating environmental contamination after HPVs was used to reduce the acquisition of multidrug-resistant organisms (MDRO), and *C. difficile* has demonstrated that the combined use of HPVs and conventional cleaning for disinfection of hospital rooms after patients with MDRO or CDI were discharged reduced the risk of transmission to newly hospitalized patients by 64 %. The CDI transmission risk was also reduced, although the observed decrease was not of significance (RR 0.00, $p = 0.30$) [265]. A different study reported that the use of HPVs in addition to routine cleaning significantly reduced the incidence of CDI (per 1000 patient-days) from 2.28 to 1.28 compared to routine cleaning only ($p < 0.05$) [123].

While these reports have shown decreases in environmental contamination with *C. difficile* and the incidence of CDI, a systematic review and meta-analysis study reported in 2018 [6], in which the above two reports [123,265] were included, did not show a significant difference. Meanwhile, a meta-analysis in 2022 has reported its effectiveness [149]. There is a paucity of currently available studies, and further studies are warranted.

Many outbreaks due to medical instruments have been reported to date [266]. These are attributable to inadequate cleaning and disinfection after use. HPVs can remove pathogens remaining in hospital rooms. HPV is also expected to have the secondary benefit of reducing contamination of medical instruments through simultaneous disinfection of contaminated medical instruments during the disinfection of hospital rooms.

23.4. Quality of evidence for overall outcome

C (recommended by experts).

23.5. Summary of benefits

Compared to environmental surface disinfection by manual wiping, no-touch disinfection with hydrogen peroxide vapor is not associated with human errors and has been demonstrated to leave fewer adherent bacteria on environmental surfaces because HPVs are delivered to every corner of environmental surfaces; thus, this technique is expected to reduce the incidence of CDI. Moreover, disinfection by manual wiping requires a substantial amount of additional labor time in the preparation of written operation procedures and comprehensive staff training on the procedures. In contrast, HPV can be expected to reduce the labor burden.

23.6. Summary of harms (adverse effects)

This method is ineffective for unexposed surfaces, such as objects stacked on each other, as hydrogen peroxide vapor is effective only against bacteria on environmental surfaces. Thus, its effect was not

observed on the disinfection of bacteria inside the fibers of linen and carpet floors.

23.7. Summary of harms (burden)

After HPV application, it takes 1.5–3 h before the hydrogen peroxide concentration decreases, allowing access to the room. Moreover, disinfection with HPVs must be conducted in closed spaces with no people inside; thus, the applicable environments are limited to single rooms, such as hospital rooms.

23.8. Benefit–harm balance

The benefits outweigh the harms in terms of the risk of developing CDI.

23.9. Healthcare costs necessary for the intervention

Costs are required for the main units of HPV and special chemicals. These are add-on costs to cleaning costs because disinfection with HPVs does not replace routine cleaning.

23.10. Feasibility of the intervention

Feasible.

23.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

23.12. Recommendations in related clinical practice guidelines

Not recommended in other clinical practice guidelines.

24. CQ: Is it recommended to use ultraviolet germicidal irradiation devices for environmental surface sterilization of hospital rooms after patients with CDI are discharged?

Recommendation: The use of ultraviolet germicidal irradiation devices for disinfection of hospital rooms after patients with CDI are discharged is weakly recommended.

Strength level: Non-use is weakly recommended. Use may be considered when CDI cases are frequently occurring.

Comment: Third-party contractors, who are usually in charge of environmental cleaning, must be trained frequently because of the high turnover of cleaning staff. However, because many medical institutions also face serious labor shortages, ultraviolet irradiation after manual cleaning is weakly recommended to standardize the quality of environmental hygiene. Although only a few studies have been conducted in Japan, the implementation of appropriate safety measures is recommended.

24.1. Background and importance of the CQ

Many studies have reported that ≥50 % of environmental surfaces are not cleaned properly [267,268]. Contaminated environmental surfaces provide potential sources for transmission of important healthcare-associated pathogens, including *C. difficile,* in hospital settings [269–274]. In response to the recently increasing attention given to resistant bacteria, the use of ultraviolet germicidal irradiation devices (hereinafter referred to as UV-C devices) has increased throughout the world, mainly in the United States, for the prevention of cross-infection in medical settings. The UV-C devices are used to irradiate hospital rooms and frequently touched surfaces with UV-C rays after cleaning and can disinfect pathogenic microorganisms that may remain on environmental surfaces even after wiping. Such devices are referred to as no-touch automated room disinfection systems (NTD systems), which also include HPV devices. Rutala et al. reported that UV-C devices achieved the decontamination of *C. difficile*-contaminated surfaces in the field of view and behind objects within 15–50 min, while HPV devices took 2–5 h. The combined use of UV-C devices and reflective barriers took an even shorter time, completing the decontamination within 5–10 min [147,275].

24.2. PICO

P (patients): Hospital rooms after patients with CDI are discharged
I (intervention): Disinfection of hospital rooms by UV irradiation after routine/terminal cleaning
C (comparison): Routine/terminal cleaning only
O (outcome): Count of remaining *C. difficile* and the infection rate or decreased rate of CDI

24.3. Summary of evidence

A study monitoring the incidence of CDI in a university hospital over time reported that the use of UV-C devices led to a 25 % decrease in the incidence of CDI and reduced direct healthcare costs (estimated ~14 million, 20 million yen worth) [276]. Some UV-C devices were greatly improved in terms of the bactericidal effectiveness in shadow areas where ultraviolet light could not reach directly, which has been a concern with this technique; the decreased rates for such areas were ≥50 % of the rates for directly irradiated areas [147,277].

However, each model differs in effectiveness; for example, the disinfection effectiveness of certain models against microorganisms, including *C. difficile,* sharply decreased when the irradiation distance was ≥1 m [278,279]. Hence, different devices should be compared in terms of performance (microorganism reduction rates at different irradiation distances and irradiation durations), costs of the devices, running costs, and other variables before the one suitable for the facility can be selected [149].

24.4. Quality of evidence for the overall outcome

C (recommended by experts).

24.5. Summary of benefits

UV-C irradiation significantly reduced the incidence of CDI (by 25 %).

24.6. Summary of harms (adverse effects)

No one should be present during irradiation because UV-C is harmful to human health. There are no residual toxic substances.

24.7. Summary of harms (burden)

There is a burden associated with purchasing UV-C devices; however, they are easy to operate and can complete disinfection in short periods of time.

24.8. Benefit–harm balance

The benefits outweigh the harms in terms of the risk of developing CDI.

24.9. Healthcare costs necessary for the intervention

Costs of purchasing UV-C devices are required; however, it has been reported that 21 cases of CDI were prevented and estimated that 14–20

million yen (~$134,568–$191,604) healthcare costs were reduced during a 12-month intervention.

24.10. Feasibility of the intervention

Feasible.

24.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

24.12. Recommendations in related clinical practice guidelines

Recommended in the APIC Implementation Guide (2013).

25. CQ: Is surveillance of carriers in asymptomatic hospitalized patients useful?

Recommendation: Non-implementation is strongly recommended.
Strength level: Non-implementation is strongly recommended.
Comment: *C. difficile*, including toxigenic strains, can be detected even in asymptomatic individuals who have not developed CDI because *C. difficile* can colonize the human intestinal tract. Currently, the risk of asymptomatic *C. difficile* carriers developing and transmitting CDI remains unknown. Nonetheless, the requirements of certain patients, such as transplant recipients, may need to be evaluated on a case-by-case basis. Additionally, there is scant evidence on the effectiveness of anti-*C. difficile* agents and transmission control measures, such as hand hygiene, isolation precautions, and environmental disinfection, in *C. difficile* carriers.

25.1. Background and importance of the CQ

C. difficile has been detected in patients with CDI and *C. difficile* carriers. Because *C. difficile* carriers have potential risks for disease onset and transmission, it is crucial to clarify the effects of *C. difficile* carriage and CDI.

25.2. PICO

P (facility requirements): Facilities providing clinical services to people with CDI
I (intervention): Surveillance of carriers in patients
C (comparison): Non-implementation of surveillance of carriers
O (outcome): Incidence of CDI and prevention of transmission

25.3. Summary of evidence

C. difficile is a pathogenic microorganism with a wide range of carriers. According to previous reports, 7%–18 % of hospitalized patients are *C. difficile* carriers and *C. difficile* has also been detected on the skin and surroundings of carriers [280]. Patients with a history of hospitalization, those with a history of CDI, those undergoing treatment with corticosteroids and immunosuppressive therapy, and those undergoing maintenance dialysis are commonly at risk of carrying *C. difficile* at the time of admission. Factors associated with the risk of becoming a *C. difficile* carrier during hospitalization include history of hospitalization, history of treatment with proton pump inhibitors, anticancer chemotherapy, and treatment with antibacterial agents [281].

Among patients with leukemia, many Ribotype (RT) 014/20 and 027 carriers were found among those with acute myeloid leukemia, and they had a history of treatment with multiple antibacterial agents and a history of hospitalization [282]. Previous treatment with antibacterial agents was a risk factor for the elderly [283]. In a study of patients hospitalized in geriatric wards of acute care hospitals, 9.8 % were *C. difficile* carriers and had a history of CDI and malnutrition (Malnutrition Universal Screening Tool $\geq$2) were risk factors [284]. Regarding the courses of carriers, 78 % of patients who were carriers at the time of admission were still carriers at the time of discharge, and the use of cephalosporins was associated with carriage [285]. In a study on nursing home residents in Germany, 4.6 % (11/240) of residents were *C. difficile* carriers and had a history of CDI and hospitalization within 3 months were considered risks [286]. Among long-term care facility residents in the United States, toxigenic *C. difficile* strains were found in 51 % (35/68) of the residents, and the risks were a history of CDI and the use of antibacterial agents [113]. In a study on residents of long-term care facilities and patients in acute care hospitals, 22.4 % of critical care hospital patients and 18.8 % of long-term care facility residents were *C. difficile* carriers, and a history of antibacterial use and a history of proton pump inhibitor use were common risk factors [63].

There are several reports showing that *C. difficile* carriers may be at risk of developing CDI. In a study on the risk of developing CDI in *C. difficile* carriers, 21/220 subjects (9.6 %) were carriers and 8/21 carriers (38.1 %) developed CDI, while 4/199 noncarriers (2.0 %) developed CDI (HR 23.9; 95 % CI, 7.2–79.6; $p < 0.0001$) [287]. In ICU patients, carriage at the time of hospitalization (RR 8.62) and carriage after hospitalization (RR 10.93) were significant independent risks for developing CDI [288]. In a study on patients with cirrhosis, 19.8 % were *C. difficile*-positive at the time of hospitalization and 25 % developed CDI during hospitalization [289]. Of the 112 patients who underwent hematopoietic cell transplantation, 21 (19 %) were *C. difficile* carriers and 13 of the 21 carriers (62 %) developed CDI after transplantation [290]. Meanwhile, the data are insufficient for the evaluation of underlying diseases, severity, outcomes, and RT-dependent differences in these patients.

Several reports have shown that *C. difficile* carriers can be considered a risk for the transmission of CDI. In a study using multilocus variable-number tandem-repeat analysis (MLVA), transmission sources were *C. difficile* carriers in 29 % of cases (16/56) and beds previously occupied by carriers in 2 cases [291]. In a study using 1549 swab samples from 474 patients, 50/474 (10.6 %) patients were PCR-positive, and the results, including MLVA analysis, suggested that the sources of transmission to 20 % of patients were carriers [292]. In nursing homes, 14.6 % of residents were carriers of toxigenic *C. difficile* and isolates from symptomatic patients were genetically identical to those from carriers; findings from this study suggest the importance of carriage in the transmission of symptomatic CDI [293]. Meanwhile, a study has reported that common *C. difficile* risk factors, such as underlying disease and history of treatment with antibacterial agents or Proton Pump Inhibitor (PPI), were not significant risk factors among nursing home residents, although carriage was observed in their population [294].

The involvement of multiple unidentified routes in *C. difficile* acquisition has been suggested based on the genetic diversity of *C. difficile* detected in carrier surveillance of *C. difficile* [63]. A study conducted in Canada, which examined transmission patterns in infected and carrier patients using whole-genome sequencing (WGS), demonstrated that while carrier patients played a role in transmission, the predominant factor influencing transmission was the isolation frequency of a virulent strain (NAP1/027/ST1 strain) [295]. Therefore, CDI patient carriers may also be one of the factors in the transmission; however, unknown factors, including differences from regionally prevalent *C. difficile* strains and characteristics of patients and medical institutions, remain unknown.

25.4. Summary of harms (adverse effects)

Adverse effects may be associated with unnecessary treatment with anti-*C. difficile* agents.

25.5. Summary of harms (burden)

In the screening for *C. difficile* carriers, fecal specimens are tested by various methods, such as the culture method, rapid diagnostic testing using immunochromatography, and the NAAT method. It is also necessary to evaluate the toxigenicity of *C. difficile* carrier screening; however, no methods have been established to test the toxigenicity of carriers. Difficulties are predictable in terms of the cost burden associated with these tests and infection control measures when *C. difficile*-positive patients are identified.

25.6. Benefit–harm balance

Given the fact that the risks of developing and transmitting CDI are not fully understood, the harms may outweigh the benefits.

25.7. Healthcare costs necessary for the intervention

Costs for *C. difficile* tests, treatment, and control measures are necessary.

25.8. Feasibility of the intervention

The feasibility of routine clinical practice is considered to be low at present.

There are reports on the management of *C. difficile* carriers, although the number is small. The introduction of contact precautions to 4.8 % (368/7599 patients) of patients who were identified as *C. difficile* carriers resulted in a 7 % decrease in HA-CDI every 4 weeks, and time-series forecasting using ARIMA predicted a prevention rate of 62.4 % of HA-CDI [296]. Investigational treatment of carriers with metronidazole, vancomycin, and placebo has shown that metronidazole treatment was ineffective and vancomycin treatment was associated with a higher rate of *C. difficile* carriage following transient eradication after treatment [297].

25.9. Quality of evidence for the overall outcome

C (recommended by experts).

25.10. Summary of benefits

The prevalence of *C. difficile* carriage among patients and the effectiveness of precautions can be evaluated. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

25.11. Recommendations in related clinical practice guidelines

The IDSA/SHEA 2017 Guidelines state the following: “There are insufficient data to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions (no recommendation)” [71]. The ESCMID guidelines state the following: “We do not recommend screening for *C. difficile* to identify colonized/carrier patients as a way of altering the risk of developing CDI in either colonized subjects or other patients and thus reducing CDI rates (conditional recommendation, low level of evidence in the endemic setting)” [163].

The American Society for Transplantation and Cellular Therapy guidelines state the following: “if a patient is found to be a carrier of *C. difficile* but without CDI, then contact precautions are recommended (BII). The treatment of asymptomatic carriers is not recommended because the risks and benefits of this approach are not known (DIII)” [298].

26. CQ: Is surveillance of carriers in asymptomatic hospitalized patients useful during outbreaks?

Recommendation: Given the insufficiency of evidence for effectiveness, the surveillance of carriers and their isolation precautions are not recommended during outbreaks.

Strength level: Non-implementation is weakly recommended.

Comment: Its implementation upon consultation with local experts is an option when no improvements are observed while other precautions are in place during outbreaks.

26.1. Background and importance of the CQ

Intestinal colonization by *C. difficile* is found in 4%–15 % of healthy individuals [281]. Half of such cases are accounted for by toxigenic strains [299]. It has been reported that the rate of *C. difficile* carriage in hospitalized patients is higher than that in healthy people and that the rate in patients hospitalized in wards where an outbreak occurred is particularly high (30.1 % vs. 6.5 %, $p = 0.01$) [156]. Moreover, carriers are at a higher risk of developing CDI during the follow-up than non-carriers (relative risk 5.86 [95 % CI, 4.21–8.16]) [300]. The surroundings of asymptomatic carriers of toxigenic *C. difficile* are frequently contaminated with toxigenic *C. difficile* [301], and these asymptomatic carriers can cause CDI in other people through transmission [113,291,302]. In addition, another report [295] has highlighted that NAP1/027/ST1 strain carriers are associated with the risk of CDI onset in other patients. Therefore, surveillance of carriers and placement of carriers under isolation precautions during outbreaks may reduce CDIs, and the usefulness of this approach should be studied further.

26.2. PICO

P (facility requirements): Wards/rooms where a CDI outbreak has occurred

I (intervention): Surveillance of carriers of toxigenic and non-toxigenic *C. difficile* and placement of carriers under isolation precautions

C (comparison): Non-implementation of surveillance of carriers and placement of carriers under isolation precautions

O (outcome): Incidence of CDI

26.3. Summary of evidence

Longtin et al. screened 7599 hospitalized patients from the emergency center of a Canadian acute care facility for carriage of toxigenic *C. difficile* and placed carriers (4.8 %, 368 patients) under contact precautions. They reported that the rate of CDI decreased significantly during outbreaks compared to the rate during the control period (3.0/10,000 patient-days vs. 6.9/10,000 patient-days, $p < 0.001$) [296]. Additional analysis has shown that after carrier screening and isolation precautions were introduced, contact precautions in the facility temporarily increased but then decreased with CDI [303].

Linsenmeyer et al. screened patients in a surgical ward of a US Veterans Affairs medical center where CDI occurred frequently for toxigenic *C. difficile* colonization and placed the carriers (3.1 %, 24 patients) under contact precautions; they reported that a decrease in CDI (10.9/10,000 patient-days vs. 3.0/patient-days) [304]. In a simulation model-based study, Barker et al. evaluated the effectiveness of infection control measures against toxigenic *C. difficile* and reported that environmental cleaning (68.9 %, $p < 0.01$) and screening for carriers (35.7 %, $p < 0.01$) were effective stand-alone measures [305]. Meanwhile, Paquet-Bolduc et al. screened 114 patients in four wards during an outbreak and detected toxigenic *C. difficile* in 15 (13 %) patients; however, the incidence of CDI (median, 7.0 vs. 7.5 patients) and the outbreak duration (26.5 vs. 34.0 days) did not differ from those in the controls [306].

26.4. Quality of evidence for the overall outcome

C (recommended by experts).

26.5. Summary of benefits

Single-center before/after comparison studies have shown that active screening of hospitalized patients who are carriers of toxigenic *C. difficile* and their isolation precautions reduces CDI.

26.6. Summary of harms (adverse effects)

Contact precautions may restrict certain activities of healthcare workers and patients within the healthcare institution. It poses risks such as decreased medical care quality and aggravation of patients' mental conditions [307–309].

26.7. Summary of harms (burden)

Screening tests and contact precautions place labor burdens on healthcare workers.

26.8. Benefit–harm balance

There are no clear data indicating that the benefits outweigh the harms.

26.9. Healthcare costs necessary for the intervention

Costs for conducting toxigenic *C. difficile* tests for patients not suspected of having CDI and for placing carriers under contact precautions.

26.10. Feasibility of the intervention

Feasible.

26.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

26.12. Recommendations in related clinical practice guidelines

The ESCMID guidelines do not recommend the testing of patients or healthcare workers for *C. difficile* carriage even during outbreaks [163]. The IDSA/SHEA 2017 Guidelines state that the available data are insufficient to determine the appropriateness of screening the patients for carriage and placing the carriers under isolation precautions [71]. The WSES guidelines recommend placing carriers under contact precautions [200].

