Infection control measures to limit the spread of *Clostridium difficile*


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ABSTRACT

*Clostridium difficile*-associated diarrhoea (CDAD) presents mainly as a nosocomial infection, usually after antimicrobial therapy. Many outbreaks have been attributed to *C. difficile*, some due to a new hyper-virulent strain that may cause more severe disease and a worse patient outcome. As a result of CDAD, large numbers of *C. difficile* spores may be excreted by affected patients. Spores then survive for months in the environment; they cannot be destroyed by standard alcohol-based hand disinfection, and persist despite usual environmental cleaning agents. All these factors increase the risk of *C. difficile* transmission. Once CDAD is diagnosed in a patient, immediate implementation of appropriate infection control measures is mandatory in order to prevent further spread within the hospital. The quality and quantity of antibiotic prescribing should be reviewed to minimise the selective pressure for CDAD. This article provides a review of the literature that can be used for evidence-based guidelines to limit the spread of *C. difficile*. These include early diagnosis of CDAD, surveillance of CDAD cases, education of staff, appropriate use of isolation precautions, hand hygiene, protective clothing, environmental cleaning and cleaning of medical equipment, good antibiotic stewardship, and specific measures during outbreaks. Existing local protocols and practices for the control of *C. difficile* should be carefully reviewed and modified if necessary.

Keywords  *Clostridium difficile*, evidence-based guidelines, infection control measures

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Levels of evidence [1]

- **Level 1a**: Systematic review (with homogeneity) of randomised controlled trials
- **Level 1b**: Individual randomised controlled trial (with narrow confidence interval)
- **Level 1c**: Studies with the outcome ‘All or none’
- **Level 2a**: Systematic review (with homogeneity) of cohort studies
- **Level 2b**: Individual cohort study (including low-quality randomised controlled trials; e.g., <80% follow-up)
- **Level 2c**: ‘Outcomes’ research; ecological studies
- **Level 3a**: Systematic review (with homogeneity) of case–control studies
- **Level 3b**: Individual case–control study
- **Level 4**: Case series (and poor quality cohort and case–control studies)
- **Level 5**: Expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’

Categories for implementation in clinical practice

- **IA**: Strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiological studies
- **IB**: Strongly recommended for implementation and strongly supported by some experimental, clinical or epidemiological studies and a strong theoretical rationale
- **IC**: Required for implementation, as mandated by federal and/or state regulation or standard (may vary among different states/countries)
- **II**: Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale

Unresolved issue: Practices for which insufficient evidence exists or no consensus regarding efficacy exists (no recommendation)

SCOPE OF THIS DOCUMENT

Several national guidelines concerning *Clostridium difficile* have been published, but they are often adapted to the local situation in the individual country or hospital and may not be appropriate in other settings [2–5]. This literature review and the recommendations contained in these guidelines were stimulated by the increased incidence of *C. difficile*-associated diarrhoea (CDAD) in multiple institutions and countries across Europe. Control measures for *C. difficile* differ in several important ways from those used to reduce the risk of other nosocomial pathogens. We recommend that this document be used to produce and/or review current local protocols for the control of nosocomial CDAD. In particular, we emphasise the need to determine local incidence on a real-time basis, compare these data with a baseline incidence (if available), and review practices (including the review of local guidelines and their implementation) as soon as an increased rate of CDAD occurs. A change in the presentation of, or complications associated with, CDAD, including an increase in the severity of infection, should also stimulate these actions, as this implies the introduction and transmission of a new strain, potentially with enhanced virulence.

BACKGROUND

**Epidemiology**

*C. difficile* is the leading cause of intestinal infections related to antimicrobial therapy [6]. Factors that may also predispose for CDAD include increased age, duration of hospital stay, and severity of underlying diseases [7–9]. The role of proton pump inhibitors and other antacids in CDAD development is still a matter of debate [10,11]. Direct or indirect contact represents the main route of *C. difficile* transmission, as spores may persist in the environment for months or years and show resistance to various environmental cleaners such as detergents and some disinfectants [12–15]. Direct transmission via the airborne route is unlikely to occur, but has been suggested recently in a pilot study; the potential for the dispersal of *C. difficile* spores in air needs further exploration [16].

A rapid change in the epidemiology of CDAD has recently been reported and, notably, the emergence and spread of a new hyper-virulent strain belonging to PCR ribotype 027 [17]. This phenomenon, together with background information on pathogenesis, is described in more detail elsewhere [18].

**Clinical presentation, diagnosis and financial impact**

Enterotoxin A and cytotoxin B represent the major virulence factors of *C. difficile* [14, 19]. Most strains are able to produce both of these antigenically distinct toxins. The severity of CDAD ranges from mild diarrhoea to pseudo-membranous
colitis or toxic megacolon and bowel perforation in a few cases [20]. Crude mortality as a result of CDAD varies according to the population affected and may be as high as 25–30%, although the attributable mortality is believed to be considerably lower unless the hyper-virulent strain ribotype 027 is involved [21].

Currently, there are different diagnostic tests for the recognition of CDAD. Detection of one or both C. difficile toxins may be performed by cytotoxicity assay or by enzyme-linked immunoassays. C. difficile strains not producing toxin A are potentially being missed if an assay directed only at this target is used. Alternative methods for diagnosis of CDAD are culturing of toxin-producing C. difficile under anaerobic conditions or (real-time) PCR-based approaches, directly from stools [22].