27. CQ: Are ward closures and partial ward closures during outbreaks recommended?

Recommendation: Ward closures and partial ward closures during outbreaks are not recommended.

Strength level: Non-implementation is weakly recommended.

Comment: The number of available beds should be adjusted based on the beds preoccupied for isolation/cohorting of positive patients and in-hospital medical staff support systems for increased workload due to infection control measures.

27.1. Background and importance of the CQ

C. difficile has been found to persist for a long period in the medical environments of patients with CDI [310,311]. In addition to the environment, instruments used for patient care and healthcare workers' hands can be contaminated with *C. difficile* spores and serve as *C. difficile* reservoirs for transmission [89,312]. In a multicenter study, Tanner et al. reported that drug-resistant bacteria were detected in 12 % of rooms without contact precautions as well as in rooms with contact precautions for drug-resistant bacteria, including *C. difficile* (32 %) [313]. Dumford et al. reported that *C. difficile* contamination was found in physician work areas (31 %), nurse work areas (10 %), and surfaces of portable devices (21 %) in a post-CDI outbreak environmental survey [314], and Ziakas et al. reported a significant increase in the rate of asymptomatic *C. difficile* carriage during outbreaks (30.1 % vs. 6.5 %, $p = 0.01$) [156]. Ward closures and partial ward closures should be considered because they may contribute to the reduction of CDI through the reduction of the transmission risk.

27.2. PICO

P (facility requirements): Wards/rooms where a CDI outbreak has occurred
I (intervention): Partial and complete ward closures
C (comparison): Non-implementation of complete ward closures
O (outcome): Incidence of CDI

27.3. Summary of evidence

Ward closures and partial ward closures are used empirically during outbreaks of infectious diseases; however, their usefulness has not been studied using the case-control design or other study designs [315]. Nagar et al. reported that they reduced the shared room occupancy from six to four patients during a CDI outbreak as part of the infection control measures [316], and Ratnayake et al. reported that they closed the outbreak ward [317]. Rhinehart et al. conducted a questionnaire survey of 822 members of the APIC in the United States and found that no member had experienced partial ward closures due to CDI, while 22.6 % of the members had experienced partial ward closures, such as cessation of accepting admission of new patients due to outbreaks of infectious diseases [318]. In conclusion, no studies have demonstrated the effectiveness of ward closures or partial ward closures during CDI outbreaks.

As an infection control measure, it is necessary to isolate patients with CDI in single rooms or cohorting of patients with CDI if single-room isolation is difficult, which may impose limitations on the availability of beds. Moreover, contact precautions place an increased workload on healthcare workers [319], and infection control measures for patients with CDI were reported to be significantly burdensome [320,321]. The number of available beds should be adjusted on a case-by-case basis considering the increased workload of healthcare workers due to infection control measures and support systems for the increased workload from other wards.

27.4. Quality of evidence for the overall outcome

C (recommended by experts).

27.5. Summary of benefits

No studies have demonstrated the effectiveness of ward closures or partial ward closures in reducing the incidence of CDI.

27.6. Summary of harms (adverse effects)

During ward closures and partial ward closures, patients who cannot be hospitalized in those wards will be hospitalized in other wards; as a consequence, the level of medical care may be negatively affected.

27.7. Summary of harms (burden)

There may be a decrease in healthcare reimbursement because a decreased number of patients can be hospitalized during partial and complete ward closures.

27.8. Benefit–harm balance

There are no clear data indicating that the benefits outweigh the harms.

27.9. Healthcare costs necessary for the intervention

The intervention requires no additional medical costs.

27.10. Feasibility of the intervention

Feasible.

27.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

27.12. Recommendations in related clinical practice guidelines

Ward closures or partial ward closures are not described in any other guidelines related to CDI.

28. CQ: Is environmental microbiology testing useful in reducing CDI?

Recommendation: It is weakly recommended not to perform environmental tests during outbreaks.

Strength level: Non-implementation is weakly recommended.

Comment: Environmental microbiology testing is recommended to evaluate the adequacy of environmental cleaning/disinfection. It can also be considered a way to assess the feasibility of lifting ward/room restrictions, which are introduced during outbreaks, after adequate cleaning/disinfection.

28.1. Background and importance of the CQ

Contamination of environments, such as frequently touched surfaces, can be responsible for the transmission of toxigenic *C. difficile* [269], and environmental surface cleaning and disinfection reduce the incidence of CDI. However, cleaning and disinfection may not be sufficient in some cases [259]. In addition to on-site guidance on cleaning and disinfection, environmental contamination levels determined before or after environmental cleaning/disinfection can serve as objective indicators. Accordingly, it is crucial to review the usefulness of environmental microbiology testing for reducing CDI.

28.2. PICO

P (facility requirements): Wards/rooms where a CDI outbreak has occurred
I (intervention): Environmental testing for toxigenic *C. difficile*
C (comparison): Non-implementation of environmental testing
O (outcome): Incidence of CDI

28.3. Summary of evidence

Eckstein et al. reported that out of nine rooms previously occupied by patients with CDI, toxigenic *C. difficile* was identified in all nine rooms after the rooms were cleaned by the usual cleaning staff, while only one room was toxigenic *C. difficile*-positive after the rooms were cleaned by research staff [305].

Methods for objective evaluation of the adequacy of environmental cleaning/disinfection include 1) direct observation and guidance and 2) environmental testing [71,322]. The environmental testing approach is divided into two methods: simple, rapid, and inexpensive methods for observation of the adequacy of wiping, such as the fluorescent marker test [323] and the adenosine triphosphate (ATP) wiping test [324]; and microbiological methods to detect toxigenic *C. difficile*, which are the culture and nucleic acid amplification tests [325].

Standard testing methods for environmental microorganisms are culture methods using alcohol treatment and selective isolation media, such as CCFA and CCMA-EX. Isolation of *C. difficile* allows for the direct confirmation of environmental contamination. Furthermore, the use of additional techniques, such as PCR ribotyping, PFGE, POT, REA, toxinotyping, multilocus sequence typing (MLST), slpA analysis, MLVA, and WGS, provides potentially useful data for epidemiological investigations. Regarding sample collection methods, detection rates of *C. difficile* are low when samples are collected with swabs, even with flocked swabs, and the detection rates are reportedly higher when samples are collected with sponges or contact plates [326–328]. A disadvantage of culture methods is that the results cannot be obtained quickly because bacterial growth is slow and it takes time to isolate toxigenic *C. difficile*.

Recently, NAAT has been used as a highly sensitive rapid testing method for toxigenic *C. difficile* [324] and has been demonstrated to have detection rates equal to or higher than those of culture tests [329]. However, the *C. difficile* nucleic acid tests used in acute care facilities, which have recently been approved in Japan, use fecal samples, and there is scant evidence for the practical usefulness of environmental testing using these fully automated genetic testing devices. Moreover, it is currently difficult to universally use these rapid NAATs for environmental testing because they are expensive.

The fluorescent marker test and ATP wiping test cannot detect toxigenic *C. difficile* directly; however, they are already commonly used as infection control measures in community hospitals, and the results can be easily evaluated immediately. Deshpande et al. studied whether ATP test results correlate with *C. difficile* culture test results and reported a significant correlation between the ATP levels and the positive culture rates; the positive culture rate for areas with ATP levels $\geq$250 RLU (Relative Light Unit) was 19 %, while the rate for areas with ATP levels $<$250 RLU was 3 % [324]. Sitzlar et al. compared the positive culture rates before and after the fluorescent marker environmental testing intervention and reported that the rate decreased by 14 % after the intervention ($p = 0.006$) [323].

28.4. Quality of evidence for overall outcome

C (recommended by experts).

28.5. Summary of benefits

Currently, available knowledge on environmental testing as an independent contributor to the reduction of the incidence of CDI is not sufficient. However, environmental testing is expected to be effective in reducing the incidence of CDI, particularly during outbreaks, because it can be used to objectively evaluate the adequacy of environmental cleaning/disinfection and identify contaminated areas after environmental cleaning/disinfection.

28.6. Summary of harms (adverse effects)

There are no harms (adverse effects) to patients or areas tested, such as environmental surfaces and devices, as the intervention is an environmental test.

28.7. Summary of harms (burden)

There are labor burdens on healthcare workers for environmental sampling and testing.

28.8. Benefit–harm balance

There is scant evidence that the benefits outweigh the labor burdens on healthcare workers for environmental sampling and testing.

28.9. Healthcare costs necessary for the intervention

Costs are incurred for tests to detect toxigenic *C. difficile* in environments.

28.10. Feasibility of the intervention

Feasible.

28.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

28.12. Recommendations in related clinical practice guidelines

The IDSA/SHEA 2017 Guidelines and the CDC infection control guidelines recommend evaluation of environmental cleaning/disinfection using the fluorescent marker test or the ATP wiping test.

29. CQ: Is the use of NAAT for patients suspected of having CDI during outbreaks recommended?

Recommendation: The use of NAAT for patients suspected of having CDI during outbreaks is weakly recommended.

Strength level: Implementation is weakly recommended.

Comment: NAAT has been included in the national health insurance coverage in Japan and introduced to clinical practice. NAAT is useful during outbreaks because its high sensitivity and short turnaround time allow for infection control that is based on early diagnosis. NAAT has some disadvantages, such as its high cost and the potential for CDI overdiagnosis when employed as a sole diagnostic method.

29.1. Background and importance of the CQ

A CDI diagnosis is suspected when a patient experiences three or more bowel movements within 24 h or when a patient experiences bowel movements more frequently than their usual pattern. The diagnosis is established by the presence of stools rated 5 or higher on the Bristol Stool Scale along with a positive fecal toxin result, or isolation of toxigenic *C. difficile* in CDI testing, or identification of pseudomembranous enteritis via lower gastrointestinal endoscopy or colorectal histopathology [102]. *C. difficile* is an obligate anaerobic bacterium, and its detection in culture tests takes many days; therefore, the culture method is not suitable for making quick decisions about the initiation of treatment or infection control measures. Kits for the detection of a *C. difficile* antigen (GDH) or toxin in feces have been developed to rapidly confirm the presence of *C. difficile* and have recently been commonly used in clinical settings. However, some reports have shown that the sensitivity and specificity of these rapid diagnostic methods are not sufficient, with values of 62.9%–100 % for sensitivity and 67.7%–92.2 for specificity [71,330,331]. More accurate diagnostic methods for CDI are needed because the diagnosis of diarrhea based solely on this testing method may underestimate CDI virulence. Detection methods using genetic testing techniques, such as PCR (NAAT), have been developed as diagnostic methods with higher sensitivity, higher specificity, and shorter turnaround times. In Japan, the NAAT for the detection of *C. difficile* toxin B DNA in feces has been covered by national health insurance since April 2019. While the results of these tests can be obtained quickly and easily, the high NAAT sensitivity raises a concern that toxin gene-positive strains that have not caused CDI may be detected [332]; however, the positive predictive value is expected to increase in outbreak settings, and the usefulness of NAAT should be considered.

29.2. PICO

P (patients): Patients suspected of having CDI during CDI outbreaks
I (intervention): Implementation of NAAT
C (comparison): Implementation of only GDH/toxin testing
O (outcome): Usefulness for diagnosis and infection control of CDI

29.3. Summary of evidence

The sensitivity of NAAT is known to be higher than that of toxin tests based on enzyme immunoassays (EIAs) [71,73,102,331] but is lower than that of the toxigenic culture (TC) method to confirm the toxigenicity of isolates. Moreover, NAAT results may reflect the carriage of toxin gene-positive strains [113,226]. Thus, it is essential to confirm the clinical symptoms satisfying the diagnostic criteria for CDI before making a diagnosis. Furthermore, studies have shown that mortality and recurrence rates were higher among cases in which toxins were detected in feces or positive cytotoxicity test results were obtained than those among cases in which only NAAT results were positive. This suggests that caution should be exercised when interpreting positive results with NAAT alone for CDI diagnosis [333–336]. Therefore, when NAAT is used for the diagnosis of CDI in routine clinical practice, it is imperative to ensure that the clinical findings align with the presence of CDI. Nevertheless, there are reports showing the effectiveness of infection control measures based on NAAT results in healthcare institutions. In a retrospective study on patients diagnosed with CDI, Catanzaro et al. compared EIA-based toxin A/B testing and PCR and reported that patients in the PCR test group were isolated for a significantly shorter period [337].

As a prospective study, Longtin et al. compared CDI diagnosis results based on NAAT alone and those obtained via a three-step method (GDH ➡ toxin test ➡ CCA; cytotoxicity test) using 1321 fecal specimens from 888 patients. In total, 85 cases of nosocomial CDI were diagnosed based on positive NAAT results, while 56 cases were diagnosed by toxin/CCA testing. Based on these findings, they suggested that the use of NAAT allows for taking precautions for patients overlooked by toxin testing [333]. Guerrero et al. demonstrated that among 132 patients with CDI diagnosed with GDH and PCR, toxins were not detected in diarrheal stools in 32 % of the patients. However, toxin-positive and -negative patients did not differ in terms of severity and recurrence rate, and some toxin-negative patients died. Moreover, a genetic analysis study has shown that even toxin-negative cases cause environmental contamination, suggesting that more sensitive detection methods, such as PCR, are useful for infection control [338]. Meanwhile, the usefulness of NAAT in outbreak settings was reported in a systematic review published in 2018 by a working group of the ESCMID [163,331]. In this report, the use of a two-step testing method (GDH or toxin gene testing by NAAT, followed by fecal toxin testing or GDH and toxin testing, followed by NAAT or TC when the first step results are GDH-positive and toxin-negative) during CDI outbreaks is strongly recommended.Quality of evidence for the overall outcome.

C (recommended by experts).

29.4. Summary of benefits

NAAT has excellent sensitivity and specificity for CDI diagnosis. The use of NAAT during outbreaks allows for early initiation of treatment

and infection control measures, preventing transmission.

29.5. Summary of harms (adverse effects)

Patients with positive NAAT results and negative fecal toxin test results have been reported to have clinical prognoses similar to those of non-CDI patients. Thus, the use of NAAT alone may result in overdiagnosis.

29.6. Summary of harms (burden)

The use of NAAT is likely to increase healthcare costs.

29.7. Benefit–harm balance

The benefits outweigh the harms.

29.8. Healthcare costs necessary for the intervention

NAAT has been increasingly introduced in clinical practice in Japan, and testing costs may be covered by health insurance systems when facility criteria, such as the introduction of testing devices and testing systems, are met.

29.9. Feasibility of the intervention

Feasible as a health insurance-covered test in institutions that have an established NAAT testing system. For institutions where NAAT is not available, it may be a good idea to consult with an institution where NAAT is available.

29.10. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

29.11. Recommendations in related clinical practice guidelines

The guide to preventing CDI published by the APIC in the United States suggests that the cost-effectiveness of NAAT is good considering the relative number of tests performed, treatment, and infection control measures, despite its high unit cost [124].

In a systematic review in 2018 by a working group of the ESCMID, the use of a two-step testing method (GDH or toxin gene testing by NAAT, followed by fecal toxin testing or GDH and toxin testing, followed by NAAT or TC when the first step results are GDH-positive and toxin-negative) during CDI outbreaks is strongly recommended [163,331].

30. CQ: Is the culture method a recommended test for patients suspected of having CDI during outbreaks?

Recommendation: The culture method is weakly recommended for testing patients suspected of having CDI during outbreaks.

Strength level: Implementation is weakly recommended.

Comment: The TC method, one of the gold standard diagnostic tests for CDI, is useful for the diagnosis of CDI when fecal test results are GDH-positive and toxin A/B-negative and NAAT methods, such as PCR, are not available. Furthermore, culture tests can facilitate detailed analysis of bacterial strains using molecular epidemiological techniques such as PFGE, POT, ribotyping, MLVA, and WGS, which may be required for evaluation in certain settings, such as outbreaks, and for the accumulation of epidemiological information. The culture method is time-consuming and is associated with TC costs in addition to costs for rapid testing of fecal specimens. Detailed procedures for TC have not been established and may differ from one laboratory to another. According to the testing algorithm proposed by the Japanese Society for Clinical Microbiology, the proactive use of NAAT and culture testing, which have higher sensitivity, is recommended in outbreak settings where confirmation of a broader range of occurrence, including the possibility of GDH false-negative results and carriers, and evaluation using molecular epidemiological techniques, such as ribotyping, are necessary [339].

30.1. Background and importance of the CQ

A CDI diagnosis is established under the folowing conditions: when a patient experiences three or more bowel movements within 24 h or when a patient experiences bowel movements more frequently than their usual pattern; a Bristol Stool Scale rating of 5 or higher; and a fecal toxin-positive result, isolation of toxigenic *C. difficile* in CDI testing, or pseudomembranous enteritis found via lower gastrointestinal endoscopy or colorectal histopathology [102]. Common fecal testing methods use reagents to detect a *C. difficile* antigen (GDH) and toxins (toxins A and B) in feces by immunochromatography based on the measurement principle of EIA; however, these methods have low toxin detection sensitivity [71,331]. Therefore, the diagnosis of diarrhea based solely on these testing methods may result in an underestimation of *C. difficile* virulence, and a more accurate diagnostic method for CDI is required. Guidelines in Europe and the United States propose a stepwise algorithm to perform a screening test, such as GDH testing or NAAT, followed by a toxin test. If the toxin test yields a negative result, a confirmatory toxin production test (e.g., TC or NAAT, if the initial screening involved GDH testing only) should be performed, as deemed necessary [71,331]. A test to detect *C. difficile* toxin B DNA in feces has also been added to the coverage of health insurance in Japan in April 2019 and is available for use in routine clinical practice. While NAAT has a short turnaround time and is simple, there is a concern that NAAT may detect toxin gene-positive strains not causing CDI due to its high sensitivity [332]. However, the clinical practice guidelines for CDI of the Japanese Society of Chemotherapy/Japanese Association for Infectious Diseases weakly recommend NAAT as the initial test in certain settings, such as outbreaks, in which the positive predictive value is likely to be elevated [102]. Meanwhile, CDI is diagnosed based on TC results in some cases in which patients are clinically suspected of having CDI but are GDH-positive and toxin A/B-negative, as systems necessary for the introduction of NAAT are currently not in place in some facilities. Given the fact that promptness of measures as well as accuracy of diagnosis are required during outbreaks, the usefulness of culture testing under such circumstances is worthy of review.

30.2. PICO

P (patients): Patients suspected of having CDI during CDI outbreaks
I (intervention): Implementation of culture tests
C (comparison): Non-implementation of culture tests
O (outcome): Usefulness for the diagnosis of infection control for CDI

30.3. Summary of evidence

Gold standard diagnostic tests for CDI include TC and cytotoxicity testing [71,226,331]. Cytotoxicity testing is regarded as the standard method for the diagnosis of CDI [226]; however, the test is often difficult to perform in ordinary laboratories because it requires equipment and techniques to maintain and manage cultured cells. Meanwhile, there are no established methods for TC. In general, TC is performed to test whether *C. difficile* strains isolated from fecal specimens have toxin A/B via cytotoxicity testing, toxin A/B EIAs, and NAAT-based toxin A/B gene detection methods [331]; the EIA method is commonly used for its versatility. Various methods of sample preparation for TC using the EIA method (e.g., whether to use a liquid culture medium or whether to prepare bacterial suspensions using bacterial isolates) have been reported, but there are no established methods [340–342].