First-choice therapeutic options for CDAD include oral vancomycin or metronidazole [23]. A number of other therapeutic agents for treatment of CDAD are being developed or available but have not yet been approved for this indication. The average attributable cost for a case of CDAD may add up to $8000 (€6120) [24] and is mainly driven by the increased length of hospital stay.

**MATERIALS AND METHODS**

**Data acquisition**

The following search strategy was applied to identify relevant publications:

1. PubMed was searched using the search term 'difficile' in combination with either 'nosocomial', 'outbreak', 'transmission', 'control', 'environment', and 'prevention'.
2. The Cochrane Library was searched using the search term 'difficile'.
3. All outbreaks filed in the Outbreak Database [25] were explored using 'C. difficile' as 'species' and the grouped-by mode for 'source', 'transmission', and 'measures'.
4. Finally, a manual search of the reference lists of all relevant articles was performed in order to identify as yet unknown publications that deal with infection control measures for C. difficile.

There were no restrictions with respect to language or type of article.

**Data evaluation**

The quality of each individual study was determined by its level of evidence according to the Oxford Centre for Evidence-Based Medicine. As infection control measures for the prevention of spread of enteric infections or multidrug-resistant pathogens (especially pathogens that persist in the environment, such as enterococci) may have some relevance for C. difficile, such recommendations (e.g., the HICPAC guidelines for the management of multidrug-resistant organisms and a systematic review on hand washing for the prevention of diarrhoeal diseases) were also considered in the preparation of this guideline [26–29].

The categories for implementation in clinical practice were based on the categories in the HICPAC guideline documents, ranging from 'IA' (strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiological studies) to 'unresolved issue'.

**RESULTS**

In total, 36 outbreaks caused by C. difficile are currently filed in the Outbreak Database [24]. In 19 of these, the route of transmission could not be determined or was not described by the authors [30–48]. In the remaining 17, pathogen spread occurred 'by contact' via carriage of spores on the hands of staff [12,49–60], by patient-to-patient-spread [13,52,54,59,61,62], or indirectly from the contaminated environment [15,49,50,54,55,57,60].

There were few other infection control studies that dealt with the transmission of C. difficile explicitly. The quality of the literature concerning interventions to prevent CDAD is often limited with respect to design, absence of details on population, setting, nature and timing of interventions, failure to assess and adjust for confounders or bias, and use of inappropriate statistical techniques [63,64]. Therefore, there is a need for well-designed studies in each research area of C. difficile infection control [65].

**CONCLUSIONS**

**Early diagnosis**

The main purpose of screening cultures is to identify carriers of pathogens at an early stage, before cross-transmission can occur. The prevalence of C. difficile carriage in asymptomatic and otherwise healthy adult stool cultures is <5% [66]. In contrast, the rate of carriage among hospitalised patients varies significantly and may be as high as 25% [67–69]. More than half of the C. difficile strains isolated from symptom-free individuals are toxigenic [68,70].

Although screening cultures for C. difficile have been performed during some outbreaks [30,37,46,60,61], there are no data showing that
active screening of non-diarrhoeal patients to identify *C. difficile* carriers will contribute to a reduction of the endemic baseline rate of CDAD. However, asymptomatic carriers have recently been reported to present a potential source of *C. difficile* transmission [71]. Besides reducing the risk of pathogen spread, the second rationale for screening cultures is to identify carriers who are at risk of developing endogenous nosocomial CDAD. However, in a prospective observational study on long-stay patients, Johnson *et al.* [12] showed that symptom-free excretors of *C. difficile* actually had a slightly decreased risk of subsequent CDAD (0 of 51 patients) as compared with patients who had been initially culture-negative (seven of 229 (3.1%) cases of CDAD). Shim *et al.* [68] also observed that there were 22 cases of CDAD among 618 previously non-colonised patients (3.6%) as compared with two of 192 (1.0%) in symptom-free carriers (p 0.021). Additionally, treatment of asymptomatic carriers is ineffective in eradicating *C. difficile* [72]. Hence, symptom-free *C. difficile* colonisation may be protective against subsequent symptomatic disease, but it is possible that asymptomatic carriers may still contribute to transmission of the organism [8,66,70,73–75].

Diarrhoeal patients are believed to represent the major reservoir for *C. difficile* transmission, and are associated with the highest rates of environmental contamination [76]. Diarrhoeal stool samples should be processed as soon as possible to diagnose CDAD. As recurrence of CDAD after a symptom-free interval is common (up to 20–50% of cases) [77–79], diagnostic testing for *C. difficile* should also be performed at a new onset of diarrhoea. Environmental screening is generally not recommended, but can be used to document contamination or poor cleaning and disinfection, especially in an outbreak situation.

A summary of the recommendations concerning early diagnosis is given in Table 1.

### Surveillance

Active surveillance of CDAD is recommended [80]. Surveillance is useful to detect an increase in CDAD incidence and severity at an early stage, or to identify risk-factors for CDAD acquisition [81], and should ideally include the identification of deaths in which CDAD is either the primary or contributory cause. The significance of surveillance is not limited to outbreaks. In the endemic setting, it may reveal high baseline rates or significant variations between locations that require interventions. Faecal testing for *C. difficile* toxins should be performed in the case of nosocomial diarrhoea, and for all patients who have been admitted for non-nosocomial diarrhoea. Microbiology laboratories should test for *C. difficile* systematically in stool specimens from patients hospitalised for more than 3 days. This is

### Table 1. Early diagnosis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Category</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>1 Promptly perform tests for <em>Clostridium difficile</em> toxins (± the bacterium) in stool specimens in each case of nosocomial diarrhoea and for individuals who are admitted with diarrhoea acquired outside the hospital. Stop repeated testing of diarrhoeal stool samples as soon as <em>C. difficile</em> has been diagnosed. Only when a recurrence of CDAD is suspected, repeat the <em>C. difficile</em> testing and exclude other potential causes of diarrhoea.</td>
<td>IB</td>
<td>3b [61], 4 [49,76,89]</td>
</tr>
<tr>
<td>2 Perform tests for <em>C. difficile</em> or its toxins only on diarrhoeal (unformed) stool specimens, unless ileus is present. Testing of stool specimens from asymptomatic patients is not recommended.</td>
<td>IB</td>
<td>2b [94,135], 3b [136], 4 [30,66]</td>
</tr>
<tr>
<td>3 Do not perform a ‘test of cure’ after treatment.</td>
<td>IA</td>
<td>1a [23]</td>
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<tr>
<td>4 Faecal samples from all CDAD cases, and especially patients (a) with severe CDAD (e.g., leading to admission to intensive care unit, undergoing colectomy, or fatal cases), or (b) in an outbreak situation, should be stored so that typing can be performed, if necessary, retrospectively.</td>
<td>IB</td>
<td>1b [26], 3b [50], 4 [31,49,51,109]</td>
</tr>
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</table>
sometimes referred to as the ‘3-day rule’ to emphasise the greater value of testing for *C. difficile* as opposed to conventional (community-associated) enteric pathogens such as *Salmonella, Shigella* and *Campylobacter* species [4]. If possible, culture of *C. difficile* toxin-positive samples, and typing of isolates, should be available. In practice, this is best achieved by storing aliquots of all toxin-positive faecal samples, for examination retrospectively, to aid *C. difficile* cluster/outbreak management, if necessary, by a reference laboratory.

A threshold CDAD incidence/prevalence should be defined locally that would trigger implementation of additional control interventions. The alert level should be based on the incidence, CDAD severity, institutional priorities, whether the patient population has risk-factors that may facilitate transmission or is at increased risk of adverse outcomes following CDAD acquisition, and whether there is suspected or proven transmission.

A summary of the recommendations concerning surveillance is given in Table 2.

Table 2. Surveillance

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Category</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ensure routine surveillance of CDAD should be carried out routinely in hospitals.</td>
<td>IB 2b [172], 3b [32], 4 [76,81], 5 [80]</td>
<td></td>
</tr>
<tr>
<td>2 Determine the unit-specific baseline incidence of CDAD by reviewing results of faecal toxin tests or <em>Clostridium difficile</em> cultures.</td>
<td>IB 2c [173]</td>
<td></td>
</tr>
<tr>
<td>3 Define a threshold incidence or frequency of CDAD that would trigger implementation of additional control interventions.</td>
<td>IB 2b [94,135]</td>
<td></td>
</tr>
<tr>
<td>4 Ensure appropriate and prompt diagnostic testing of patients with an acute diarrhoeal illness not otherwise explained (especially with diarrhoea associated with antimicrobial therapy).</td>
<td>IB 3b [32], 4 [20]</td>
<td></td>
</tr>
<tr>
<td>5 Be alert for changes in the rate, complications (including recurrences) or severity of CDAD that may indicate the introduction of new strain(s).</td>
<td>Unresolved No data</td>
<td></td>
</tr>
</tbody>
</table>

CDAD, *Clostridium difficile*-associated diarrhoea.

Training of staff should include not only medical personnel (nurses or physicians), but also non-medical personnel, especially those involved in cleaning.

Education of visitors about contact precautions is also necessary to prevent further spread of spores [33]. Visitors should be encouraged to basic infection control measures, with emphasis on appropriate hand hygiene. Individuals suffering from acute diarrhoea themselves should not visit patients in a hospital [82].

A summary of the recommendations concerning education and communication is given in Table 3.

### Isolation precautions

Contact isolation is universally applied for patients with diseases that spread through contact. The patient is preferably nursed in a single-bedded room with dedicated equipment, and personal protective clothing (gloves and gowns) is used when contact with a patient occurs [83,84]. However, isolation for CDAD patients requires additional and special measures for hand hygiene and environmental cleaning, since *C. difficile* spores play an important role in the transmission of infection.

Isolation of patients with infectious agents in single rooms or cohorts is a basic hygiene measure of contact isolation to limit pathogen spread [83,84]. Occasional reports note that a *C. difficile* outbreak ended following identification of stored, contaminated medical equipment as a point source [85]. Usually, isolation of symptomatic
patients with CDAD is the key measure to control *C. difficile* outbreaks [30,33,37,86,87]. Occasionally, even closure of a complete ward/department is necessary [86,87]. Additionally, re-isolation of patients presenting with diarrhoea at a subsequent readmission, who were previously known to suffer from CDAD, may reduce the occurrence of new nosocomial CDAD cases, reducing the overall healthcare cost [88].