Chang et al. compared the toxin-positive rates between the liquid and solid culture methods and reported that the liquid culture method had a higher detection rate (liquid culture-positive rate 26/68; 38 % vs. solid culture-positive rate 23/68, 34 %) and allowed for rapid detection [340]. Meanwhile, bacterial strains grown on solid media are often used for toxin detection in routine clinical practice, and Tanino et al. have reported that EIA using bacteria suspensions at concentrations of ≥McF4.0 had a sensitivity and specificity of 100 % each compared to the PCR method [341]. In the event of an outbreak, prompt measures are needed to end the prevalence, and the use of NAAT, which has recently been approved for health insurance coverage in Japan, is desirable for diagnosing CDI [102]. However, systems necessary for the introduction of NAAT are currently not in place in some facilities. There are no meta-analyses on whether *C. difficile* culturing, including TC, is worthwhile during outbreaks; nonetheless, a systematic review by a working group of the ESCMID has strongly recommended the use of a two-step method (GDH or toxin gene testing by NAAT, followed by fecal toxin testing or GDH and toxin testing, followed by NAAT or TC when the first step results are GDH-positive and toxin-negative) during CDI outbreaks. Meanwhile, there is a concern that the proactive use of TC for cases that are GDH-positive and toxin A/B-negative may detect carriers frequently, as was the case for NAAT, but it has been reported that carriers also contribute to transmission.

Riggs et al. have reported carrier-mediated transmission based on a prospective study conducted in long-term care facilities [113], and Blixt et al. have reported carrier-mediated transmission in hospitals through a multicenter prospective cohort study [343]. In light of these findings, the clinical practice guidelines for CDI published by the Japanese Society of Chemotherapy/Japanese Association for Infectious Diseases recommend more proactive use of NAAT and culture testing, which have higher sensitivity, during outbreaks in which the confirmation of a broader range of occurrences, including the possibility of GDH false-negative results and carriers, and evaluation using molecular epidemiological techniques, such as ribotyping, are necessary [102]. While culture tests are time-consuming and require TC costs in addition to the costs of rapid testing with fecal specimens, it is desirable to perform culture testing because it allows for the detailed analysis of strains and the accumulation of epidemiological information.

30.4. Quality of evidence for the overall outcome

C (recommended by experts).

30.5. Summary of benefits

TC, one of the gold standard diagnostic tests for CDI, is useful for the diagnosis of CDI when fecal test results are GDH-positive and toxin A/B-negative and NAAT methods are not available. Furthermore, evaluation using molecular epidemiological techniques, such as ribotyping, may be required in certain settings, such as outbreaks; culture tests can facilitate detailed analysis of bacterial strains and help with the accumulation of epidemiological information.

30.6. Summary of harms (adverse effects)

Culture tests are time-consuming and are associated with TC costs in addition to costs for rapid testing of fecal specimens. Moreover, detailed procedures for TC have not been established and may differ from one laboratory to another.

30.7. Summary of harms (burden)

The use of culture testing is likely to increase healthcare costs. Moreover, it takes time to obtain test results, and test procedures may differ between laboratories.

30.8. Benefit–harm balance

Benefits outweigh harms in outbreak settings.

30.9. Healthcare costs necessary for the intervention

Costs for TC are required in addition to costs for rapid testing of fecal specimens.

30.10. Feasibility of the intervention

Feasible in institutions that have an established testing system.

30.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

TC may be perceived differently by laboratories.

30.12. Recommendations in related clinical practice guidelines

The IDSA/SHEA 2017 Guidelines have no descriptions of the usefulness of TC during outbreaks [71]. The APIC guide states that TC may be impractical in routine clinical practice because several days are needed before the results are obtained, and the results depend on technical skills but may be useful as a gold standard for certain purposes, such as the evaluation of test performance or as a supplementary test for investigations in certain settings, such as outbreaks [124]. A systematic review by a working group of the ESCMID has strongly recommended the use of the two-step test method during CDI outbreaks [163,331].

31. CQ: Are bundle approaches effective during outbreaks?

Recommendation: Implementation of multiple measures in parallel is weakly recommended.

Strength level: Implementation is weakly recommended.

Comment: The effectiveness of bundles during outbreaks has not been studied in randomized controlled trials. There are also differences among reports, including reports on bundle items, details of individual measures, methods for evaluating adherence rates, and ward characteristics. Therefore, it is difficult to recommend which specific measures should be implemented, although bundles can be expected to be effective. Appropriate bundle components differ depending on the actual situations of the respective institutions.

31.1. Background and importance of the CQ

There are various CDI control measures, including hand hygiene, private-room isolation, and environmental disinfection. Multiple measures selected from these effective ones have been implemented as bundles to reduce the incidence of CDI. Bundles are expected to be more effective for containing outbreaks early. Here, a systematic review of papers published in or after 2000 on the effectiveness of bundle approaches during outbreaks was conducted.

31.2. PICO

P (event): During CDI outbreaks
I (intervention): Implementation of bundle approaches
C (comparison): Non-implementation of bundle approaches
O (outcome): Reduced incidence of CDI

31.3. Summary of evidence

It is difficult to conduct randomized studies comparing a group in which a bundle approach was implemented and another group in which the bundle approach was not implemented during CDI outbreaks. We

found nine papers published in or after 2000 on the effectiveness of implementing multiple measures in parallel [164,168,169,344–349]. In these studies, the number of measures per bundle varied from three to eight. The component measures in bundles used in the studies are listed in Table 14. Although the reduction in the incidence of CDI after the measures were implemented broadly ranged from 28.4 % [347] to 85.5 % [344], such CDI incidences have significantly decreased in all studies, demonstrating the effectiveness of the bundles. However, the reduction rate of CDI incidence did not correlate with the number of measures.

Among the component measures, environmental disinfection was implemented in all studies and hand hygiene was also implemented in most studies. However, the specifics of each measure differed from one study to another. In the case of environmental disinfection, for example, a study focused on the frequency of disinfection, while another study tested different disinfectants. Additionally, various methods were used to evaluate the rate of adherence to the measures. Rates of adherence to hand hygiene have been evaluated with multiple methods, such as direct observation and the consumption of alcohol-based hand rubs. However, given that the use of S/W is recommended for hand hygiene during outbreaks [71], it is questionable whether alcohol-based hand rub consumption is an appropriate indicator of adherence to the bundle. Accordingly, it is difficult to recommend which specific measures are effective and should be included in bundles. Evidence for hand hygiene is described first.

31.4. Quality of evidence for overall outcome

C (recommended by experts).

31.5. Summary of benefits

Implementation of multiple measures in parallel can be expected to contain outbreaks more quickly.

31.6. Summary of harms

Because it is not clear how much individual measures contribute to outbreak containment, the human resource and cost burdens associated with infection control may increase owing to the implementation of excessive measures.

31.7. Benefit–harm balance

By selecting and implementing countermeasures that have been implemented in many reports, the benefits can be expected to outweigh the harms of the burden on human resources and the increase in the cost of countermeasures.Healthcare costs necessary for the intervention.

① Environmental disinfection
② Hand hygiene
③ PPE

31.8. Feasibility of the intervention

Feasible.

31.9. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

31.10. Recommendations in related clinical practice guidelines

The IDSA/SHEA 2017 guidelines [71] and ESCMID guidelines [163] do not mention bundled approaches, although the effectiveness of individual measures during outbreaks is described. The WSES guidelines [200] recommend that a bundled approach during an outbreak should include appropriate antibacterial use, hand hygiene, private-room isolation, and environmental disinfection.

32. CQ: Are AS activities useful in reducing CDI?

Recommendation: AS activities are strongly recommended to reduce CDI incidence.

Strength level: Implementation is strongly recommended.

Comment: Risk factors for the development of CDI include the use of antibacterial agents. Systematic reviews and meta-analyses have shown that AS activities (e.g., discontinuation of unnecessary antibacterial agents, selection of appropriate antibacterial agents, and optimization of doses and dosing intervals) reduce CDI incidence.

32.1. Background and importance of the CQ

AS activities are performed to support the appropriate use of antibacterial agents by a team comprising multiple professionals specializing in infectious diseases and antibacterial chemotherapy. AS activities aim to control resistant bacteria, improve patients' prognoses and quality of life (QOL), prevent adverse effects, and reduce medical costs. As the use of antibacterial agents is a risk for the development of CDI, it is necessary to review whether AS activities are useful in reducing the incidence of CDI.

32.2. PICO

P (patients): Patients at risk of developing CDI
I (intervention): Implementation of AS activities

Table 14
Component measures in bundles used in the respective studies.

	Environmental disinfection	Hand hygiene	Private room/ cohorting	Contact precautions	Appropriate use of antibacterial agents	Staff education	System introduction	Patient education	Use of dedicated items
Oleastro [344]	○	○	○	○	○	○	○	○	
Weiss [169]	○	○	○	○	○	○	○	○	
Muto [168]	○	○	○	○	○	○	○		
Hanna [345]	○	○	○	○		○			○
Valiquette [346]	○		○		○	○			○
Wong-McClure [347]	○	○	○	○	○				
Apisanthanarak [348]	○	○		○		○			
Färber [349]	○	○	○		○				
Salgado [164]	○	○		○					

Measures are listed according to the order in the basic infection control measures, rather than the order of rates of adoption in bundles.
For measures not marked with "○," it is checked if complete adherence was assumed.

C (comparison): Non-implementation of AS activities
O (outcome): Reduced incidence of CDI

32.3. Summary of evidence

Risk factors for the development of CDI include the use of antibacterial agents and proton pump inhibitors. The use of antibacterial agents is highly involved in the development of CDI because it can disturb the intestinal microbiota [350]. Antibacterial agents implicated in the development of CDI include fluoroquinolones and cephalosporins [351,352]. Carbapenems have been reported to play a substantial role in the development of CDI compared to fluoroquinolones (risk ratio 2.44: 95 % CI 1.32–4.49) and cephalosporins (risk ratio 2.24: 95 % CI 1.46–3.42) [353].

Moreover, the use of antibacterial agents at increased doses for prolonged durations and the combined use of a large number of antibacterial agents present risks for the development of CDI [354]. Therefore, the incidence of CDI can be reduced theoretically through the implementation of AS activities, such as the discontinuation of unnecessary antibacterial agents, the selection of appropriate antibacterial agents, and the optimization of doses and dosing intervals.

In 2017, Cochrane conducted a systematic review to determine whether AS activities affected the incidence of CDI in hospitalized patients. The result showed that AS activities reduced the incidence of CDI (median, −48.6 %; interquartile range, −80.7% to −19.2 %, seven studies), albeit the evidence level was low [355]. Other reported systematic reviews and meta-analyses have shown that AS activities reduced the incidence to 0.68 (95 % CI 0.45–0.88, $p = 0.0029$) [139]. Furthermore, a report has demonstrated that the risk ratio was reduced to 0.48 (95 % CI 0.38–0.62, $p < 0.00001$) [356].

As systematic reviews and meta-analyses have indicated that AS activities represent one of the most useful approaches to reducing the incidence of CDI, the implementation of AS activities is strongly recommended.

Besides the appropriate use of antibacterial agents to reduce CDI incidence, AS activities include discontinuation of gastric antisecretory drugs, concomitant use of probiotics with antibacterial agents, selection of drugs for the treatment of CDI, and administration of bezlotoxumab depending on the patient's condition.

Proton pump inhibitors and histamine H_2 receptor blockers have been identified as risk factors for the development of CDI via systematic reviews and meta-analyses. Proton pump inhibitors have been associated with a 38.6 % higher risk than histamine H_2 receptor blockers [357]. Recently, proton pump inhibitor stewardship programs have been developed and increasingly implemented to promote the appropriate use of proton pump inhibitors [358–360]. Inappropriate use of proton pump inhibitors should be discontinued, but evidence of CDI incidence reduction via discontinuation of proton pump inhibitors or switching thereof to different drugs is still pending, and further studies are warranted.

Moreover, the use of proton pump inhibitors with new mechanisms of action, such as potassium-competitive acid blockers, may also be a risk factor for the development of CDI [361,362]. Further studies with larger sample sizes are needed in the future.

Cochrane conducted a meta-analysis in 2017 to determine if probiotics prevent the development of CDI in adults and children treated with antibacterial agents [363]. The result showed that combining antibacterial agents and probiotics reduced the incidence to a risk ratio of 0.40 (95 % CI 0.30–0.52, $p < 0.00001$). Furthermore, no increases in the incidence of adverse effects were associated with the use of probiotics, and the combined use of antibacterial agents and probiotics for a short time was demonstrated to be safe and effective, except when patients were immunosuppressed or severely debilitated. However, as probiotics contain various bacterial species and strains in various quantities, available clinical evidence is insufficient to recommend any specific preparation of probiotics [364]. Moreover, there are reports describing the occurrence of bacteremia in immunosuppressed patients [365] and an increased mortality rate in patients with acute pancreatitis [366].

Therapeutic agents for CDI commercially available in Japan include metronidazole, vancomycin, and fidaxomicin. A systematic review/meta-analysis study has shown that fidaxomicin was associated with a significantly lower recurrence rate than vancomycin and metronidazole, with ORs of 0.47 and 0.42, respectively, and 95 % CIs of 0.37–0.60 and 0.18–0.96, respectively [367]. Therefore, fidaxomicin may be selected to reduce the recurrence rate of CDI.

A phase III study conducted in Japan has shown that bezlotoxumab prevented the recurrence of CDI significantly and more effectively than the placebo [368]. Gerding et al. evaluated the bezlotoxumab efficacy in participants with recurrence risk factors, i.e., age ≥65 years, history of CDI, compromised immunity, severe CDI, and ribotype 027/078/244 infection, and reported that bezlotoxumab reduced the recurrence rate by 14.2 % and 24.8 % in patients with one and three risk factors, respectively, while bezlotoxumab and placebo were equally effective for preventing recurrent CDI in patients with no risk factors [369].

Accordingly, the discontinuation of the inappropriate use of proton pump inhibitors, the use of probiotics concomitantly with antibacterial agents as needed, the treatment of CDI with fidaxomicin, and the use of bezlotoxumab in patients at high risk for recurrence are likely to reduce the incidence of CDI. However, no previous studies have investigated whether AS activities, including activities related to these factors, help reduce the incidence of CDI, and this point remains to be addressed in future research.

32.4. Quality of evidence for overall outcome

A.

32.5. Summary of benefits

AS activities reduce the incidence of CDI.

32.6. Summary of harms (adverse effects)

CDI may relapse after antibacterial agents are discontinued or switched.

32.7. Summary of harms (burden)

AS activities cause no harm (adverse effects) to patients.

32.8. Benefit–harm balance

The benefits outweigh the harms because AS activities can reduce the incidence of CDI.

32.9. Healthcare costs necessary for the intervention

Costs are incurred to train and recruit the necessary personnel specializing in infectious diseases and antibacterial chemotherapy.

32.10. Feasibility of the intervention

Feasible.

32.11. Is the intervention perceived differently by patients/families/allied health professionals/doctors?

No.

32.12. Recommendations in related clinical practice guidelines

Implementation of AS activities is "strongly recommend" in the Japanese Society of Chemotherapy/Japanese Association for Infectious Diseases guidelines 2018 [102]; "good practice recommendation" in the IDSA/SHEA 2017 Guidelines [71]; and "1B (strong recommendation, moderate-quality evidence)" in the WSES guidelines 2019 [200].

Conflicts of interest (COI)

The Japanese Society for Infection Prevention and Control has formed the Conflict of Interest Committee, which appropriately manages COI situations based on the guidelines and detailed rules regarding COI. Below are COI-related matters for members of the editorial committee for "Guide to *Clostridioides difficile* Infection Prevention and Control."

1) Research grants and the like received
2) Lecture fees, manuscript fees, and the like received
3) Personal incomes received by members of the drafting committee

Hiroyuki Kunishima received lecture fees from MSD Co., Ltd., Astellas Pharma Inc., Shionogi & Co., Ltd., and Miyarisan Pharmaceutical Co., Ltd.

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Kaoru Ichiki, Fumie Sakamoto, Yuka Sato, Tetsu Mizutani, Minako Mori, and Sadako Yoshizawa have no COI to declare.

References

[1] Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of *Clostridium difficile* as Clostridioides difficile (Hall and O'Toole 1935) Prevot 1938. Anaerobe 2016;40:95–9. https://doi.org/10.1016/j.anaerobe.2016.06.008.

[2] Paredes-Sabja D, Shen A, Sorg JA. *Clostridium difficile* spore biology: sporulation, germination, and spore structural proteins. Trends Microbiol 2014;22:406–16. https://doi.org/10.1016/j.tim.2014.04.003.

[3] Leggett MJ, Setlow P, Sattar SA, Maillard JY. Assessing the activity of microbicides against bacterial spores: knowledge and pitfalls. J Appl Microbiol 2016;120:1174–80. https://doi.org/10.1111/jam.13061.

[4] Leas BF, Sullivan N, Han JH, Pegues DA, Kaczmarek JL, Umscheid CA. Environmental cleaning for the prevention of healthcare-associated infections. Technical Brief No.22. Agency for Healthcare Research and Quality; 2015.

[5] Barbut F. How to eradicate *Clostridium difficile* from the environment. J Hosp Infect 2015;89:287–95. https://doi.org/10.1016/j.jhin.2014.12.007.

[6] Marra AR, Schweizer ML, Edmond MB. No-touch disinfection methods to decrease multidrug-resistant organism infections: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2018;39:20–31. https://doi.org/10.1017/ice.2017.226.

[7] George WL, Sutter VL, Citron D, Finegold SM. Selective and differential medium for isolation of *Clostridium difficile*. J Clin Microbiol 1979;9:214–9. https://doi.org/10.1128/jcm.9.2.214-219.1979.

[8] Monot M, Eckert C, Lemire A, Hamiot A, Dubois T, Tessier C, et al. *Clostridium difficile*: new insights into the evolution of the pathogenicity locus. Sci Rep 2015;5:15023. https://doi.org/10.1038/srep15023.

[9] Abt MC, McKenney PT, Pamer EG. *Clostridium difficile* colitis: pathogenesis and host defence. Nat Rev Microbiol 2016;14:609–20. https://doi.org/10.1038/nrmicro.2016.108.

[10] Aktories K. Bacterial protein toxins that modify host regulatory GTPases. Nat Rev Microbiol 2011;9:487–98. https://doi.org/10.1038/nrmicro2592.

[11] Burnham CA, Carroll KC. Diagnosis of *Clostridium difficile* infection: an ongoing conundrum for clinicians and for clinical laboratories. Clin Microbiol Rev 2013;26:604–30. https://doi.org/10.1128/CMR.00016-13.

[12] Matamouros S, England P, Dupuy B. *Clostridium difficile* toxin expression is inhibited by the novel regulator TcdC. Mol Microbiol 2007;64:1274–88. https://doi.org/10.1111/j.1365-2958.2007.05739.x.

[13] Carter GP, Douce GR, Govind R, Howarth PM, Mackin KE, Spencer J, et al. The anti-sigma factor TcdC modulates hypervirulence in an epidemic BI/NAP1/027 clinical isolate of Clostridium difficile. PLoS Pathog 2011;7:e1002317. https://doi.org/10.1371/journal.ppat.1002317.

[14] Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet 2005;366:1079–84. https://doi.org/10.1016/S0140-6736(05)67420-X.

[15] McDonald LC, Killgore GE, Thompson A, Owens Jr RC, Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 2005;353:2433–41. https://doi.org/10.1056/NEJMoa051590.

[16] Haglund CM, Welch MD. Pathogens and polymers: microbe-host interactions illuminate the cytoskeleton. J Cell Biol 2011;195:7–17. https://doi.org/10.1083/jcb.201103148.

[17] Schwan C, Kruppke AS, Nölke T, Schumacher L, Koch-Nolte F, Kudryashev M, et al. *Clostridium difficile* toxin CDT hijacks microtubule organization and reroutes vesicle traffic to increase pathogen adherence. Proc Natl Acad Sci U S A 2014;111:2313–8. https://doi.org/10.1073/pnas.1311589111.

[18] Tagashira Y, Kato H, Senoh M, Nakamura A. Two cases of fulminant colitis due to binary toxin-positive *Clostridium difficile* that are not PCR ribotype 027 or type 078. J Med Microbiol 2013;62:1486–9. https://doi.org/10.1099/jmm.0.057968-0.

[19] Okada Y, Kaku N, Kosai K, Uno N, Morinaga Y, Hasegawa H, et al. Molecular epidemiology of *Clostridioides difficile* and risk factors for the detection of toxin gene-positive strains. J Infect Chemother 2019;25:262–6. https://doi.org/10.1016/j.jiac.2018.12.004.

[20] Watanabe H, Koizumi Y, Matsumoto A, Asai N, Yamagishi Y, Mikamo H. Association between *Clostridioides difficile* ribotypes, restriction endonuclease analysis types, and toxin gene expression. Anaerobe 2018;54:140–3. https://doi.org/10.1016/j.anaerobe.2018.09.002.

[21] Clements AC, Magalhães RJ, Tatem AJ, Paterson DL, Riley TV. *Clostridium difficile* PCR ribotype 027: assessing the risks of further worldwide spread. Lancet Infect Dis 2010;10:395–404. https://doi.org/10.1016/S1473-3099(10)70080-3.

[22] Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442–9. https://doi.org/10.1056/NEJMoa051639.

[23] Knight DR, Elliott B, Chang BJ, Perkins TT, Riley TV. Diversity and evolution in the genome of *Clostridium difficile*. Clin Microbiol Rev 2015;28:721–41. https://doi.org/10.1128/CMR.00127-14.
[24] Gerding DN, Johnson S, Rupnik M, Aktories K. *Clostridium difficile* binary toxin CDT: mechanism, epidemiology, and potential clinical importance. Gut Microb 2014;5:15–27. https://doi.org/10.4161/gmic.26854.
[25] Goorhuis A, Bakker D, Corver J, Debast SB, Harmanus C, Notermans DW, et al. Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. Clin Infect Dis 2008;47:1162–70. https://doi.org/10.1086/592257.
[26] Yamagishi Y, Tsukada A, Tani H, Inukai T, Takayasu M, Kato Y, et al. A case antibiotics-associated colitis caused by binary toxin producing gene positive *Clostridium difficile*. J. Jpn. Soc. Surg. Infect. 2010;7:179–83.
[27] Riley TV, Kimura T. The epidemiology of *Clostridium difficile* infection in Japan: a systematic review. Infect Dis Ther 2018;7:39–70. https://doi.org/10.1007/s40121-018-0186-1.
[28] Senoh M, Kato H, Fukuda T, Niikawa A, Hori Y, Hagiya H, et al. Predominance of PCR-ribotypes, 018 (smz) and 369 (trf) of Clostridium difficile in Japan: a potential relationship with other global circulating strains? J Med Microbiol 2015;64:1226–36. https://doi.org/10.1099/jmm.0.000149.
[29] Kato H, Senoh M, Honda H, Fukuda T, Tagashira Y, Horiuchi H, et al. Clostridioides (Clostridium) difficile infection burden in Japan: a multicenter prospective study. Anaerobe 2019;60:102011. https://doi.org/10.1016/j.anaerobe.2019.03.007.
[30] Collins DA, Hawkey PM, Riley TV. Epidemiology of *Clostridium difficile* infection in Asia. Antimicrob Resist Infect Control 2013;2:21. https://doi.org/10.1186/2047-2994-2-21.
[31] Mori N, Yoshizawa S, Saga T, Ishii Y, Murakami H, Iwata M, et al. Incorrect diagnosis of *Clostridium difficile* infection in a university hospital in Japan. J Infect Chemother 2015;21:718–22. https://doi.org/10.1016/j.jiac.2015.06.009.
[32] Komatsu M, Kato H, Aihara M, Shimakawa K, Iwasaki M, Nagasaka Y, et al. High frequency of antibiotic-associated diarrhea due to toxin A-negative, toxin B-positive *Clostridium difficile* in a hospital in Japan and risk factors for infection. Eur J Clin Microbiol Infect Dis 2003;22:525–9. https://doi.org/10.1007/s10096-003-0992-5.
[33] Sato H, Kato H, Kenji Koiwai K, Sakai C. A nosocomial outbreak of diarrhea caused by toxin A-negative. Toxin B-positive Clostridium difficile in A Cancer Center Hospital, Kansenshogaku Zasshi 2004;78:312–9.
[34] Ando T, Kono M, Sasaki M, Nagano Y, Kanemoto S, Hirata R, et al. Molecular epidemiological analysis on toxin A-negative, toxin B-positive type *Clostridium difficile* which mainly broken out among orthopedic patients. The journal of the Japanese Society for Clinical Microbiology 2013;23:186–93.
[35] Iwashima Y, Nakamura A, Kato H, Kato H, Wakimoto Y, Wakiyama N, et al. A retrospective study of the epidemiology of *Clostridium difficile* infection at a university hospital in Japan: genotypic features of the isolates and clinical characteristics of the patients. J Infect Chemother 2010;16:329–33. https://doi.org/10.1007/s10156-010-0066-4.
[36] Kato H, Kato H, Ito Y, Akahane T, Izumida S, Yokoyama T, et al. Typing of *Clostridium difficile* isolates endemic in Japan by sequencing of slpA and its application to direct typing. J Med Microbiol 2010;59:556–62. https://doi.org/10.1099/jmm.0.016147-0.
[37] Kuwata Y, Tanimoto S, Sawabe E, Shima M, Takahashi Y, Ushizawa H, et al. Molecular epidemiology and antimicrobial susceptibility of *Clostridium difficile* isolated from a university teaching hospital in Japan. Eur J Clin Microbiol Infect Dis 2015;34:763–72. https://doi.org/10.1007/s10096-014-2290-9.
[38] Mori N, Aoki Y. Clinical characteristics and risk factors for community-acquired *Clostridium difficile* infection: a retrospective, case-control study in a tertiary care hospital in Japan. J Infect Chemother 2015;21:864–7. https://doi.org/10.1016/j.jiac.2015.09.004.
[39] Sawabe E, Kato H, Osawa K, Chida T, Tojo N, Arakawa Y, et al. Molecular analysis of *Clostridium difficile* at a university teaching hospital in Japan: a shift in the predominant type over a five-year period. Eur J Clin Microbiol Infect Dis 2007;26:695–703. https://doi.org/10.1007/s10096-007-0355-8.
[40] Hara T, Furushimo M, Onodera M, Koba Y, Nagaoka R, Ohge H, et al. Prevalence of *Clostridium difficile* binary toxin genes in Hiroshima university hospital, Igakukensa, 64; 2015. p. 242–6.
[41] Ishimura S, Orita T, Kobayashi A, Kato H. A case of community-acquired pseudomembranous colitis caused by binary toxin-positive *Clostridioides difficile* (*Clostridium difficile*). The journal of the Japanese Society for Clinical Microbiology 2017;27:313–9.
[42] Collins DA, Riley TV. *Clostridium difficile* in Asia: opportunities for one health management. Trav Med Infect Dis 2018;4:7. https://doi.org/10.3390/tropicalmed4010007.
[43] Kim J, Kang JO, Kim H, Seo MR, Choi TY, Pai H, et al. Epidemiology of *Clostridium difficile* infections in a tertiary-care hospital in Korea. Clin Microbiol Infect 2013;19:521–7. https://doi.org/10.1111/j.1469-0691.2012.03910.x.
[44] Seo MR, Kim J, Lee Y, Lim DG, Pai H. Prevalence, genetic relatedness and antibiotic resistance of hospital-acquired clostridium difficile PCR ribotype 018 strains. Int J Antimicrob Agents 2018;51:762–7. https://doi.org/10.1016/j.ijantimicag.2018.01.025.
[45] Huang H, Fang H, Weintraub A, Nord CE. Distinct ribotypes and rates of antimicrobial drug resistance in *Clostridium difficile* from Shanghai and Stockholm. Clin Microbiol Infect 2009;15:1170–3. https://doi.org/10.1111/j.1469-0691.2009.02992.x.
[46] Du P, Cao B, Wang J, Li W, Jia H, Zhang W, et al. Sequence variation in tcdA and tcdB of *Clostridium difficile*: ST37 with truncated tcdA is a potential epidemic strain in China. J Clin Microbiol 2014;52:3264–70. https://doi.org/10.1128/JCM.03487-13.
[47] Jin D, Luo Y, Huang C, Cai J, Ye J, Zheng Y, et al. Molecular epidemiology of *Clostridium difficile* infection in hospitalized patients in eastern China. J Clin Microbiol 2017;55:801–10. https://doi.org/10.1128/JCM.01898-16.
[48] Cheng VC, Yam WC, Lam OT, Tsang JL, Tse EY, Siu GK, et al. *Clostridium difficile* isolates with increased sporulation: emergence of PCR ribotype 002 in Hong Kong. Eur J Clin Microbiol Infect Dis 2011;30:1371–81. https://doi.org/10.1007/s10096-011-1231-0.
[49] Kim H, Lee Y, Moon HW, Lim CS, Lee K, Chong Y. Emergence of *Clostridium difficile* ribotype 027 in Korea. Korean J Lab Med 2011;31:191–6. https://doi.org/10.3343/kjlm.2011.31.3.191.
[50] Jia H, Du P, Yang H, Zhang Y, Wang J, Zhang W, et al. Nosocomial transmission of Clostridium difficile ribotype 027 in a Chinese hospital, 2012-2014, traced by whole genome sequencing. BMC Genom 2016;17:405. https://doi.org/10.1186/s12864-016-2708-0.
[51] Liu XS, Li WG, Zhang WZ, Wu Y, Lu JX. Molecular characterization of *Clostridium difficile* isolates in China from 2010 to 2015. Front Microbiol 2018;9:845. https://doi.org/10.3389/fmicb.2018.00845.
[52] He M, Miyajima F, Roberts P, Ellison L, Pickard DJ, Martin MJ, et al. Emergence and global spread of epidemic healthcare-associated *Clostridium difficile*. Nat Genet 2013;45:109–13. https://doi.org/10.1038/ng.2478.
[53] Hung YP, Huang IH, Lin HJ, Tsai BY, Liu HC, Liu HC, et al. Predominance of *Clostridium difficile* ribotypes 017 and 078 among toxigenic clinical isolates in southern Taiwan. PLoS One 2016;11:e0166159. https://doi.org/10.1371/journal.pone.0166159.
[54] Hung YP, Tsai PJ, Lee YT, Tang HJ, Lin HJ, Liu HC, et al. Nationwide surveillance of ribotypes and antimicrobial susceptibilities of toxigenic *Clostridium difficile* isolates with an emphasis on reduced doxycycline and tigecycline susceptibilities among ribotype 078 lineage isolates in Taiwan. Infect Drug Resist 2018;11:1197–203. https://doi.org/10.2147/IDR.S162874.
[55] Jin H, Ni K, Wei L, Shen L, Xu H, Kong Q, et al. Identification of *Clostridium difficile* RT078 from patients and environmental surfaces in Zhejiang Province, China. Infect Control Hosp Epidemiol 2016;37:745–6. https://doi.org/10.1017/ice.2016.58.
[56] Tickler IA, Goering RV, Whitmore JD, Lynn AN, Persing DH, Tenover FC, et al. Strain types and antimicrobial resistance patterns of *Clostridium difficile* isolates from the United States, 2011 to 2013. Antimicrob Agents Chemother 2014;58:4214–8. https://doi.org/10.1128/AAC.02775-13.
[57] Giancola SE, Williams IIRJ, Gentry CA. Prevalence of the *Clostridium difficile* BI/NAP1/027 strain across the United States veterans health administration. Clin Microbiol Infect 2018;24:877–81. https://doi.org/10.1016/j.cmi.2017.11.011.
[58] Cheknis A, Johnson S, Chesnel L, Petrella L, Sambol S, Dale SE, et al. Molecular epidemiology of *Clostridioides (Clostridium) difficile* strains recovered from clinical trials in the US, Canada and Europe from 2006-2009 to 2012-2015. Anaerobe 2018;53:38–42. https://doi.org/10.1016/j.anaerobe.2018.05.009.
[59] Martin JS, Monaghan TM, Wilcox MH. *Clostridium difficile* infection: epidemiology, diagnosis and understanding transmission. Nat Rev Gastroenterol Hepatol 2016;13:206–16. https://doi.org/10.1038/nrgastro.2016.25.
[60] Freeman J, Vernon J, Morris K, Nicholson S, Todhunter S, Longshaw C, et al. Pan-European longitudinal surveillance of antibiotic resistance among prevalent Clostridium difficile ribotypes. Clin Microbiol Infect 2015;21. https://doi.org/10.1016/j.cmi.2014.09.017. 248.e9–248.e16.
[61] Eyre DW, Davies KA, Davis G, Fawley WN, Dingle KE, De Maio N, et al. Two distinct patterns of *Clostridium difficile* diversity across Europe indicating contrasting routes of spread. Clin Infect Dis 2018;67:1035–44. https://doi.org/10.1093/cid/ciy252.
[62] Freeman J, Vernon J, Pilling S, Morris K, Nicholson S, Shearman S, et al. The ClosER study: results from a three-year pan-European longitudinal surveillance of antibiotic resistance among prevalent Clostridium difficile ribotypes, 2011-2014. Clin Microbiol Infect 2018;24:724–31. https://doi.org/10.1016/j.cmi.2017.10.008.
[63] Mallia G, Van Toen J, Rousseau J, Jacob L, Boerlin P, Greer A, et al. Examining the epidemiology and microbiology of *Clostridium difficile* carriage in elderly patients and residents of a healthcare facility in southern Ontario, Canada. J Hosp Infect 2018;99:461–8. https://doi.org/10.1016/j.jhin.2018.01.020.
[64] Karlowsky JA, Adam HJ, Kosowan T, Baxter MR, Nichol KA, Laing NM, et al. PCR ribotyping and antimicrobial susceptibility testing of isolates of *Clostridium difficile* cultured from toxin-positive diarrheal stools of patients receiving medical care in Canadian hospitals: the Canadian *Clostridium difficile* Surveillance Study (CAN-DIFF) 2013-2015. Diagn Microbiol Infect Dis 2018;91:105–11. https://doi.org/10.1016/j.diagmicrobio.2018.01.017.
[65] Eyre DW, Tracey L, Elliott B, Slimings C, Huntington PG, Stuart RL, et al. Emergence and spread of predominantly community-onset *Clostridium difficile* PCR ribotype 244 infection in Australia, 2010 to 2012. Euro Surveill 2015;20:21059. https://doi.org/10.2807/1560-7917.es2015.20.10.21059.
[66] Plaza-Garrido Á, Barra-Carrasco J, Macias JH, Carman R, Fawley WN, Wilcox MH, et al. Predominance of *Clostridium difficile* ribotypes 012, 027 and 046 in a university hospital in Chile, 2012. Epidemiol Infect 2016;144:976–9. https://doi.org/10.1017/S0950268815002459.
[67] Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, et al. *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet 2011;377:63–73. https://doi.org/10.1016/S0140-6736(10)61266-4.
[68] Durovic A, Widmer AF, Tschudin-Sutter S. New insights into transmission of *Clostridium difficile* infection-narrative review. Clin Microbiol Infect 2018;24:483–92. https://doi.org/10.1016/j.cmi.2018.01.027.