If daily clinical practice does not allow the isolation of symptomatic patients in single rooms on a regular ward, cohorting several patients on a separate cohort/isolation ward may be considered. Staff on CDAD cohort wards may have more experience in caring for such cases; cleaning protocols for CDAD may be more easily facilitated in separate areas; materials used on a cohort ward are usually not used elsewhere; and there are fewer people entering a cohort ward unnecessarily. Another possible positive effect of cohorting is to localise environmental contamination to a small part of the hospital. This is different from having isolation rooms used for CDAD dispersed throughout a hospital in numerous locations. Each failure of hygiene in these locations represents a high risk of extended local contamination and secondary cases. The overall effect may be to reduce significantly the burden of environmental contamination to a single focus (cohort ward), where it is recognised and containable [89].

Apart from isolation procedures, it is essential that patients suffering from any form of diarrhoea have a dedicated toilet or commode; i.e. they should not be allowed to use general toilet facilities.

One critical issue is for how long isolation and other control measures need to be continued. Few data are available on the excretion of vegetative cells/spores during an episode of CDAD. The consensus is that nosocomial outbreaks can be terminated if precautions are kept in place until bowel functioning has returned to normal for at least 48 h [33]. The environment of symptomatic patients with CDAD is more frequently contaminated than that of asymptomatic carriers [67]. However, even after adequate therapy for CDAD and return to normal bowel movements, patients may still have detectable *C. difficile* toxins in faeces and continue to excrete *C. difficile*. It is possible for up to 30% of stool samples to remain toxin-positive in patients treated with vancomycin or metronidazole [90], and a correlation between stool cytotoxin levels and severity of gastrointestinal symptoms may not be present in all cases [19]. There is, however, no clinical value in retesting CDAD cases once symptoms resolve; i.e., knowing the carriage status of patients has no known clinical benefit, as a role for asymptomatic carriers in the spread of *C. difficile* has not been defined. Basic hygiene measures must therefore be an integral part of normal practice. Furthermore, for most other pathogens, alcohol-based hand hygiene is recommended, unless major contamination of hands has occurred, and then guidance must be provided locally with regard to recommencement (see below) [91].

A summary of the recommendations concerning isolation precautions is given in Table 4.

**Table 3. Education and communication**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Category</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Everyone who enters a patient’s room/environment, including healthcare workers and visitors, should be educated about the clinical features, transmission and epidemiology of CDAD.</td>
<td>IA</td>
<td>1a [156,157], 2b [172], 4 [86,174], 5 [128]</td>
</tr>
</tbody>
</table>

**Hand hygiene**

Hand hygiene is the primary action to reduce healthcare-associated infections [92]. Thus, hand hygiene guidelines have been revisited and should improve standards and practices [93]. Standard hand hygiene practices today use alcohol-based products, unless hands are in contact with body fluids or are visibly contaminated. When hands are clearly contaminated, decontamination by soap-based washing has to be performed (possibly prior to hand disinfection) [91–93]. It is clear that the hands of healthcare workers (HCWs) are likely to become contaminated when caring for patients with CDAD [35,67,75,94]. Unfortunately, bacterial spores are
not killed by alcohols [95], and, indeed, alcohol is used in the laboratory setting to select for C. difficile spores. Importantly, none of the other agents (chlorhexidine, hexachlorophene, iodophors, chloroxylenol, or triclosan) used in antiseptic hand-wash or hand-rub preparations is reliably effective against C. difficile spores [93]. In an experimental study using hands of volunteers contaminated by C. difficile, Barbut et al. [96] showed that 4% polyvidone soap was significantly more effective in reducing the C. difficile count than chlorhexidine or non-medicated soap, and these products were also more effective than alcohol-based products. In a recent observational study, the introduction of alcohol-based hand rub was not associated with an increase in the incidence of nosocomial CDAD (3-year incidence per 10 000 patient-days before, 3.24; 3-year incidence after, 3.38; p 0.78) [97]. Boyce et al. showed that a ten-fold increase in the use of alcohol-based hand rub (p <0.001) within 4 years did not alter the incidence of CDAD [98]. Bacterial spores can be removed from hands by the physical action of washing and rinsing [91,94], using either non-antimicrobial liquid soap or antiseptic substances such as chlorhexidine. In a crossover study, no differences in residual counts of C. difficile on bare hands were observed after comparing liquid soap and chlorhexidine gluconate [99], while others found significantly improved removal of spores on HCWs who used soap containing chlorhexidine gluconate as compared to non-disinfectant soap (p <0.01) [67]. Leischner et al. recently found that alcohol gels were significantly less effective at removing C. difficile spores from the hands of volunteers than hand washing with chlorhexidine (p <0.009). However, in their study, there was a higher than expected reduction of spore counts following use of alcohol gels [100]. Although gloving will dramatically reduce the degree of contamination of hands by C. difficile spores, there is still a need for optimal hand hygiene after removal of gloves [93].

The role of the patient remains uncertain in the transmission of C. difficile, although direct person-to-person transmission has been proposed [61,94,101]. Endogenous infections can also occur, in principle, even though there are some data suggesting that primary C. difficile carriage, or carriage in the absence of ever having CDAD, is relatively protective against CDAD [73]. Thus, hand washing by patients should be strongly encouraged [86], especially after a toilet visit and before eating.

A summary of the recommendations concerning hand hygiene is given in Table 5.

## Protected clothing

The use of gloves to protect the hands of HCWs from contamination is generally recommended by the HICPAC as a part of contact precautions [102]. Since none of the agents used in antiseptic hand-wash or antiseptic hand-rub preparations is reliably sporocidal against C. difficile spores, HCWs should be encouraged to wear gloves when caring for patients with CDAD. In a prospective controlled trial of vinyl glove use

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Table 4. Isolation precautions

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Category</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Patients with CDAD represent a source for pathogen spread to others and should be isolated in single rooms whenever possible.</td>
<td>IB</td>
<td>1b [26,102, 2b [84,172]</td>
</tr>
<tr>
<td>2 A designated toilet or commode (transportable toilet) for CDAD patients should be provided.</td>
<td>IB</td>
<td>1b [26,102]</td>
</tr>
<tr>
<td>3 If isolation in single rooms is not possible, isolation in cohorts should be undertaken. If there is a lack of capacity, then consideration should be given to using a designated ward or unit for cohort isolation.</td>
<td>IB</td>
<td>1b [26,102], 4 [86,89]</td>
</tr>
<tr>
<td>4 Cohorted patients should be managed by designated staff to minimise the risk of cross-infection to other patients.</td>
<td>IB</td>
<td>1b [26], 4 [86]</td>
</tr>
<tr>
<td>5 Isolation precautions may be discontinued 48 h after symptomatic CDAD has resolved and bowel movements have returned to normal.</td>
<td>II</td>
<td>4 [33,34,175]</td>
</tr>
</tbody>
</table>

CDAD, Clostridium difficile-associated diarrhoea.
to prevent *C. difficile* spread, the incidence of CDAD decreased significantly from 7.7 to 1.5 per 1000 patient discharges within a 6-month intervention period [103]. In another observational study, the hands of all four members of staff using gloves remained free of *C. difficile* spores. This contrasts with hand contamination in seven of 15 staff who did not use gloves and did not observe further hand hygiene practices [67]. Contaminated gloves need to be removed prior to touching non-contaminated surfaces [52]. Contamination of hands may occur during removal of contaminated gloves [104]. Therefore, hand washing and drying remain important regardless of previous glove use.

Gowns and aprons represent an additional step in infection control standard precautions to prevent contamination of the regular working clothes by infectious agents, and should therefore be used when caring for known CDAD cases [30,33,37,86,102]. Few data exist on the use of gowns specifically to prevent inter-patient spread of *C. difficile*. Perry et al. [105] showed *C. difficile* contamination of nurses’ uniforms during work and therefore recommended the wearing of appropriate plastic aprons; some nurses’ uniforms were already *C. difficile*-positive before duty. Uniforms had been laundered by staff at home, but no information on whether these were ironed or how they were stored was provided. A hospital laundry service may be preferable to home laundry for the elimination of spores in the washing process. However, it should be emphasised that recovery of *C. difficile* from uniforms could simply represent either direct or indirect contamination (e.g. from the environment) and does not necessarily implicate such fomites in transmission.

A summary of the recommendations concerning protective clothing is given in Table 6.
Environmental cleaning

It is well-documented that environmental contamination occurs as a result of CDAD, especially if patients have large amounts of liquid stool or stool incontinence [35,52,53,59,74,75,94,106]. Remarkably heavy contamination takes place on floors, commodes, toilets, bed pans, and bed frames [62,67,96,106–108]. The actual degree of spore recovery from environmental swabs may directly correlate with the incidence of CDAD [75,94,107–109], although a recent molecular epidemiological study was unable to determine whether environmental contamination is the consequence of CDAD or the source of infection, primarily because of the often clonal nature of nosocomial CDAD [109]. Once released in the environment, *C. difficile* spores may persist for long periods (months or years), due to their resistance to drying, heat, and disinfection substances [110,111].

There is good evidence that environmental contamination plays a role in *C. difficile* transmission [112,113]. Cleaning with detergents only may be insufficient for environments contaminated with *C. difficile* [107], and there is a need for effective and user-friendly sporocidal products [114]. Various disinfection substances are available to inactivate *C. difficile* spores; however, subinhibitory concentrations of some disinfectants or non-chlorine-based products may enhance sporulation [115]. The sporulation capacity of outbreak strains such as ribotypes 027 or 001 may also exceed that of other *C. difficile* strains. In the current CDC/HICPAC guidelines, no specific disinfection agent for standard environmental control of *C. difficile* is recommended (i.e., in the absence of known CDAD cases) [116].

Hypochlorite-based disinfectants are recommended by the HICPAC for regular use, especially on frequently touched surfaces in patient care areas where surveillance indicates ongoing *C. difficile* transmission [116], and are frequently used in many hospitals [53,86,106]. It is of potential importance that chlorine-based products are significantly less likely to enhance sporulation of *C. difficile* strains *in vitro* [115]. In comparison with cleaning with a detergent only, hypochlorite use at a concentration of 1000 parts per million (p.p.m.) was associated with a significant reduction in the incidence of CDAD on one of two study wards [108,117,118]. Phosphate-buffered hypochlorite (1600 p.p.m. available chlorine) may be more effective against *C. difficile* spores than unbuffered hypochlorite solution (500 p.p.m. chlorine) [53]. A possible disadvantage that needs to be considered in the choice of disinfectants is the corrosive nature of hypochlorite on metal surfaces [119], especially if very high concentrations are used (e.g. 5000 p.p.m. available chlorine). Furthermore, products containing hypochlorite alone are not suitable for removing organic matter. Products containing a combination of hypochlorite and a detergent may overcome this problem.