[69] Freeman J, Bauer MP, Baines SD, Corver J, Fawley WN, Goorhuis B, et al. The changing epidemiology of Clostridium difficile infections. Clin Microbiol Rev 2010;23:529–49. https://doi.org/10.1128/CMR.00082-09.
[70] Gould LH, Limbago B. *Clostridium difficile* in food and domestic animals: a new foodborne pathogen? Clin Infect Dis 2010;51:577–82. https://doi.org/10.1086/655692.
[71] McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the infectious diseases society of America (IDSA) and society for healthcare epidemiology of America (SHEA). Clin Infect Dis 2018;66:e1–48. https://doi.org/10.1093/cid/cix1085.
[72] Furuya-Kanamori L, Marquess J, Yakob L, Riley TV, Paterson DL, Foster NF, et al. Asymptomatic *Clostridium difficile* colonization: epidemiology and clinical implications. BMC Infect Dis 2015;15:516. https://doi.org/10.1186/s12879-015-1258-4.
[73] Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. Am J Gastroenterol 2013;108:478–98. https://doi.org/10.1038/ajg.2013.4. quiz 499.
[74] Clabots CR, Johnson S, Olson MM, Peterson LR, Gerding DN. Acquisition of *Clostridium difficile* by hospitalized patients: evidence for colonized new admissions as a source of infection. J Infect Dis 1992;166:561–7. https://doi.org/10.1093/infdis/166.3.561.
[75] Al-Jumaili IJ, Shibley M, Lishman AH, Record CO. Incidence and origin of *Clostridium difficile* in neonates. J Clin Microbiol 1984;19:77–8. https://doi.org/10.1128/jcm.19.1.77-78.1984.
[76] Bacon AE, Fekety R, Schaberg DR, Faix RG. Epidemiology of *Clostridium difficile* colonization in newborns: results using a bacteriophage and bacteriocin typing system. J Infect Dis 1988;158:349–54. https://doi.org/10.1093/infdis/158.2.349.
[77] Matsuki S, Ozaki E, Shozu M, Inoue M, Shimizu S, Yamaguchi N, et al. Colonization by *Clostridium difficile* of neonates in a hospital, and infants and children in three day-care facilities of Kanazawa, Japan. Int Microbiol 2005;8:43–8.
[78] Furuichi M, Imajo E, Sato Y, Tanno S, Kawada M, Sato S. Characteristics of *Clostridium difficile* colonization in Japanese children. J Infect Chemother 2014;20:307–11.
[79] Eglow R, Pothoulakis C, Itzkowitz S, Israel EJ, O'Keane CJ, Gong D, et al. Diminished *Clostridium difficile* toxin A sensitivity in newborn rabbit ileum is associated with decreased toxin A receptor. J Clin Invest 1992;90:822–9. https://doi.org/10.1172/JCI115957.
[80] Rousseau C, Lemée L, Le Monnier A, Poilane I, Pons JL, Collignon A. Prevalence and diversity of *Clostridium difficile* strains in infants. J Med Microbiol 2011;60:1112–8. https://doi.org/10.1099/jmm.0.029736-0.
[81] Borren NZ, Ghadermarzi S, Hutfless S, Ananthakrishnan AN. The emergence of *Clostridium difficile* infection in Asia: a systematic review and meta-analysis of incidence and impact. PLoS One 2017;12:e0176797. https://doi.org/10.1371/journal.pone.0176797.
[82] Bouza E. Consequences of *Clostridium difficile* infection: understanding the healthcare burden. Clin Microbiol Infect 2012;18(suppl 6):5–12. https://doi.org/10.1111/1469-0691.12064.
[83] Zhang D, Prabhu VS, Marcella SW. Attributable healthcare resource utilization and costs for patients with primary and recurrent *Clostridium difficile* infection in the United States. Clin Infect Dis 2018;66:1326–32. https://doi.org/10.1093/cid/cix1021.
[84] Gupta A, Patel R, Baddour LM, Pardi DS, Khanna S. Extraintestinal *Clostridium difficile* infections: a single-center experience. Mayo Clin Proc 2014;89:1525–36. https://doi.org/10.1016/j.mayocp.2014.07.012.
[85] Kazanji N, Gjeorgjievski M, Yadav S, Mertens AN, Lauter C. Monomicrobial vs polymicrobial *Clostridium difficile* bacteremia: a case report and review of the literature. Am J Med 2015;128:e19–26. https://doi.org/10.1016/j.amjmed.2015.05.014.
[86] Mattila E, Arkkila P, Mattila PS, Tarkka E, Tissari P, Anttila VJ. Extraintestinal *Clostridium difficile* infections. Clin Infect Dis 2013;57:e148–53. https://doi.org/10.1093/cid/cit392.
[87] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372:825–34. https://doi.org/10.1056/NEJMoa1408913.
[88] Honda H, Yamazaki A, Sato Y, Dubberke ER. Incidence and mortality associated with *Clostridium difficile* infection at a Japanese tertiary care center. Anaerobe 2014;25:5–10. https://doi.org/10.1016/j.anaerobe.2013.10.004.
[89] Sunkesula VC, Kundrapu S, Jury LA, Deshpande A, Sethi AK, Donskey CJ. Potential for transmission of spores by patients awaiting laboratory testing to confirm suspected *Clostridium difficile* infection. Infect Control Hosp Epidemiol 2013;34:306–8. https://doi.org/10.1086/669510.
[90] McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med 1989;320:204–10. https://doi.org/10.1056/NEJM198901263200402.
[91] Sethi AK, Al-Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of *Clostridium difficile* during and after treatment of *C. difficile* infection. Infect Control Hosp Epidemiol 2010;31:21–7.
[92] Echaiz JF, Veras L, Zervos M, Dubberke E, Johnson L. Hospital roommates and development of health care-onset *Clostridium difficile* infection. Am J Infect Control 2014;42:1109–11. https://doi.org/10.1016/j.ajic.2014.06.023.
[93] Sammons JS, Toltzis P, Zaoutis TE. *Clostridium difficile* Infection in children. JAMA Pediatr 2013;167:567–73. https://doi.org/10.1001/jamapediatrics.2013.441.
[94] Dubberke ER, Reske KA, Olsen MA, McDonald LC, Fraser VJ. Short- and long-term attributable costs of *Clostridium difficile*-associated disease in nonsurgical inpatients. Clin Infect Dis 2008;46:497–504. https://doi.org/10.1086/526530.
[95] Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clin Infect Dis 2002;34:346–53. https://doi.org/10.1086/338260.
[96] Vonberg RP, Reichardt C, Behnke M, Schwab F, Zindler S, Gastmeier P. Costs of nosocomial *Clostridium difficile*-associated diarrhoea. J Hosp Infect 2008;70:15–20. https://doi.org/10.1016/j.jhin.2008.05.004.
[97] Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S, Fushimi K. The burden of *Clostridium difficile*-associated disease following digestive tract surgery in Japan. J Hosp Infect 2012;82:175–80. https://doi.org/10.1016/j.jhin.2012.07.023.
[98] Wilcox MH, Ahir H, Coia JE, Dodgson A, Hopkins S, Llewelyn MJ, et al. Impact of recurrent Clostridium difficile infection: hospitalization and patient quality of life. J Antimicrob Chemother 2017;72:2647–56. https://doi.org/10.1093/jac/dkx174.
[99] Kunishima H, Ito K, Laurent T, Abe M. Healthcare burden of recurrent *Clostridioides difficile* infection in Japan: a retrospective database study. J Infect Chemother 2018;24:892–901. https://doi.org/10.1016/j.jiac.2018.07.020.
[100] van Beurden YH, Bomers MK, van der Werff SD, Pompe EAPM, Spiering S, Vandenbroucke-Grauls CMJE, et al. Cost analysis of an outbreak of *Clostridium difficile* infection ribotype 027 in a Dutch tertiary care centre. J Hosp Infect 2017;95:421–5. https://doi.org/10.1016/j.jhin.2016.12.019.
[101] Kuijper EJ, Coignard B, Tull P, Difficile ESGfC, States EUM, European Centre for Disease P, et al. Emergence of *Clostridium difficile*-associated disease in North America and Europe. Clin Microbiol Infect 2006;12(suppl 6):2–18. https://doi.org/10.1111/j.1469-0691.2005.01273.x.
[102] Committee for development of the Japanese clinical practice guidelines for management of Clostridioides (Clostridium) difficile infection. The Japanese clinical practice guidelines for management of *Clostridioides (Clostridium) difficile* infections. Tokyo: Japanese Society of Chemotherapy, Japanese Association for Infectious Diseases; 2018.
[103] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920–4. https://doi.org/10.3109/00365529709011203.
[104] Erb S, Frei R, Strandén AM, Dangel M, Tschudin-Sutter S, Widmer AF. Low sensitivity of fecal toxin A/B enzyme immunoassay for diagnosis of *Clostridium difficile* infection in immunocompromised patients. Clin Microbiol Infect 2015;21. https://doi.org/10.1016/j.cmi.2015.07.016. 998.e9–998.e15.
[105] Kim KH, Fekety R, Batts DH, Brown D, Cudmore M, Silva J, et al. Isolation of *Clostridium difficile* from the environment and contacts of patients with antibiotic-associated colitis. J Infect Dis 1981;143:42–50. https://doi.org/10.1093/infdis/143.1.42.
[106] Fekety R, Kim KH, Brown D, Batts DH, Cudmore M, Silva J. Epidemiology of antibiotic-associated colitis; isolation of *Clostridium difficile* from the hospital environment. Am J Med 1981;70:906–8. https://doi.org/10.1016/0002-9343(81)90553-2.
[107] Weber DJ, Rutala WA, Miller MB, Huslage K, Sickbert-Bennett E. Role of hospital surfaces in transmission of emerging healthcare-associated pathogens. In: Rutala WA, editor. Disinfection, sterilization, and anti-sepsis. Washington, DC: association for professionals in infection control and epidemiology, Inc; 2010.
[108] Weber DJ, Rutala WA, Miller MB, Huslage K, Sickbert-Bennett E. Role of hospital surfaces in the transmission of emerging health care-associated pathogens: Norovirus, *Clostridium difficile*, and *Acinetobacter* species. Am J Infect Control 2010;38(suppl 1):S25–33. https://doi.org/10.1016/j.ajic.2010.04.196.
[109] Best EL, Fawley WN, Parnell P, Wilcox MH. The potential for airborne dispersal of *Clostridium difficile* from symptomatic patients. Clin Infect Dis 2010;50:1450–7. https://doi.org/10.1086/652648.
[110] Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J. *Clostridium difficile*-associated diarrhea and colitis. Infect Control Hosp Epidemiol 1995;16:459–77. https://doi.org/10.1086/648363.
[111] Brooks SE, Veal RO, Kramer M, Dore L, Schupf N, Adachi M. Reduction in the incidence of *Clostridium difficile*-associated diarrhea in an acute care hospital and a skilled nursing facility following replacement of electronic thermometers with single-use disposables. Infect Control Hosp Epidemiol 1992;13:98–103. https://doi.org/10.1086/646480.
[112] Samore MH, DeGirolami PC, Tlucko A, Lichtenberg DA, Melvin ZA, Karchmer AW. *Clostridium difficile* colonization and diarrhea at a tertiary care hospital. Clin Infect Dis 1994;18:181–7. https://doi.org/10.1093/clinids/18.2.181.
[113] Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RLP, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic Clostridium difficile strains among long-term care facility residents. Clin Infect Dis 2007;45:992–8. https://doi.org/10.1086/521854.
[114] Tartof SY, Rieg GK, Wei R, Tseng HF, Jacobsen SJ, Yu KC. A comprehensive assessment across the healthcare continuum: risk of hospital-associated *Clostridium difficile* infection due to outpatient and inpatient antibiotic exposure. Infect Control Hosp Epidemiol 2015;36:1409–16. https://doi.org/10.1017/ice.2015.220.
[115] Johnson S, Gerding DN, Olson MM, Weiler MD, Hughes RA, Clabots CR, et al. Prospective, controlled study of vinyl glove use to interrupt Clostridium difficile nosocomial transmission. Am J Med 1990;88:137–40. https://doi.org/10.1016/0002-9343(90)90462-m.

[116] Badr RI, Badr HI, Ali NM. Mobile phones and nosocomial infections. Int J Infect Control 2012;8:1–5. https://doi.org/10.3396/ijic.v8i2.014.12.
[117] Tarrant J, Jenkins RO, Laird KT. From ward to washer: the survival of Clostridium difficile spores on hospital bed sheets through a commercial UK NHS healthcare laundry process. Infect Control Hosp Epidemiol 2018;39:1406–11. https://doi.org/10.1017/ice.2018.255.
[118] Janezic S, Mlakar S, Rupnik M. Dissemination of Clostridium difficile spores between environment and households: dog paws and shoes. Zoonoses Public Health 2018;65:669–74. https://doi.org/10.1111/zph.12475.
[119] Jencson AL, Cadnum JL, Wilson BM, Donskey CJ. Spores on wheels: wheelchairs are a potential vector for dissemination ofpathogens in healthcare facilities. Am J Infect Control 2019;47:459–61. https://doi.org/10.1016/j.ajic.2018.09.030.
[120] Samore MH, Venkataraman L, DeGirolami PC, Arbeit RD, Karchmer AW. Clinical and molecular epidemiology of sporadic and clustered cases of nosocomial Clostridium difficile diarrhea. Am J Med 1996;100:32–40. https://doi.org/10.1016/s0002-9343(96)90008-x.
[121] Fawley WN, Parnell P, Verity P, Freeman J, Wilcox MH. Molecular epidemiology of endemic Clostridium difficile infection and the significance of subtypes of the United Kingdom epidemic strain (PCR ribotype 1). J Clin Microbiol 2005;43:2685–96. https://doi.org/10.1128/JCM.43.6.2685-2696.2005.
[122] Shaughnessy M, Micielli R, Depestel D. Eval. In: Uation of hospital room assignment and acquisition of Clostridium difficile associated diarrhea (CDAD), 48th annual Interscience Conference on antimicrobial agents and chemotherapy and the infections disease society of America; DC: Washington; 2008. Abstract K-4194.
[123] Boyce JM, Havill NL, Otter JA, McDonald LC, Adams NM, Cooper T, et al. Impact of hydrogen peroxide vapor room decontamination on Clostridium difficile environmental contamination and transmission in a healthcare setting. Infect Control Hosp Epidemiol 2008;29:723–9. https://doi.org/10.1086/589906.
[124] APIC (Association for Professionals in Infection Control and Epidemiology). APIC implementation guide: guide to preventing Clostridium difficile infections. The association for professionals in infection control and epidemiology. https://apic.org/professional-practice/implementation-guides/; 2013.
[125] Eckstein BC, Adams DA, Eckstein EC, Rao A, Sethi AK, Yadavalli GK, et al. Reduction of *Clostridium difficile* and vancomycin-resistant *Enterococcus* contamination of environmental surfaces after an intervention to improve cleaning methods. BMC Infect Dis 2007;7:1–6. https://doi.org/10.1186/1471-2334-7-61.
[126] Doyle ME. Clostridium difficile as a risk associated with animal sources. Food Research Institute 2013:1–18.
[127] Asai T, Usui M, Hiki M, Kawanishi M, Nagai H, Sasaki Y. Clostridium difficile isolated from the fecal contents of swine in Japan. J Vet Med Sci 2013;75:539–41. https://doi.org/10.1292/jvms.12-0353.
[128] Usui M, Nanbu Y, Oka K, Takahashi M, Inamatsu T, Asai T, et al. Genetic relatedness between Japanese and European isolates of Clostridium difficile originating from piglets and their risk associated with human health. Front Microbiol 2014:1–8. https://doi.org/10.3389/fmicb.2014.00513.
[129] Usui M, Kawakura M, Yoshizawa N, San LL, Nakajima C, Suzuki Y, et al. Survival and prevalence of Clostridium difficile in manure compost derived from pigs. Anaerobe 2017;43:15–20. https://doi.org/10.1016/j.anaerobe.2016.11.004.
[130] Usui M, Suzuki K, Oka K, Miyamoto K, Takahashi M, Inamatsu T, et al. Distribution and characterization of Clostridium difficile isolated from dogs in Japan. Anaerobe 2016;37:58–61. https://doi.org/10.1016/j.anaerobe.2015.10.002.
[131] Loo VG, Brassard P, Miller MA. Household transmission of Clostridium difficile to family members and domestic pets. Infect Control Hosp Epidemiol 2016;37:1342–8. https://doi.org/10.1017/ice.2016.178.
[132] Lefebvre SL, Arroyo LG, Weese JS. Epidemic Clostridium difficile Strain in hospital visitation dog. Emerg Infect Dis 2006;12:1036–7. https://doi.org/10.3201/eid1206.060115.
[133] Obata A. Contamination of C. difficile in public park sandpits. J Juzen Med Soc 2007;116:36–40.
[134] Perumalsamy S, Putsathit P, Riley TV. High prevalence of Clostridium difficile in soil, mulch and lawn samples from the grounds of Western Australian hospitals. Anaerobe 2019;60:102065. https://doi.org/10.1016/j.anaerobe.2019.06.018.
[135] Zilberberg MD, Shorr AF, Micek ST, Kollef MH. Clostridium difficile recurrence is a strong predictor of 30-day rehospitalization among patients in intensive care. Infect Control Hosp Epidemiol 2015;36:273–9. https://doi.org/10.1017/ice.2014.47.
[136] Landelle C, Verachten M, Legrand P, Girou E, Barbut F, Brun-Buisson CB. Contamination of healthcare workers' hands with Clostridium difficile spores after caring for patients with C. difficile infection. Infect Control Hosp Epidemiol 2014;35:10–5. https://doi.org/10.1086/674396.
[137] Sunenshine RH, McDonald LC. Clostridium difficile-associated disease: new challenges from an established pathogen. Cleve Clin J Med 2006;73:187–97. https://doi.org/10.3949/ccjm.73.2.187.
[138] Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. J Antimicrob Chemother 2012;67:742–8. https://doi.org/10.1093/jac/dkr508.
[139] Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis 2017;17:990–1001. https://doi.org/10.1016/S1473-3099(17)30325-0.
[140] Dubberke ER, Carling P, Carrico R, Donskey CJ, Loo VG, McDonald LC, et al. Strategies to prevent *Clostridium difficile* infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35:628–45. https://doi.org/10.1086/676023.
[141] Mayfield JL, Leet T, Miller J, Mundy LM. Environmental control to reduce transmission of *Clostridium difficile*. Clin Infect Dis 2000;31:9951000.
[142] Islam J, Cheek E, Navani V, Rajkumar C, Cohen J, Llewelyn MJ. Influence of cohorting patients with *Clostridium difficile* infection on risk of symptomatic recurrence. J Hosp Infect 2013;85:17–21. https://doi.org/10.1016/j.jhin.2013.06.009.
[143] Oughton MT, Loo VG, Dendukuri N, Fenn S, Libman MD. Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of *Clostridium difficile*. Infect Control Hosp Epidemiol 2009;30:939–44. https://doi.org/10.1086/605322.
[144] Boyce JM, Ligi C, Kohan C, Dumigan D, Havill NL. Lack of association between the increased incidence of *Clostridium difficile*-associated disease and the increasing use of alcohol-based hand rubs. Infect Control Hosp Epidemiol 2006;27:479–83. https://doi.org/10.1086/504362.
[145] Miura M. Effectiveness of the introduction of a complex-type chlorine-based disinfectant cleaner for *Clostridium difficile* infection control. Kurume Med J 2017;80:51–6.
[146] Doan L, Forrest H, Fakis A, Craig J, Claxton L, Khare M. Clinical and cost effectiveness of eight disinfection methods for terminal disinfection of hospital isolation rooms contaminated with *Clostridium difficile* 027. J Hosp Infect 2012;82:114–21. https://doi.org/10.1016/j.jhin.2012.06.014.
[147] Rutala WA, Gergen MF, Weber DJ. Room decontamination with UV radiation. Infect Control Hosp Epidemiol 2010;31:1025–9. https://doi.org/10.1086/656244.
[148] Sampathkumar P, Folkert C, Barth JE, Nation L, Benz M, Hesse A, et al. A trial of pulsed xenon ultraviolet disinfection to reduce *Clostridioides difficile* infection. Am J Infect Control 2019;47:406–8. https://doi.org/10.1016/j.ajic.2018.09.018.
[149] Kato H, Hagihara M, Asai N, Shibata Y, Yamagishi Y, Iwamoto T, et al. A systematic review and meta-analysis of decontamination methods to prevent hospital environmental contamination and transmission of Clostridioidesdifficile. Anaerobe 2022;73:102478. https://doi.org/10.1016/j.anaerobe.2021.102478.
[150] Daniels T, Earlywine M, Breeding V. Environmental services impact on healthcare-associated Clostridium difficile reduction. Am J Infect Control 2019;47:400–405.e1. https://doi.org/10.1016/j.ajic.2018.09.016.
[151] Japan infection prevention and control Conference for national and public university hospitals: guidelines for infection control in university hospitals. Tokyo: Jiho; 2018.
[152] Kelly CP, LaMont JT. *Clostridium difficile*—more difficult than ever. N Engl J Med 2008;359:1932–40.
[153] Badger VO, Ledeboer NA, Graham MB, Edmiston CE. *Clostridium difficile*: epidemiology, pathogenesis, management, and prevention of a recalcitrant healthcare-associated pathogen, 36. JPEN J Parenter Enteral Nutr; 2012. p. 645–62.
[154] Viswanathan VK, Mallozzi MJ, Vedantam G. *Clostridium difficile* infection: an overview of the disease and its pathogenesis, epidemiology and interventions. Gut Microb 2010;1:234–42.
[155] Lanzas C, Dubberke ER. Effectiveness of screening hospital admissions to detect asymptomatic carriers of *Clostridium difficile*: a modeling evaluation. Infect Control Hosp Epidemiol 2014;35:1043–50.
[156] Ziakas PD, Zacharioudakis IM, Zervou FN, Grigoras C, Pliakos EEP, Mylonakis E. Asymptomatic carriers of toxigenic *C. diffcile* in long-term care facilities: a meta-analysis of prevalence and risk factors. PLoS One 2015;10:e0117195.
[157] Balsells E, Filipescu T, Kyaw MH, Wiuff C, Campbell H, Nair H. Infection prevention and control of *Clostridium difficile*: a global review of guidelines, strategies, and recommendations. J Glob Health 2016;6:020410. https://doi.org/10.7189/jogh.06.020410.
[158] Kizu J, Hori S, Iwata S. Status of infection control education in medical and paramedical faculties. Jpn J Infect Prev Control 2015;30:202–6.
[159] Yamagishi Y, Mikamo H. Recent epidemiology of *Clostridium difficile* infection in Japan. Jpn J Antibiot 2015;68:345–58.
[160] Goldstein EJC, Johnson S, Maziade PJ, McFarland LV, Trick W, Dresser L, et al. Pathway to prevention of nosocomial *Clostridium difficile* Infection. Clin Infect Dis. CID 2015;60(Supplement 2):S148–58.
[161] Vonberg RP, Kuijper EJ, Wilcox MH, Barbut F, Tüll P, Gastmeier P, et al. Infection control measures to limit the spread of *Clostridium difficile*. Clin Microbiol Infect 2008;14(Supplement 5):2–20.
[162] Dubberke E. Strategies for prevention of *Clostridium difficile* infection. J Hosp Med 2012;7(Supplement 3):S14–7.
[163] Tschudin-Sutter S, Kuijper EJ, Durovic A, Vehreschild MJGT, Barbut F, Eckert C, et al. Guidance document for prevention of *Clostridium difficile* infection in acute healthcare settings. Clin Microbiol Infect 2018;24:1051–4.
[164] Salgado CD, Mauldin PD, Fogle PJ, Bosso JA. Analysis of an outbreak of *Clostridium difficile* infection controlled with enhanced infection control measures. Am J Infect Control 2009;37:458–64.
[165] Ramphal L, Suzuki S, McCracken IM, Addai A. Improving hospital staff compliance with environmental cleaning behavior. SAVE Proc 2014;27:88–91.
[166] Martinez FJ, Leffler DA, Kelly CP. *Clostridium difficile* outbreaks: prevention and treatment strategies. Risk Manag Healthc Pol 2012;5:55–64.
[167] Barker AK, Ngam C, Musuuza JS, Vaughn VM, Safdar N. Reducing *Clostridium difficile* in the inpatient setting: a systematic review of the adherence to and effectiveness of *C. difficile* prevention bundles. Infect Control Hosp Epidemiol 2017;38:639–50.
[168] Muto CA, Blank MK, Marsh JW, Vergis EN, O'Leary MM, Shutt KA, et al. Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a