Quaternary ammonium (QA) solutions have also been used for environmental *C. difficile* decontamination [94]. However, while no differences in the CDAD incidence were observed in patient care areas with low CDAD incidences, the change from QA solutions to unbuffered 1:10 hypochlorite (5000 p.p.m. available chlorine) for disinfection in the rooms of CDAD-positive patients in a bone marrow transplant unit led to a significant reduction in the incidence of CDAD (8.6–3.3 per 1000 patient-days); the incidence of CDAD increased to 8.1 per 1000 patient-days after reverting back to QA cleaning [118].

Hydrogen peroxide vapour recently proved to be effective in environmental *C. difficile* eradication. However, this method is expensive and involves having to vacate and seal clinical areas. It does not address the issue of recontamination, which may occur on a daily basis.

Glutaraldehyde is known to be effective in inactivation of *C. difficile* spores [120] and has been used for this purpose in nosocomial *C. difficile* outbreaks [85]. However, due to risks to human health, and for environmental safety reasons, it should not be used for environmental decontamination.

Peracetic acid 0.2% is more active *in vitro* than chlorine-releasing agents such as sodium dichloroisocyanurate at 1000 p.p.m. available chlorine [121]. This high-level disinfection substance may also be a substitute for glutaraldehyde [122], although long contact times of 15–20 min are required [123]. Peracetic acid has not been used for environmental decontamination.

For eradicating *C. difficile* spores from the environment, the maximum permissible concentration of chemicals (e.g. chlorine) may differ depending upon national health and safety regulations. Each organisation responsible for cleaning hospitals...
should have specific protocols for the treatment of rooms of patients with CDAD. All objects frequently touched by patients and staff, such as tables, chairs, or telephones, should be disinfected at least once a day. In clinical practice, it is essential to educate cleaning personnel on a regular basis, especially emphasising the difference in cleaning and disinfection of areas used by patients with CDAD and those used by patients colonised/infected by methicillin-resistant Staphylococcus aureus or other multidrug-resistant pathogens.

A summary of the recommendations concerning environmental cleaning is given in Table 7.

### Table 7. Environmental cleaning

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Category</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Regular environnemental disinfection of rooms of CDAD patients should be done using sporocidal agents, ideally chlorine-containing agents (at least 1000 p.p.m. available chlorine). The choice of cleaning regimen will depend on local policy.</td>
<td>IB</td>
<td>2b [108], 2c [115,117], 4 [53]</td>
</tr>
<tr>
<td>2 Hospital wards should be cleaned regularly (at least once a day), concentrating on frequently touched surfaces.</td>
<td>IB</td>
<td>1b [26], 2a [116], 4 [107]</td>
</tr>
<tr>
<td>3 Cleaning staff should be notified immediately when environmental faecal soiling has occurred. Cleaning needs to be done as soon as possible.</td>
<td>IB</td>
<td>1b [26], 2a [116]</td>
</tr>
<tr>
<td>4 Toilets and items such as commodes and bed pans, which are likely to be faecally contaminated, are important sources of Clostridium difficile spores and must therefore be cleaned scrupulously. Cleaned commodes and bed pans should be stored under dry conditions.</td>
<td>IB</td>
<td>1b [26], 2a [116]</td>
</tr>
<tr>
<td>5 After discharge of a CDAD patient, rooms must be cleaned and disinfected thoroughly.</td>
<td>IB</td>
<td>2b [178], 2c [121], 5 [114]</td>
</tr>
</tbody>
</table>

CDAD, Clostridium difficile-associated diarrhoea.

Use of medical equipment

Ideally, for medical equipment that cannot be easily decontaminated, disposable items should be used to control CDAD outbreaks [85]. Notably, rectal thermometers can play a significant role in transmission of C. difficile. Although electronic thermometers do not necessarily become contaminated with C. difficile [52], there are numerous investigations in which positive C. difficile cultures were obtained from these devices. For example, Samore et al. showed that three of 38 thermometers became contaminated by C. difficile during use [94]. Shared rectal thermometers should therefore be replaced by individual thermometers [35], or alternatively, a change to tympanic thermometers should be considered, as these have been associated with a 40% risk reduction [54]. An even greater risk reduction (56%; p 0.026) was accomplished by using disposable vs. shared electronic thermometers in a randomised crossover study [124].

There have been no reports of endoscopes transmitting C. difficile in the hospital setting. However, Hughes et al. [125] found that ten of 15 endoscopes were contaminated with C. difficile immediately after use in patients with CDAD. Since single use is not an option for such expensive equipment, endoscopes need to be re-processed adequately before further use. Disinfection of endoscopes with alkaline glutaraldehyde solution 2% or with peracetic acid led to inactivation of C. difficile spores after thorough cleaning and an exposure time of 5–10 min [120,125,126]. Thus, endoscope cleaning followed by exposure to sporocidal disinfectants or thermal re-processing, as is standard in most hospitals, should be adequate for killing of C. difficile spores.

Additional devices found to be C. difficile-positive include blood pressure cuffs [52,59] and oximeters [94]. Although it tested negative in one investigation [85], equipment for enemas may also be critical in this context. In general, instruments and equipment, including stethoscopes and blood pressure cuffs, should be patient-specific and cleaned carefully after use.