university hospital using a comprehensive "bundle" approach. Clin Infect Dis 2007;45:1266–73.
[169] Weiss K, Boisvert A, Chagnon M, Duchesne C, Habash S, Lepage Y, et al. Multipronged intervention strategy to control an outbreak of *Clostridium difficile* infection (CDI) and its impact on the rates of CDI from 2002 to 2007. Infect Control Hosp Epidemiol 2009;30:156–62.
[170] Bommiasamy AK, Connelly C, Moren A, Dodgion C, Bestall K, Cline A, et al. Institutional review of the implementation and use of a *Clostridium difficile* infection bundle and probiotics in adult trauma patients. Am J Surg 2018;215:825–30.
[171] Mitchell BG, Russo PL, Race P. *Clostridium difficile* infection: nursing considerations. Nurs Stand 2014;28:43–8.
[172] Crogan NL, Evans BC. *Clostridium difficile*: an emerging epidemic in nursing homes. Geriatr Nurs 2007;28:161–4.
[173] Public Health Agency of Canada. Infection prevention and control guidance for management in acute care settings. 2013.
[174] Stuart RL, Marshall C, McLaws M, Boardman C, Russo PL, Harrington G, et al. ASID/AICA position statement—infection control guidelines for patients with *Clostridium difficile* infection in healthcare settings. Healthc Infect 2011;16:33–9.
[175] Watanabe Y, Saito H, Abe S, Kurosawa K, Edo T, Konno Y, et al. Validation of CDI infection control by ICT in our hospital after a *Clostridium difficile* infection outbreak. J Jpn. Municipal Hosp Assoc 2019;58:362–6.
[176] Ishii Y. New developments in pathology, diagnosis, and treatment for *Clostridium difficile*. Practical infection control. Clin Microbiol 2015;42:61–5.
[177] Murabata M, Kato H, Oinishi K, Yano H. Environmental contamination of *Clostridium difficile* in the pediatric ward of a university hospital in Japan. Jpn J Infect Prev Control 2015;30:22–8.
[178] CDC. *Clostridium difficile* (C. diff), https://www.cdc.gov/cdiff/index.html.
[179] Pokrywka M, Buraczewski M, Frank D, Dixon H, Ferrelli J, Shutt K, et al. Can improving patient hand hygiene impact *Clostridium difficile* infection evens at an academic medical center? AJIC (Am J Infect Control) 2017;45:959–63.
[180] Scottish Health Protection Network. Guidance on prevention and control of Clostridium difficile infection (CDI) in health and social care settings in Scotland. Scott Guid No6 2017 edition.
[181] Carrico RM, Bryant K, Lessa F, Limbago B, Fau-erbach LL, Marx JF, et al. Guide to preventing *Clostridium difficile* infections. APIC 2013.
[182] Jabbar U, Leischner J, Kasper D, Gerber R, Sambol SP, Parada JP, et al. Effectiveness of alcohol-based hand rubs for removal of *Clostridium difficile* spores from hands. Infect Control Hosp Epidemiol 2010;31:565–70. https://doi.org/10.1086/652772.
[183] Kundrapu S, Sunkesula V, Jury I, Deshpande A, Donskey CJ. A randomized trial of soap and water hand wash versus alcohol hand rub for removal of *Clostridium difficile* spores from hands of patients. Infect Control Hosp Epidemiol 2014;35:204–6. https://doi.org/10.1086/674859.
[184] Bobulsky GS, Al-Nassir WN, Riggs MM, Sethi AK, Donskey CJ. *Clostridium difficile* skin contamination in patients with *C. difficile*-associated disease. Clin Infect Dis 2008;46:447–50. https://doi.org/10.1086/525267.
[185] Deyneko A, Cordeiro F, Berlin L, Ben-David D, Perna S, Longtin Y. Impact of sink location on hand hygiene compliance after care of patients with *Clostridium difficile* infection: a cross-sectional study. BMC Infect Dis 2016;16:203. https://doi.org/10.1186/s12879-016-1535-x.
[186] Donskey CJ, Ray AJ, Hoyen CK, Fuldauer PD, Aron DC, Salvator A, et al. Colonization and infection with multiple nosocomial pathogens among patients colonized with vancomycin-resistant *Enterococcus*. Infect Control Hosp Epidemiol 2003;24:242–5. https://doi.org/10.1086/502207.
[187] Fujitani S, George WL, Morgan MA, Nichols S, Murthy AR. Implications for vancomycin-resistant Enterococcus colonization associated with Clostridium difficile infections. Am J Infect Control 2011;39:188–93. https://doi.org/10.1016/j.ajic.2010.10.024.
[188] McKinley L, Becerra B, Moriarty H, Short TH, Hagle M, Reymann A, et al. Vancomycin-resistant *Enterococcus* co-colonization rates with methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile* in critically ill veterans. Am J Infect Control 2016;44:1047–9. https://doi.org/10.1016/j.ajic.2016.02.005.
[189] Özsoy S, İlki A. Detection of vancomycin-resistant enterococci (VRE) in stool specimens submitted for Clostridium difficile toxin testing. Braz J Microbiol 2017;48:489–92. https://doi.org/10.1016/j.bjm.2016.12.012.
[190] Amorim ML, Vasconcelos C, Oliveira DC, Azevedo A, Calado E, Faria NA, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal colonization among patients and healthcare workers in a Portuguese hospital: a pre-intervention study toward the control of MRSA. Microb Drug Resist 2009;15:19–26. https://doi.org/10.1089/mdr.2009.0881.
[191] Verwer PE, Robinson JO, Coombs GW, Wijesuriya T, Murray RJ, Verbrugh HA, et al. Prevalence of nasal methicillin-resistant Staphylococcus aureus colonization in healthcare workers in a Western Australian acute care hospital. Eur J Clin Microbiol Infect Dis 2012;31:1067–72. https://doi.org/10.1007/s10096-011-1408-6.
[192] Sassmannshausen R, Deurenberg RH, Köck R, Hendrix R, Jurke A, Rossen JWA, et al. MRSA prevalence and associated risk factors among health-care workers in non-outbreak situations in the Dutch-German EUREGIO. Front Microbiol 2016;7:1273. https://doi.org/10.3389/fmicb.2016.01273.
[193] Gopal Rao G, Jeanes A, Osman M, Aylott C, Green J. Marketing hand hygiene in hospitals-a case study. J Hosp Infect 2002;50:42–7. https://doi.org/10.1053/jhin.2001.1119.
[194] Gordin FM, Schultz ME, Huber RA, Gill JA. Reduction in nosocomial transmission of drug-resistant bacteria after introduction of an alcohol-based handrub. Infect Control Hosp Epidemiol 2005;26:650–3. https://doi.org/10.1086/502596.
[195] Vernaz N, Sax H, Pittet D, Bonnabry P, Schrenzel J, Harbarth S. Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA and *Clostridium difficile*. J Antimicrob Chemother 2008;62:601–7. https://doi.org/10.1093/jac/dkn199.
[196] Kaier K, Hagist C, Frank U, Conrad A, Meyer E. Two time-series analyses of the impact of antibiotic consumption and alcohol-based hand disinfection on the incidences of nosocomial methicillin-resistant *Staphylococcus aureus* infection and *Clostridium difficile* infection. Infect Control Hosp Epidemiol 2009;30:346–53. https://doi.org/10.1086/596605.
[197] Gagné D, Bédard G, Maziade PJ. Systematic patients' hand disinfection: impact on meticillin-resistant Staphylococcus aureus infection rates in a community hospital. J Hosp Infect 2010;75:269–72. https://doi.org/10.1016/j.jhin.2010.02.028.
[198] Boyce JM, Kelliher S, Vallande N. Skin irritation and dryness associated with two hand-hygiene regimens: soap-and-water hand washing versus hand antisepsis with an alcoholic hand gel. Infect Control Hosp Epidemiol 2000;21:442–8. https://doi.org/10.1086/501785.
[199] Kampf G, Löffler H. Dermatological aspects of a successful introduction and continuation of alcohol-based hand rubs for hygienic hand disinfection. J Hosp Infect 2003;55:1–7. https://doi.org/10.1016/s0195-6701(03)00223-8.
[200] Sartelli M, Di Bella S, McFarland LV, Khanna S, Furuya-Kanamori L, Abuzeid N, et al. 2019 update of the WSES guidelines for management of Clostridioides (Clostridium) difficile infection in surgical patients. World J Emerg Surg 2019;14:1–29. https://doi.org/10.1186/s13017-019-0228-3.
[201] Chang S, Sethi AK, Eckstein BC, Stiefel U, Cadnum JL, Donskey CJ. Skin and environmental contamination with methicillin-resistant *Staphylococcus aureus* among carriers identified clinically versus through active surveillance. Clin Infect Dis 2009;48:1423–8. https://doi.org/10.1086/598505.
[202] Istenes N, Bingham J, Hazelett S, Fleming E, Kirk J. Patients' potential role in the transmission of health care-associated infections: prevalence of contamination with bacterial pathogens and patient attitudes toward hand hygiene. Am J Infect Control 2013;41:793–8. https://doi.org/10.1016/j.ajic.2012.11.012.
[203] Lemmen SW, Häfner H, Zolldann D, Stanzel S, Lütticken R. Distribution of multi-resistant Gram-negative versus Gram-positive bacteria in the hospital inanimate environment. J Hosp Infect 2004;56:191–7. https://doi.org/10.1016/j.jhin.2003.12.004.
[204] Hayden MK, Blom DW, Lyle EA, Moore CG, Weinstein RA. Risk of hand or glove contamination after contact with patients colonized with vancomycin-resistant *enterococcus* or the colonized patients' environment. Infect Control Hosp Epidemiol 2008;29:149–54. https://doi.org/10.1086/524331.
[205] Stiefel U, Cadnum JL, Eckstein BC, Guerrero DM, Tima MA, Donskey CJ. Contamination of hands with methicillin-resistant *Staphylococcus aureus* after contact with environmental surfaces and after contact with the skin of colonized patients. Infect Control Hosp Epidemiol 2011;3:185–7. https://doi.org/10.1086/657944.
[206] Jury LA, Guerrero DM, Burant CJ, Cadnum JL, Donskey CJ. Effectiveness of routine patient bathing to decrease the burden of spores on the skin of patients with *Clostridium difficile* infection. Infect Control Hosp Epidemiol 2011;32:181–4. https://doi.org/10.1086/657911.
[207] Burnett E. Perceptions, attitudes, and behavior towards patient hand hygiene. Am J Infect Control 2009;37:638–42. https://doi.org/10.1016/j.ajic.2009.04.281.
[208] Pokrywka M, Feigel J, Douglas B, Grossberger S, Hensler A, Hensler A, et al. A bundle strategy including patient hand hygiene to decrease *Clostridium difficile* infections. Medsurg Nurs 2014;23:145–64.
[209] Rai H, Knighton S, Zabarsky TF, Donskey CJ. A randomized trial to determine the impact of a 5 moments for patient hand hygiene educational intervention on patient hand hygiene. Am J Infect Control 2017;45:551–3. https://doi.org/10.1016/j.ajic.2016.12.022.
[210] Sunkesula VCK, Knighton S, Zabarsky TF, Kundrapu S, Higgins PA, Donskey CJ. Four moments for patient hand hygiene: a patient-centered, provider-facilitated model to improve patient hand hygiene. Infect Control Hosp Epidemiol 2015;36:986–9. https://doi.org/10.1017/ice.2015.78.
[211] Sunkesula VCK, Kundrapu S, Knighton S, Cadnum JL, Donskey CJ. A randomized trial to determine the impact of an educational patient hand-hygiene intervention on contamination of hospitalized Patient's hands with healthcare-associated pathogens. Infect Control Hosp Epidemiol 2017;38:595–7. https://doi.org/10.1017/ice.2016.323.
[212] Manian FA, Meyer L, Jenne J. *Clostridium difficile* contamination of blood pressure cuffs: a call for a closer look at gloving practices in the era of universal precautions. Infect Control Hosp Epidemiol 1996;17:180–2. https://doi.org/10.1017/S019594170000655X.
[213] Brooks S, Khan A, Stoica D, Griffith J, Friedeman L, Mukherji R, et al. Reduction in vancomycin-resistant Enterococcus and *Clostridium difficile* infections following change to tympanic thermometers. Infect Control Hosp Epidemiol 1998;19:333–6. https://doi.org/10.1086/647824.
[214] Perry C, Marshall R, Jones E. Bacterial contamination of uniforms. J Hosp Infect 2001;48:238–41. https://doi.org/10.1053/jhin.2001.0962.
[215] Shrestha SK, Sunkesula VCK, Kundrapu S, Tomas ME, Nerandzic MM, Donskey CJ. Acquisition of *Clostridium difficile* on hands of healthcare personnel caring for patients with resolved *C. difficile* infection. Infect Control Hosp Epidemiol 2016;37:475–7. https://doi.org/10.1017/ice.2015.335.
[216] Verbeek JH, Rajamaki B, Ijaz S, Sauni R, Toomey E, Blackwood B, et al. Personal protective equipment for preventing highly infectious diseases due to exposure to contaminated body fluids in healthcare staff. Emerge 2021;33:59–61. https://doi.org/10.1002/14651858.CD011621.