A summary of the recommendations concerning the use of medical equipment is given in Table 8.
Good antibiotic stewardship

Antibiotic therapy or prophylaxis [127] alters the colonic microbiota and potentially allows *C. difficile* to proliferate, produce toxins, and cause diarrhea [6]. Antibiotics constitute the most important predisposing factor for CDAD [7,9,128]. However, a systematic review of the studies that have examined the risk of CDAD associated with different antibiotics revealed that most are flawed because of failure to control for potential confounding factors [129]. Exposure to *C. difficile*, therapy with a combination of, or sequential, antibiotics and duration of antibiotics are frequently not addressed as causes of bias [129,130]. Furthermore, host humoral immunity to *C. difficile* toxin(s) and the antibiotic susceptibility of the *C. difficile* strain are likely to influence the risk of CDAD development [131,132]. It is not surprising, therefore, that there are conflicting studies regarding the risk of CDAD in relation to specific antibiotics or classes. Good antibiotic stewardship should be promoted as standard, and CDAD cases can be used to reinforce such principles [133].

A policy for prudent use of antibiotics should be an evidence-based approach to reduce the incidence of CDAD, but the application will vary among countries and institutions. A recent study from Canada reported no change in CDAD incidence after strengthening of infection control procedures, but implementation of an antimicrobial stewardship programme was followed by a marked reduction in incidence. This suggests that non-restrictive measures to optimise antibiotic usage can yield exceptional results when physicians are motivated and that such measures should be a mandatory component of CDAD control [134]. However, in practice, in virtually all situations where CDAD rates increase, changes in antibiotic usage are implemented in addition to enhancements of infection control measures. Thus, the true effect of restrictive or non-restrictive antibiotic control measures alone on CDAD rates is difficult to assess.

Almost any antibiotic may induce CDAD, but broad-spectrum cephalosporins (in particular, second- and third-generation cephalosporins), broad-spectrum penicillins and clindamycin are most frequently implicated [31,129,135–145]. Since 2000, fluoroquinolones have also been identified as a possible risk-factor for CDAD, including CDAD caused by the new hyper-virulent PCR ribotype 027 [34,36,50,55,146–148]. The PCR ribotype 027 strain of *C. difficile* is resistant to fluoroquinolones, and increased use of these antibiotics may have contributed to some outbreaks. Fluoroquinolones, especially ciprofloxacin, were associated with the highest relative risk for CDAD caused by the new hyper-virulent PCR ribotype 027 *C. difficile* in Canada and The Netherlands [146,149]. However, in the above-mentioned study that reported that the implementation of an antimicrobial stewardship programme led to a marked reduction in CDAD incidence, respiratory fluoroquinolone usage had increased by 79% [134].

Ureidopenicillins (with or without β-lactamase inhibitors) appear to have a low propensity to induce CDAD [143,150,151]. The reasons why anti-pseudomonal penicillins appear rarely to promote *C. difficile* infection as compared with cephalosporins may include relative activity against *C. difficile* itself and the absence of a propensity to select and/or induce spore germination. In a gut model, despite widespread disruption of bacterial populations during piper-
acillin–tazobactam administration, C. difficile populations remained principally as spores, and no sustained proliferation or high-level cytotoxin production was seen [152].

Many hospital inpatients receive combinations of antibiotics or multiple antibiotic courses. Given that antibiotic use is unnecessary or inappropriate in as many as 50% of cases, a Cochrane analysis indicated that interventions to improve antibiotic prescribing can reduce hospital-acquired infections, most notably CDAD [31,63,153]. The exact duration of risk of developing CDAD after antibiotic exposure still needs to be determined, but there is some evidence that the duration of therapy with certain antibiotics may also influence this risk [146]. Aggressive restriction of high-risk antibiotics, reducing polypharmacy, prevention of long-term therapy and avoiding inappropriate prescribing are the first steps in reducing a high incidence of CDAD. Some measures to achieve this goal comprise automatic stop-dates, electronic prescribing [154], banning of certain antibiotics [34], prescriber education, and production of guidelines or policies [4,133].

There is also a need for continuous training of medical staff about appropriate antimicrobial use and for feedback of success [150,155], since systematic reviews have shown the positive effect of audit and feedback in helping HCWs to implement evidence-based practice [156–159]. In a controlled, interrupted time-series on a geriatric ward, Fowler et al. showed that feedback on improved antibiotic prescribing can be successful in reducing the use of broad-spectrum antibiotics (amoxycillin–clavulanic acid and cephalosporins) in favour of more pathogen-focused treatment (benzylpenicillin and trimethoprim). Consequently, the altered antimicrobial treatment regimen was associated with a significant decrease in CDAD (p 0.009) [137]. Defining so-called ‘alert antimicrobials’, drugs that need patient-specific feedback by an authorised person (e.g., the hospital pharmacist), may also be useful to further improve antibiotic use in the hospital [160]. In addition, surveillance of hospital antibiotic use (at least of the ‘high-risk’ agents mentioned above) by pharmacists, in close cooperation with medical microbiologists, is recommended [137,161].

Exposure to antibiotics is believed to lead to disturbance of the normal gastrointestinal microbiota. This may predispose to diarrhoea after acquisition (or selection) and proliferation of C. difficile. Probiotics (bacteria and yeasts) are thought to restore the balance of the gut microbiota when administered orally to patients. At present, few data exist on the treatment or prevention of CDAD with probiotics. There are some randomised controlled trials that show a significant reduction in the risk of antibiotic-associated diarrhoea by the use of Saccharomyces boulardii [162,163], but newer studies using S. boulardii or Lactobacillus GG failed to confirm these findings [164,165]. Three published systematic reviews did not show sufficient evidence to support the use of probiotics for CDAD prevention or treatment [166–168]. It was claimed that the results of a recent trial with a Lactobacillus preparation showed a beneficial effect of probiotics in antibiotic-associated diarrhoea [169]. However, the design of this study has been criticised, because the highly selective inclusion and exclusion criteria meant that <7% of the potential target population was examined, and the use of a milk-based placebo may have introduced bias [170].

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A summary of the recommendations concerning good antibiotic stewardship is given in Table 9.

### Specific measures in outbreaks

The key to reducing risk of infection is the prevention of transmission of C. difficile. When an increased number of cases of C. difficile is identified, the infection control strategy should be informed by risk assessment that takes into...
account the background epidemiological pattern and the risk status of the patients involved. Outbreak situations require immediate action. Usually, this involves a combination of different infection control measures [171]. Hence, the effectiveness of each individual measure is difficult to determine. First of all, adherence to recommendations that apply in the endemic setting needs to be strengthened. These measures include strict separation of symptomatic patients, education of staff, increased awareness of CDAD, and restriction of the use of high-risk antibiotics [37]. Zafar et al. [172] reported a 60% reduction in the rate of CDAD following implementation of isolation, surveillance, education, environmental disinfection, optimal hand washing, and centralised re-processing of devices. Struelens et al. [76] observed a 73% decrease in CDAD incidence as a result of early isolation precautions, active initial surveillance, environmental surface disinfection, and early therapy for CDAD.

Specific measures may be helpful in a nosocomial CDAD outbreak. Early and rapid diagnosis is important. Also, the threshold should be low for the rapid evaluation of patients with mild diarrhoea on wards with active cases of CDAD. Cohort nursing of confirmed CDAD patients, and isolation of suspected CDAD cases before labora-

Table 10. Specific measures during outbreaks

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Category</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection control staff should always be informed when there is an increased number or severity of CDAD cases.</td>
<td>IB</td>
<td>1b [26]</td>
</tr>
<tr>
<td>All hygiene measures should be reinforced in case of a CDAD outbreak.</td>
<td>IB</td>
<td>1b [26], 4 [89]</td>
</tr>
<tr>
<td>Review the standard of environmental cleaning to ensure high quality and frequency of decontamination. If possible, implement a designated and well-educated cleaning team especially for the rooms of CDAD patients.</td>
<td>II</td>
<td>4 [86]</td>
</tr>
<tr>
<td>Perform good antibiotic stewardship. Antimicrobial prescribing (frequency, duration, and types of agents) should be reviewed as soon as possible, with emphasis on avoiding the use of high-risk agents (e.g. cephalosporins, fluorquinolones and clindamycin) in at-risk patients. Use these agents only when medically needed.</td>
<td>IB</td>
<td>1a [133], 2b [7,31,135,137,146], 3b [36,50,55,136,138–140,147,148], 4 [32,34,37,38]</td>
</tr>
<tr>
<td>Faecal samples from all CDAD cases should be stored, so that they can be cultured, either locally or in a reference laboratory, and typing can performed, if necessary, retrospectively.</td>
<td>IB</td>
<td>1b [26], 3b [50], 4 [31,49,51,109]</td>
</tr>
<tr>
<td>In order to elucidate the epidemiology of <em>Clostridium difficile</em>, isolates from infected patients should ideally be compared by molecular methods.</td>
<td>II</td>
<td>2b [94]</td>
</tr>
<tr>
<td>Implement interim policies for patient admissions, placement, and staffing as needed to prevent <em>C. difficile</em> transmission.</td>
<td>IB</td>
<td>1b [26]</td>
</tr>
<tr>
<td>For details on isolation procedures and dedicated nursing staff, please refer to Table 4.</td>
<td>IB</td>
<td>1b [26]</td>
</tr>
<tr>
<td>When transmission continues despite the assignment of dedicated staff, close the unit or facility to new admissions.</td>
<td>IB</td>
<td>1b [26]</td>
</tr>
<tr>
<td>When transmission continues despite all of the above measures (e.g. re-opened unit), vacate the unit for intensive environmental cleaning to eliminate all potential environmental reservoirs of <em>C. difficile</em>.</td>
<td>II</td>
<td>2a [26]</td>
</tr>
</tbody>
</table>

CDAD, *Clostridium difficile*-associated diarrhoea.
tory test results are available, have been shown to be effective during a CDAD outbreak [46]. In a recently published report of an epidemic of CDAD on a geriatric ward, Cherifi et al. [89] reported that cohorting of infected patients on one ward with a single medical team was a key way of limiting the spread of infection. However, the capacity to establish a dedicated unit and nursing team for CDAD patients will need to be considered alongside competing pressures. Similarly, the measures used in outbreaks may depend on the wards involved and on the clinical severity of cases. However, a written local protocol should exist so that early adoption and/or review of control measures occurs when CDAD cases are identified.

An additional key to CDAD prevention is to reduce the number of susceptible patients. This can result from good antimicrobial stewardship, which will minimise the antimicrobial exposure of patients in the hospital, thus reducing the number of patients susceptible to developing CDAD even if C. difficile transmission occurs [133].

A summary of the recommendations concerning specific measures during outbreaks is given in Table 10.

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