[217] Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infect Dis 2006;6:130. https://doi.org/10.1186/1471-2334-6-130.
[218] Chemaly RF, Simmons S, Dale C, Ghantoji SS, Rodriguez M, Gubb J, et al. The role of the healthcare environment in the spread of multidrug-resistant organisms: update on current best practices for containment. Ther Adv Infect Dis 2014;2:79–90. https://doi.org/10.1177/2049936114543287.
[219] Davies K, Mawer D, Walker AS, Berry C, Planche T, Stanley P, et al. An analysis of Clostridium difficile environmental contamination during and after treatment for C difficile infection. Open Forum Infect Dis 2020;7:ofaa362. https://doi.org/10.1093/ofid/ofaa362.
[220] Teltsch DY, Hanley J, Loo V, Goldberg P, Gursahaney A, Buckeridge DL. Infection acquisition following intensive care unit room privatization. Arch Intern Med 2011;171:32–8. https://doi.org/10.1001/archinternmed.2010.469.
[221] Evans ME, Kralovic SM, Simbartl LA, Jain R, Roselle GA. Effect of a *Clostridium difficile* infection prevention initiative in Veterans Affairs acute care facilities. Infect Control Hosp Epidemiol 2016;37:720–2. https://doi.org/10.1017/ice.2016.27.
[222] Waqar S, Nigh K, Sisler L, Fanning M, Tancin S, Brozik E, et al. Multidisciplinary performance improvement team for reducing health care-associated Clostridium difficile infection. Am J Infect Control 2016;44:352–4. https://doi.org/10.1016/j.ajic.2015.09.022.
[223] Koll BS, Ruiz RE, Calfee DP, Jalon HS, Stricof RL, Adams A, et al. Prevention of hospital-onset *Clostridium difficile* infection in the New York metropolitan region using a collaborative intervention model. J Healthc Qual 2014;36:35–45. https://doi.org/10.1111/jhq.12002.
[224] Centers for Disease Control and Prevention. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html; 2007.
[225] Otter JA, Yezli S, Frcpath French GL. The role played by contaminated surfaces in the transmission of nosocomial pathogens. Infect Control Hosp Epidemiol 2011;32:687–99. https://doi.org/10.1086/660363.
[226] Gerding DN, Young VB, Donskey CJ, Mandell Douglas. Bennett's principles & practice of infectious diseases. ninth ed. J. edsELSEVIER: E. Bennett RD & MJB; 2019. p. 2933–46.
[227] Care QH, of Health Department, Health England Public, Abou Chakra CN, Pepin J, Sirard S, et al. ASID/AICA position statement–infection control guidelines for patients with *Clostridium difficile* infection in healthcare settings. Clin Microbiol Infect 2014;16:207–30.
[228] Stuart RL, Marshall C, Harrington G, Sasko L, McLaws ML, Ferguson J. ASID/ACIPC position statement - infection control for patients with *Clostridium difficile* infection in healthcare facilities. Infect Dis Health 2019 Feb;24(1):32–43. https://doi.org/10.1016/j.idh.2018.10.001.
[229] Gibson CV, Swindell JE, Collier GD. Assessment of prehospital monitor/defibrillators for *Clostridioides difficile* contamination. Prehospital Disaster Med 2021;36:412–3. https://doi.org/10.1017/S1049023X21000376.
[230] Jernigan JA, Siegman-Igra Y, Guerrant RC, Farr BM. A randomized crossover study of disposable thermometers for prevention of *Clostridium difficile* and other nosocomial infections. Infect Control Hosp Epidemiol 1998;19:494–9. https://doi.org/10.1086/647855.
[231] Vajravelu RK, Guerrero DM, Jury LA, Donskey CJ. Evaluation of stethoscopes as vectors of *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus*. Infect Control Hosp Epidemiol; Epi: Infect Control Hosp 2012;33:96–8. https://doi.org/10.1086/663338.
[232] Lawley TD, Croucher NJ, Yu L, Clare S, Sebaihia M, Goulding D, et al. Proteomic and genomic characterization of highly infectious *Clostridium difficile* 630 spores. J Bacteriol 2009;191:5377–86. https://doi.org/10.1128/JB.00597-09.
[233] Endres BT, Dotson KM, Poblete K, McPherson J, Lancaster C, Bassères E, et al. Environmental transmission of *Clostridioides difficile* ribotype 027 at a long-term care facility; an outbreak investigation guided by whole genome sequencing. Infect Control Hosp Epidemiol 2018;39:1322–9. https://doi.org/10.1017/ice.2018.230.
[234] Buggy BP, Wilson KH, Fekety R. Comparison of methods for recovery of *Clostridium difficile* from an environmental surface. J Clin Microbiol 1983;18:348–52. https://doi.org/10.1128/jcm.18.2.348-352.1983.
[235] Jump RLP, Pultz MJ, Donskey CJ. Vegetative *Clostridium difficile* survives in room air on moist surfaces and in gastric contents with reduced acidity: a potential mechanism to explain the association between proton pumps inhibitors and *C difficile*-associated diarrhea. Antimicrob Agents Chemother 2007;51:2883–7.
[236] Fawley WN, Wilcox MH. Molecular epidemiology of endemic *Clostridium difficile* infection. Epidemiol Infect 2001;126:343–50. https://doi.org/10.1017/s095026880100557x.
[237] Best EL, Sandoe JA, Wilcox MH. Potential for aerosolization of *Clostridium difficile* after flushing toilets: the role of toilet lids in reducing environmental contamination risk. J Hosp Infect 2012;80:1–5. https://doi.org/10.1016/j.jhin.2011.08.010.
[238] Aithinne KAN, Cooper CW, Lynch RA, Johnson DL. Toilet plume aerosol generation rate and environmental contamination following bowl water inoculation with *Clostridium difficile* spores. Am J Infect Control 2019;47:515–20. https://doi.org/10.1016/j.ajic.2018.11.009.
[239] Shaughnessy MK, Bobr A, Kuskowski MA, Johnston BD, Sadowsky MJ, Khoruts A, et al. Environmental contamination in households of patients with recurrent *Clostridium difficile* infection. Appl Environ Microbiol 2016;82:2686–92. https://doi.org/10.1128/AEM.03888-15.
[240] Centers for Disease Control and Prevention. Strategies to prevent *Clostridioides difficile* infection in acute care facilities. https://www.cdc.gov/hai/prevent/cdi-prevention-strategies.html. [Accessed 24 October 2019].
[241] Rutala WA, Gergen MF, Weber DJ. Efficacy of different cleaning and disinfection methods against *Clostridium difficile* spores: importance of physical removal versus sporicidal inactivation. Infect Control Hosp Epidemiol 2012;33:1255–8. https://doi.org/10.1086/668434.
[242] Wilcox MH, Fawley WN, Wigglesworth N, Parnell P, Verity P, Freeman J. Comparison of the effect of detergent versus hypochlorite cleaning on environmental contamination and incidence of *Clostridium difficile* infection. J Hosp Infect 2003;54:109–14. https://doi.org/10.1016/s0195-6701(02)00400-0.
[243] Hacek DM, Ogle AM, Fisher A, Robicsek A, Peterson LR. Significant impact of terminal room cleaning with bleach on reducing nosocomial *Clostridium difficile*. Am J Infect Control 2010;38:350–3. https://doi.org/10.1016/j.ajic.2009.11.003.
[244] Orenstein R, Aronhalt KC, McManus Jr JE, Fedraw LA. A targeted strategy to wipe out *Clostridium difficile*. Infect Control Hosp Epidemiol 2011;32:1137–9. https://doi.org/10.1086/662586.
[245] Louh IK, Greendyke WG, Hermann EA, Davidson KW, Falzon L, Vawdrey DK, et al. *Clostridium difficile* Infection in acute care hospitals: systematic review and best practices for prevention. Infect Control Hosp Epidemiol 2017;38:476–82. https://doi.org/10.1017/ice.2016.324.
[246] Siani H, Cooper C, Maillard JY. Efficacy of "sporicidal" wipes against *Clostridium difficile*. Am J Infect Control 2011;39:212–8. https://doi.org/10.1016/j.ajic.2011.01.006.
[247] Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431–55. https://doi.org/10.1086/651706.
[248] Ogura Y, Ozawa T, Nojima Y, Kikuno R. Antimicrobial efficacy of complex-type chlorine-based disinfectant cleaner against several pathogenic microorganisms. Jpn J Infect Prev Control 2015;30:391–8. https://doi.org/10.4058/jsei.30.391.
[249] Kawaguchi Y, Oie S, Furukawa H. Efficacy of complex-type chlorine-based disinfectant cleaner against MDRP and MDRA. Jpn J Infect Prev Control 2016;31:366–9. https://doi.org/10.4058/jsei.31.366.
[250] Ikeda Y, Shigemura K, Nomi M, Tabata C, Kitagawa K, Arakawa S, et al. Infection control following an outbreak of expanded-spectrum beta-lactamase-producing *Klebsiella pneumoniae* isolated from catheter-associated urinary tract infection. Jpn Infect Dis 2018;71:158–61. https://doi.org/10.7883/yoken.JJID.2017.330.
[251] Nakagawa H, Imamura M, Ito J, Baba A, Muro T, Sasaki H, et al. Appropriate disinfection method against BCG in urine. J Jpn Soc Hosp Pharm 2017;53:859–62.
[252] Okaue A, Ozawa T, Ogura Y, Nojima Y, Kikuno R, Shiraishi T. Evaluation of corrosiveness to various surface materials of complex type chlorine-based disinfectant cleaner. Jpn J Infect Prev Control 2015;30:325–30. https://doi.org/10.4058/jsei.30.325.
[253] Kizu J, Takagi K, Kuroda Y, Maezawa K, Matsumoto K, Hori S. Stability and color degradation in solutions of complex-type chlorine-based disinfectant cleaners. Jpn J Infect Prev Control 2014;29:411–6. https://doi.org/10.4058/jsei.29.411.
[254] Imai K, Ichiman Y, Yoshimori N, Hasegawa K, Kise D, Tujii T. Evaluation of infection prevention of *Clostridium difficile* infection by potassium peroxymonosulfate disinfectant cleaner. Jpn J Pharmaceut Health Care Sci 2017;43:279–84. https://doi.org/10.5649/jjphcs.43.279.
[255] Anderson DJ, Moehring RW, Weber DJ, Lewis SS, Chen LF, Schwab JC, et al. Effectiveness of targeted enhanced terminal room disinfection on hospital-wide acquisition and infection with multidrug-resistant organisms and Clostridium difficile: a secondary analysis of a multicentre cluster randomised controlled trial with crossover design (BETR Disinfection). Lancet Infect Dis 2018;18:845–53. https://doi.org/10.1016/S1473-3099(18)30278-0.
[256] Hota B. Contamination, disinfection, and cross-colonization: are hospital surfaces reservoirs for nonsocomial infection? Clin Infecr Dis 2004;39:1182–9. https://doi.org/10.1086/424667.
[257] Shaughnessy MK, Micielli RL, DePestel DD, Arndt J, Strachan CL, Welch KB, et al. Evaluation of hospital room assignment and acquisition of Clostridium difficile infection. Infect Control Hosp Epidemiol 2011;32:201–6. https://doi.org/10.1086/658669.
[258] Mitchell BG, Dancer SJ, Anderson M, Dehn E. Risk of organism acquisition from prior room occupants: a systematic review and meta-analysis. J Hosp Infect 2015;91:211–7. https://doi.org/10.1016/j.jhin.2015.08.005.
[259] Carling PC. Optimizing health care environmental hygiene. Infect Dis Clin 2016;30:639–60. https://doi.org/10.1016/j.idc.2016.04.010.
[260] Weber DJ, Rutala WA, Anderson DJ, Chen LF, Sickbert-Bennett EE, Boyce JM. Effectiveness of ultraviolet devices and hydrogen peroxide systems for terminal room decontamination: focus on clinical trials. Am J Infect Control 2016;44:e77–84. https://doi.org/10.1016/j.ajic.2015.11.015.
[261] Totaro M, Casini B, Profeti S, Tuvo B, Privitera G, Baggiani A. Role of hydrogen peroxide vapor (HPV) for the disinfection of hospital surfaces contaminated by multiresistant bacteria pathogens 2020 May 24;9(5):408. https://doi.org/10.3390/pathogens9050408.
[262] Rutala WA, Weber DJ. Guideline for disinfection and sterilization in healthcare facilities. 2008. Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008 (cdc.gov), . [Accessed 7 June 2022].
[263] Anderson DJ, Chen LF, Weber DJ, Moehring RW, Lewis SS, Triplett PF, et al. Enhanced terminal room disinfection and acquisition and infection caused by multidrug-resistant organisms and Clostridium difficile (the Benefits of Enhanced

Terminal Room Disinfection study): a cluster- randomised, multicentre, crossover study. Lancet 2017;389:805–14.
[264] Shapey S, Machin K, Levi K, Boswell TC. Activity of a dry mist hydrogen peroxide system against environmental Clostridium difficile contamination in elderly care wards. J Hosp Infect 2008;70:136–41.
[265] Passaretti CL, Otter JA, Reich NG, Myers J, Shepard J, Ross T, et al. An evaluation of environmental decontamination with hydrogen peroxide vapor for reducing the risk of patient acquisition of multidrug-resistant organisms. Clin Infect Dis 2013;56:27–35.
[266] Kanamori H, Rutala WA, Weber DJ. The role of patient care items as a fomite in healthcare-associated outbreaks and infection prevention. Clin Infect Dis 2017; 65:1412–9.
[267] Anderson RE, Young V, Stewart M, Robertson C, Dancer SJ. Cleanliness audit of clinical surfaces and equipment: who cleans what? J Hosp Infect 2011;78:178–81. https://doi.org/10.1016/j.jhin.2011.01.030.
[268] Carling PC, Parry MF, Bruno-Murtha LA, Dick B. Improving environmental hygiene in 27 intensive care units to decrease multidrug-resistant bacterial transmission. Crit Care Med 2010;38:1054–9. https://doi.org/10.1097/CCM.0b013e3181cdf705.
[269] Weber DJ, Anderson D, Rutala WA. The role of the surface environment in healthcare-associated infections. Curr Opin Infect Dis 2013;26:338–44. https://doi.org/10.1097/QCO.0b013e3283630f04.
[270] Rutala WA, Weber DJ. Disinfectants used for environmental disinfection and new room decontamination technology. Am J Infect Control 2013;41(5):S36–41. https://doi.org/10.1016/j.ajic.2012.11.006. suppl.
[271] Weber DJ, Anderson DJ, Sexton DJ, Rutala WA. Role of the environment in the transmission of *Clostridium difficile* in healthcare facilities. Am J Infect Control 2013;41:S105–10.
[272] Otter JA, Yezli S, Salkeld JAG, French GL. Evidence that contaminated surfaces contribute to the transmission of hospital pathogens and an overview of strategies to address contaminated surfaces in hospital settings. Am J Infect Control 2013;41 (5):S6–SS11. https://doi.org/10.1016/j.ajic.2012.12.004. suppl.
[273] Gebel J, Exner M, French G, Chartier Y, Christiansen B, Gemein S, et al. The role of surface disinfection in infection prevention. GMS Hyg Infect Control 2013;8: Doc10. https://doi.org/10.3205/dgkh000210.
[274] Donskey CJ. Does improving surface cleaning and disinfection reduce health care-associated infections? Am J Infect Control 2013;41(5):S12–9. https://doi.org/10.1016/j.ajic.2012.12.010. suppl.
[275] Rutala WA, Gergen MF, Tande BM, Weber DJ. Room decontamination using an ultraviolet-C device with short ultraviolet exposure time. Infect Control Hosp Epidemiol 2014;35:1070–2. https://doi.org/10.1086/677149.
[276] Pegues DA, Han J, Gilmar C, McDonnell B, Gaynes S. Impact of ultraviolet germicidal irradiation for no-touch terminal room disinfection on *Clostridium difficile* infection incidence among hematology-oncology patients. Infect Control Hosp Epidemiol 2017;38:39–44. https://doi.org/10.1017/ice.2016.222.
[277] Kanamori H, Rutala WA, Gergen MF, Weber DJ. Patient room decontamination against Car- bapenem-resistant *Enterobacteriaceae* and Meth-icillin-resistant *Staphylococcus aureus* using a fixed cycle-time ultraviolet-C device and two different radiation designs. Infect Control Hosp Epidemiol 2016;37:994–6. https://doi.org/10.1017/ice.2016.80.
[278] Nerandzic MM, Thota P, Sankar CT, Jencson A, Cadnum JL, Ray AJ, et al. Evaluation of a pulsed xenon ultraviolet disinfection system for reduction of healthcare-associated pathogens in hospital rooms. Infect Control Hosp Epidemiol 2015;36:192–7. https://doi.org/10.1017/ice.2014.36.
[279] Cadnum JL, Jencson AL, Gestrich SA, Livingston SH, Karaman BA, Benner KJ, et al. A comparison of the efficacy of multiple ultraviolet light room decontamination devices in a radiology procedure room. Infect Control Hosp Epidemiol 2019;40:158–63. https://doi.org/10.1017/ice.2018.296.
[280] Donskey CJ, Kundrapu S, Deshpande A. Colonization versus carriage of *Clostridium difficile*. Infect Dis Clin 2015;29:13–28. https://doi.org/10.1016/j.idc.2014.11.001.
[281] Crobach MJT, Vernon JJ, Loo VG, Kong LY, Péchiné S, Wilcox MH, et al. Understanding *Clostridium difficile* colonization. Clin Microbiol Rev 2018;31. https://doi.org/10.1128/CMR.00021-17.
[282] Ford CD, Lopansri BK, Webb BJ, Coombs J, Gouw L, Asch J, et al. *Clostridioides difficile* colonization and infection in patients with newly diagnosed acute leukemia: incidence, risk factors, and patient outcomes. Am J Infect Control 2019; 47:394–9. https://doi.org/10.1016/j.ajic.2018.09.027.
[283] Ryan J, Murphy C, Twomey C, Paul Ross R, Rea MC, MacSharry J, et al. Asymptomatic carriage of *Clostridium difficile* in an Irish continuing care institution for the elderly: prevalence and characteristics. Ir J Med Sci 2010;179: 245–50. https://doi.org/10.1007/s11845-009-0361-1.
[284] Behar L, Chadwick D, Dunne A, Jones CI, Proctor C, Rajkumar C, et al. Toxigenic *Clostridium difficile* colonization among hospitalised adults; risk factors and impact on survival. J Infect 2017;75:20–5. https://doi.org/10.1016/j.jinf.2017.04.006.
[285] Dubberke ER, Reske KA, Seiler S, Hink T, Kwon JH, Burnham CA. Risk factors for acquisition and loss of *Clostridium difficile* colonization in hospitalized patients. Antimicrob Agents Chemother 2015;59:4533–43. https://doi.org/10.1128/AAC.00642-15.
[286] Arvand M, Moser V, Schwehn C, Bettge-Weller G, Hensgens MP, Kuijper EJ. High prevalence of *Clostridium difficile* colonization among nursing home residents in Hesse, Germany. PLoS One 2012;7:e30183. https://doi.org/10.1371/journal.pone.0030183.
[287] Baron SW, Ostrowsky BE, Nori P, Drory DY, Levi MH, Szymczak WA, et al. Screening of *Clostridioides difficile* carriers in an urban academic medical center: understanding implications of disease. Infect Control Hosp Epidemiol 2020;41: 149–53. https://doi.org/10.1017/ice.2019.309.
[288] Tschudin-Sutter S, Carroll KC, Tamma PD, Sudekum ML, Frei R, Widmer AF, et al. Impact of toxigenic *Clostridium difficile* colonization on the risk of subsequent *C. difficile* infection in Intensive Care Unit patients. Infect Control Hosp Epidemiol 2015;36:1324–9. https://doi.org/10.1017/ice.2015.177.
[289] Chen Y, Gu H, Lv T, Yan D, Xu Q, Gu S, et al. Longitudinal investigation of carriage rates and genotypes of toxigenic *Clostridium difficile* in hepatic cirrhosis patients. Epidemiol Infect 2019;147:e166. https://doi.org/10.1017/S0950268819000554.
[290] Kubiak J, Davidson E, Soave R, Kodiyanplakkal RP, Robertson A, Besien KV, et al. Colonization with gastrointestinal pathogens prior to hematopoietic cell transplantation and associated clinical implications. Transplant Cell Ther 2021; 27:499.e1–6. https://doi.org/10.1016/j.jtct.2021.02.012.
[291] Curry SR, Muto CA, Schlackman JL, Pasculle AW, Shutt KA, Marsh JW, et al. Use of multilocus variable number of tandem repeats analysis genotyping to determine the role of asymptomatic carriers in *Clostridium difficile* transmission. Clin Infect Dis 2013;57:1094–102. https://doi.org/10.1093/cid/cit475.
[292] Sheth PM, Douchant K, Uyanwune Y, Larocque M, Anantharajah A, Borgundvaag E, et al. Evidence of transmission of *Clostridium difficile* in asymptomatic patients following admission screening in a tertiary care hospital. PLoS One 2019;14:e0207138. https://doi.org/10.1371/journal.pone.0207138.
[293] Halstead FD, Ravi A, Thomson N, Nuur M, Hughes K, Brailey M, et al. Whole genome sequencing of toxigenic *Clostridium difficile* in asymptomatic carriers: insights into possible role in transmission. J Hosp Infect 2019;102:125–34. https://doi.org/10.1016/j.jhin.2018.10.012.
[294] Rivera EV, Woods S. Prevalence of asymptomatic *Clostridium difficile* colonization in a nursing home population: a cross-sectional study. J Gend Specif Med 2003;6: 27–30.
[295] Kong LY, Eyre DW, Corbeil J, Raymond F, Walker AS, Wilcox MH, et al. *Clostridium difficile*: investigating transmission patterns between infected and colonized patients using whole genome sequencing. Clin Infect Dis 2019;68: 204–9. https://doi.org/10.1093/cid/ciy457.
[296] Longtin Y, Paquet-Bolduc B, Gilca R, Garenc C, Fortin E, Longtin J, et al. Effect of detecting. And isolating *Clostridium difficile* carriers at hospital admission on the incidence of *C difficile* infections: a quasi-experimental controlled study. JAMA Intern Med 2016;176:796–804.
[297] Johnson S, Homann SR, Bettin KM, Quick JN, Clabots CR, Peterson LR, et al. Treatment of asymptomatic *Clostridium difficile* carriers (fecal excretors) with vancomycin or metronidazole. A randomized, placebo-controlled trial. Ann Intern Med 1992;117:297–302. https://doi.org/10.7326/0003-4819-117-4-297.
[298] Alonso CD, Maron G, Kamboj M, Carpenter PA, Gurunathan A, Mullane KM, et al. American society for transplantation and cellular therapy series: #5-Management of Clostridioides difficile Infection in Hematopoietic Cell Transplant Recipients. Transpl Cell Ther 2022;28. https://doi.org/10.1016/j.jtct.2022.02.013. 225–2.
[299] Kato H, Kita H, Karasawa T, Maegawa T, Koino Y, Takakuwa H, et al. Colonisation and transmission of *Clostridium difficile* in healthy individuals examined by PCR ribotyping and pulsed-field gel electrophoresis. J Med Microbiol 2001;50:720–7. https://doi.org/10.1099/0022-1317-50-8-720.
[300] Zacharioudakis IM, Zervou FN, Pliakos EE, Ziakas PD, Mylonakis E. Colonization with toxinogenic *C. difficile* upon hospital admission, and risk of infection: a systematic review and meta-analysis. Am J Gastroenterol 2015;110:381–90. https://doi.org/10.1038/ajg.2015.22.
[301] Biswas JS, Patel A, Otter JA, van Kleef E, Goldenberg SD. Contamination of the hospital environment from potential *clostridium difficile* excretors without active infection. Infect Control Hosp Epidemiol 2015;36:975–7. https://doi.org/10.1017/ice.2015.79.
[302] Eyre DW, Cule ML, Wilson DJ, Griffiths D, Vaughan A, O'Connor L, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. N Engl J Med 2013;369:1195205. https://doi.org/10.1056/NEJMoa1216064.
[303] Xiao Y, Paquet-Bolduc B, Garenc C, Gervais P, Trottier S, Roussy JF, et al. Impact of isolating *Clostridium difficile* carriers on the burden of isolation precautions: a time series analysis. Clin Infect Dis 2018;66:1377–82. https://doi.org/10.1093/cid/cix1024.
[304] Linsenmeyer K, O'Brien W, Brecher SM, Strymish J, Rochman A, Itani K, et al. *Clostridium difficile* screening for colonization during an outbreak setting. Clin Infect Dis 2018;67:1912–4. https://doi.org/10.1093/cid/ciy455.
[305] Barker AK, Alagoz O, Safdar N. Interventions to Reduce the incidence of hospital-onset *clostridium difficile* infection: an agent-based modeling approach to evaluate clinical effectiveness in adult acute care hospitals. Clin Infect Dis 2018;66: 1192–203. https://doi.org/10.1093/cid/cix962.
[306] Paquet-Bolduc B, Gervais P, Roussy JF, Trottier S, Oughton M, Brukner I, et al. Detection and isolation of *clostridium difficile* asymptomatic carriers during *clostridium difficile* infection outbreaks: an exploratory study. Clin Infect Dis 2018; 67:1781–3. https://doi.org/10.1093/cid/ciy425.
[307] Tran K, Bell C, Stall N, Tomlinson G, McGeer A, Morris A, et al. The effect of hospital isolation precautions on patient outcomes and cost of care: a multi-site, retrospective, propensity score-matched cohort study. J Gen Intern Med 2017;32: 262–8. https://doi.org/10.1007/s11606-016-3862-4.
[308] Stelfox HT, Bates DW, Redelmeier DA. Safety of patients isolated for infection control. JAMA 2003;290:1899–905. https://doi.org/10.1001/jama.290.14.1899.
[309] Abad C, Fearday A, Safdar N. Adverse effects of isolation in hospitalised patients: a systematic review. J Hosp Infect 2010;76:97–102. https://doi.org/10.1016/j.jhin.2010.04.027.

[310] Reigadas E, Vazquez-Cuesta S, Villar-Gomara L, Onori R, Alcala L, Marin M, et al. Role of *Clostridioides difficile* in hospital environment and healthcare workers. Anaerobe 2020;63. https://doi.org/10.1016/j.anaerobe.2020.102204.
[311] Verity P, Wilcox MH, Fawley W, Parnell P. Prospective evaluation of environmental contamination by *Clostridium difficile* in isolation side rooms. J Hosp Infect 2001;49:204–9. https://doi.org/10.1053/jhin.2001.1078.
[312] Jullian-Desayes I, Landelle C, Mallaret MR, Brun-Buisson C, Barbut F. *Clostridium difficile* contamination of health care workers' hands and its potential contribution to the spread of infection: review of the literature. Am J Infect Control 2017;45:51–8. https://doi.org/10.1016/j.ajic.2016.08.017.
[313] Tanner WD, Leecaster MK, Zhang Y, Stratford KM, Mayer J, Visnovsky LD, et al. Environmental contamination of contact precaution and non-contact precaution patient rooms in six acute care facilities. Clin Infect Dis 2021;72:S8–16. https://doi.org/10.1093/cid/ciaa1602.
[314] Dumford DM, Nerandzic MM, Eckstein BC, Donskey CJ. What is on that keyboard? Detecting hidden environmental reservoirs of *Clostridium difficile* during an outbreak associated with North American pulsed-field gel electrophoresis type 1 strains. Am J Infect Control 2009;37:15–9. https://doi.org/10.1016/j.ajic.2008.07.009.
[315] Wong H, Eso K, Ip A, Jones J, Kwon Y, Powelson S, et al. Use of ward closure to control outbreaks among hospitalized patients in acute care settings: a systematic review. Syst Rev 2015;4:152. https://doi.org/10.1186/s13643-015-0131-2.
[316] Nagar A, Yew P, Fairley D, Hanrahan M, Cooke S, Thompson I, et al. Report of an outbreak of *Clostridium difficile* infection caused by ribotype 053 in a neurosurgery unit. J Infect Prev 2015;16:126–30. https://doi.org/10.1177/1757177414560250.
[317] Ratnayake L, McEwen J, Henderson N, Nathwani D, Phillips G, Brown D, et al. Control of an outbreak of diarrhoea in a vascular surgery unit caused by a high-level clindamycin-resistant *Clostridium difficile* PCR ribotype 106. J Hosp Infect 2011;79:242–7. https://doi.org/10.1016/j.jhin.2011.06.013.
[318] Rhinehart E, Walker S, Murphy D, O'Reilly K, Leeman P. Frequency of outbreak investigations in US hospitals: results of a national survey of infection preventionists. Am J Infect Control 2012;40:2–8. https://doi.org/10.1016/j.ajic.2011.10.003.
[319] Barker AK, Codella J, Ewers T, Dundon A, Alagoz O, Safdar N. Changes to physician and nurse time burdens when caring for patients under contact precautions. Am J Infect Control 2017;45:542–3. https://doi.org/10.1016/j.ajic.2017.01.026.
[320] Guillemin I, Marrel A, Beriot-Mathiot A, Doucet C, Kazoglou O, Luxemburger C, et al. How do *Clostridium difficile* infections affect nurses' everyday hospital work: a qualitative study. Int J Nurs Pract 2015;21:38–45. https://doi.org/10.1111/ijn.12166.
[321] Hessels AJ, Kelly AM, Chen L, Cohen B, Zachariah P, Larson EL. Impact of infectious exposures and outbreaks on nurse and infection preventionist workload. Am J Infect Control 2019;47. https://doi.org/10.1016/j.ajic.2019.02.007.
[322] Centers for Disease Control and Prevention. Options for evaluating environmental cleaning: appendix B objective methods for evaluating environmental hygiene. https://www.cdc.gov/HAI/toolkits/AppendicesEvaluatingEnviron-Cleaning.html#b. [Accessed 7 June 2022].
[323] Sitzlar B, Deshpande A, Fertelli D, Kundrapu S, Sethi AK, Donskey CJ. An environmental disinfection odyssey: evaluation of sequential interventions to improve disinfection of *Clostridium difficile* isolation rooms. Infect Control Hosp Epidemiol 2013;34:459–65. https://doi.org/10.1086/670217.
[324] Deshpande A, Sitzlar B, Fertelli D, Kundrapu S, Sunkesula VC, Ray AJ, et al. Utility of an adenosine triphosphate bioluminescence assay to evaluate disinfection of *Clostridium difficile* isolation rooms. Infect Control Hosp Epidemiol 2013;34:865–7. https://doi.org/10.1086/671272.
[325] Grainger RJ, Stevens NT, Humphreys H. Approaches to the detection of *Clostridioidesdifficile* in the healthcare environment. J Hosp Infect 2019:375–81.
[326] Claro T, Daniels S, Humphreys H. Detecting *Clostridium difficile* spores from inanimate surfaces of the hospital environment: which method is best? J Clin Microbiol 2014;52:3426–8. https://doi.org/10.1128/JCM.01011-14.
[327] Engelhardt NEP, Foster NF, Hong S, Riley TV, McGechie DB. Comparison of two environmental sampling tools for the detection of *Clostridium difficile* spores on hard bathroom surfaces in the hospital setting. J Hosp Infect 2017;96:295–6. https://doi.org/10.1016/j.jhin.2017.03.028.
[328] Otter JA, Havill NL, Adams NM, Cooper T, Tauman A, Boyce JM. Environmental sampling for *Clostridium difficile*: swabs or sponges? Am J Infect Control 2009;37:517–8. https://doi.org/10.1016/j.ajic.2009.01.005.
[329] MacDougall LK, Broukhanski G, Simor A, Johnstone J, Mubareka S, McGeer A, et al. Comparison of qPCR versus culture for the detection and quantification of *Clostridium difficile* environmental contamination. PLoS One 2018;13:e0201569. https://doi.org/10.1371/journal.pone.0201569.
[330] Dubberke ER, Han Z, Bobo L, Hink T, Lawrence B, Copper S, et al. Impact of clinical symptoms on interpretation of diagnostic assays for Clostridium difficile infections. J Clin Microbiol 2011;49:2887–93. https://doi.org/10.1128/JCM.00891-11.
[331] Crobach MJT, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection. Clin Microbiol Infect 2016;22:S63–81. https://doi.org/10.1016/j.cmi.2016.03.010.
[332] Gateau C, Couturier J, Coia J, Barbut F. How to: diagnose infection caused by Clostridium difficile. Clin Microbiol Infect 2018;24:463–8. https://doi.org/10.1016/j.cmi.2017.12.005.
[333] Longtin Y, Trottier S, Brochu G, Paquet-bolduc B, Garenc C, Loungnarath V, et al. Impact of thetype of diagnostic assay on *Clostridium difficile* infection and complication rates in a mandatory reporting program. Clin Infect Dis 2013;56:67–73. https://doi.org/10.1093/cid/cis840.
[334] Kaltsas A, Simon M, Unruh LH, Son C, Wroblewski D, Musser KA, et al. Clinical and laboratory characteristics of *Clostridium difficile* infection in patients with discordant diagnostic test results. J Clin Microbiol 2012;50:1303–7. https://doi.org/10.1128/JCM.05711-11.
[335] Polage CR, Gyorke CE, Kennedy MA, Leslie JL, Chin DL, Wang S, et al. Overdiagnosis of *Clostridium difficile* infection in the molecular test era. JAMA Intern Med 2015;175:1792–801. https://doi.org/10.1001/jamainternmed.2015.4114.
[336] Kumar S, Pollok R, Muscat I, Planche T. Diagnosis and outcome of *Clostridium difficile* infection by toxin enzyme immunoassay and polymerase chain reaction in an island population. J Gastroenterol Hepatol 2017;32:415–9. https://doi.org/10.1111/jgh.13504.
[337] Catanzaro MR, Cirone JB. Real-time polymerase chain reaction testing for *Clostridium difficile* reduces isolation time and improves patient management in a small community hospital. Am J Infect Control 2012;40:663–6. https://doi.org/10.1016/j.ajic.2011.09.005.
[338] Guerrero DM, Chou C, Jury LA, Nerandzic MM, Cadnum JC, Donskey CJ. Clinical and infection control implications of *Clostridium difficile* infection with negative enzyme immunoassay for toxin. Clin Infect Dis 2011;53:287–90. https://doi.org/10.1093/cid/cir361.
[339] Kaku M, Mikamo H, Yanagihara K, Ishii Y, Ohkusu K, Otsuka Y, et al. Testing algorithms based on Clostridium difficile toxin test results. J Jpn Soc Clin Microbiol 2017;27:222–4.
[340] Chang TW, Gorbach SL. Rapid identification of *Clostridium difficile* by toxin detection. J Clin Microbiol 1982;15:465–7. https://doi.org/10.1128/jcm.15.3.465-467.1982.
[341] Tanino Y, Kimura T, Ushiyama M, Kurahashi S, Kyotani N, Yamada Yukiji, et al. Detecting *Clostridium difficile* toxins by toxigenic culture. Jpn J Med Technol 2015;64:680–5.
[342] Prehn J Van, Vandenbroucke-Grauls CM, van Beurden YH, van Houdt R, Vainio S, Ang CW. Diagnostic yield of repeat sampling with immunoassay, real-time PCR, and toxigenic culture for the detection of toxigenic *Clostridium difficile* in an epidemic and a non-epidemic setting. Eur J Clin Microbiol Infect Dis 2015;34:2325–30. https://doi.org/10.1007/s10096-015-2484-9.
[343] Blixt T, Gradel KO, Homann C, Seidelin JB, Schønning K, Lester A, et al. Asymptomatic carriers contribute to nosocomial *Clostridium difficile* infection: a cohort study of 4508 patients. Gastroenterology 2017;152. https://doi.org/10.1053/j.gastro.2016.12.035. 10311041.e2.
[344] Oleastro M, Coelho M, Gião M, Coutinho S, Mota S, Santos A, et al. Outbreak of Clostridium difficile PCR ribotype 027—the recent experience of a regional hospital. BMC Infect Dis 2014;14:209. https://doi.org/10.1186/1471-2334-14-209.
[345] Hanna H, Raad I, Gonzalez V, Umphrey J, Tarrand J, Neumann J, et al. Control of nosocomial *Clostridium difficile* transmission in bone marrow transplant patients. Infect Control Hosp Epidemiol 2000;2:226–8. https://doi.org/10.1086/501751.
[346] Valiquette L, Cossette B, Garant MP, Diab H, Pépin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of Clostridium difficile-associated disease caused by the hypervirulent NAP1/027 strain. Clin Infect Dis 2007;45(suppl 2):S112–21. https://doi.org/10.1086/519258.
[347] Wong-McClure RA, Ramírez-Salas E, Mora-Brenes N, Aguero-Sandí L, Morera-Sigler M, Badilla-Vargas X, et al. Long term effect of infection control practices and associated factors during a major *Clostridium difficile* outbreak in Costa Rica. J Infect Dev Ctries 2013;7:914–21. https://doi.org/10.3855/jidc.2854.
[348] Apisarnthanarak A, Zack JE, Mayfield JL, Freeman J, Dunne WM, Little JR, et al. Effectiveness of environmental and infection control programs to reduce transmission of *Clostridium difficile*. Clin Infect Dis 2004;39:601–2. https://doi.org/10.1086/422523.
[349] Färber J, Illiger S, Berger F, Gärtner B, von Müller L, Lohmann CH, et al. Management of a cluster of *Clostridium difficile* infections among patients with osteoarticular infections. Antimicrob Resist Infect Control 2017;6:22. https://doi.org/10.1186/s13756-017-0181-4.
[350] Piacenti FJ, Leuthner KD. Antimicrobial stewardship and Clostridium difficile-associated diarrhea. J Pharm Pract 2013;26:506–13. https://doi.org/10.1177/0897190013499528.
[351] Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Golubchik T, et al. Effects of control interventions on *Clostridium difficile* infection in England: an observational study. Lancet Infect Dis 2017;17:411–21. https://doi.org/10.1016/S1473-3099(16)30514-X.
[352] Marufu O, Desai N, Aldred D, Brown T, Eltringham I. Analysis of interventions to reduce the incidence of *Clostridium difficile* infection at a London teaching hospital trust, 2003-2011. J Hosp Infect 2015;89:38–45. https://doi.org/10.1016/j.jhin.2014.10.003.
[353] Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. *Clostridium difficile* infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. Int J Antimicrob Agents 2016;48:1–10. https://doi.org/10.1016/j.ijantimicag.2016.03.008.
[354] Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. Clin Infect Dis 2011;53:42–8. https://doi.org/10.1093/cid/cir301.
[355] Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients.

Cochrane Database Syst Rev 2017;2:CD003543. https://doi.org/10.1002/14651858.CD003543.pub4.
[356] Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69:1748–54. https://doi.org/10.1093/jac/dku046.
[357] Azab M, Doo L, Doo DH, Elmofti Y, Ahmed M, Cadavona JJ, et al. Comparison of the hospital-acquired *clostridium difficile* infection risk of Using proton pump inhibitors versus Histamine-2 receptor antagonists for prophylaxis and treatment of stress ulcers: a systematic review and meta-analysis. Gut Liver 2017;11:781–8. https://doi.org/10.5009/gnl16568.
[358] Davis KW, Hanners RE, Lockwood SM. Implementation of a proton pump inhibitor stewardship program. Am J Health Syst Pharm 2017;74:932–7. https://doi.org/10.2146/ajhp160670.
[359] Wahking RA, Steele RL, Hanners RE, Lockwood SM, Davis KW. Outcomes from a pharmacist –led proton pump inhibitor stewardship program at a single institution. Hosp Pharm 2018;53:59–67. https://doi.org/10.1177/0018578717747192.
[360] Kandel CE, Gill S, McCready J, Matelski J, Powis JE. Reducing co-administration of proton pump inhibitors and antibiotics using a computerized order entry alert and prospective audit and feedback. BMC Infect Dis 2016;16:355. https://doi.org/10.1186/s12879-016-1679-8.
[361] Otsuka T, Sugimoto M, Inoue R, Ohno M, Ban H, Nishida A, et al. Influence of potassium-competitive acid blocker on the gut microbiome of *Helicobacter pylori*-negative healthy individuals. Gut 2017;66:1723–5. https://doi.org/10.1136/gutjnl-2016-313312.
[362] Nei T, Hagiwara J, Takiguchi T, Yokobori S, Shiei K, Yokota H, et al. Fatal fulminant *Clostridioides difficile* colitis caused by *Helicobacter pylori* eradication therapy; a case report. J Infect Chemother 2020;26:305–8. https://doi.org/10.1016/j.jiac.2019.10.021.
[363] Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. Cochrane Database Syst Rev 2017;12:CD006095. https://doi.org/10.1002/14651858.CD006095.pub4.
[364] Ma Y, Yang JY, Peng X, Xiao KY, Xu Q, Wang C. Which probiotic has the best effect on preventing *Clostridium difficile*-associated diarrhea? A systematic review and network meta-analysis. J Dig Dis 2020;21:69–80. https://doi.org/10.1111/1751-2980.12839.
[365] Doron S, Snydman DR. Risk and safety of probiotics. Clin Infect Dis 2015;60:S129–34. https://doi.org/10.1093/cid/civ085.
[366] Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 2008;371:651–9. https://doi.org/10.1016/S0140-6736(08)60207-X.
[367] Cornely OA, Nathwani D, Ivanescu C, Odufowora-Sita O, Retsa P, Odeyemi IA. Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in *Clostridium difficile* infections: a meta-analysis and indirect treatment comparison. J Antimicrob Chemother 2014;69:2892–900. https://doi.org/10.1093/jac/dku261.
[368] Mikamo H, Aoyama N, Sawata M, Fujimoto G, Dorr MB, Yoshinari T. The effect of bezlotoxumab for prevention of recurrent *Clostridium difficile* infection (CDI) in Japanese patients. J Infect Chemother 2018;24:123–9. https://doi.org/10.1016/j.jiac.2017.10.005.
[369] Gerding DN, Kelly CP, Rahav G, Lee C, Dubberke ER, Kumar PN, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection in patients at increased risk for recurrence. Clin Infect Dis 2018;67:649–56. https://doi.org/10.1093/cid/ciy171.