

EXPERT
REVIEWS

Clostridium difficile: improving the prevention paradigm in healthcare settings

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Clostridium difficile infection (CDI) is a major public health problem worldwide with significant morbidity and mortality that is spread by spores and fecal oral transmission. A variety of risk factors have been identified. Some risk factors such as age, are not amenable to change, while others such as antimicrobial utilization have resulted in broadly implemented antimicrobial stewardship programs. New risk factors are emerging such as proton pump inhibitor (PPI) use, irritable bowel disease (IBD) and obesity, with others yet to be determined. Prevention of spread of CDI is imperative, since therapy remains imperfect. We review established and emerging risks for CDI and offer potential preventative strategies with the use of a multidisciplinary CDI prevention bundle checklist.

KEYWORDS: antibiotic resistance • antibiotic stewardship • *Clostridium difficile* • *C. difficile* bundle • *Clostridium difficile* infection • contact isolation • contact precautions • disinfection • fecal microbiome • hand hygiene • hydrogen peroxide vapor infection prevention • probiotics • UV light

Clostridium difficile infection (CDI) is a US \$6 billion per year public health problem in the USA [1]. *C. difficile* is an obligate anaerobic, spore, forming Gram-positive bacillus that was first described in 1935 [2] but was not established as a human pathogen until 1978 [3]. Pathogenic strains of *C. difficile* may produce one to three toxins (toxin A, toxin B and binary toxin), which inactivate intestinal cell actin-regulating GTPases, thereby causing disease [4]. Since the 1980s, a new epidemic strain (027, NAP1, BI) has arisen and led to a 400% increase in mortality from 2000 to 2007 and in 2012 14,000 deaths annually were linked to CDI in the USA alone [5]. The risk of both acquiring CDI and mortality is increased in the elderly (>65 years of age). There are approximately 300,000 healthcare-associated infections with CDI in the USA each year [6]. Costs of patient care associated with CDI range from US\$2500 to US\$3500 extra per admission; not including surgical interventions to eradicate CDI such as colectomy, which can cost from US\$15,000 to US\$19,000 [7].

CDI is associated with a perturbation of the normal fecal flora, often occurring due to the

use of antibiotics coupled with the ingestion of spores of a toxin producing strain of *C. difficile* and a limited host response to the toxin. Although most CDI patients have been associated with some form of inpatient medical care, an increasing number are now recognized as being associated with outpatient care [8].

Studies have shown that unrecognized cases of CDI are admitted to healthcare facilities [9] or transferred from one facility to another and may spread it within a facility via healthcare workers' hands. However, CDI can be prevented. Early results from a 2-year US hospital prevention project showed a 20% decline in CDI associated with infection prevention and control measures [10]. Similarly, in England, after a number of deadly CDI outbreaks and national publicity, a program of Infection Prevention measures and antimicrobial stewardship efforts reduced CDI rates by >50% in 3 years.

The CDC has promoted a 6-point program for prevention of CDI as summarized in Box 1. Sustained prevention of CDI remains an elusive challenge, especially when differentiating between initial and recurrent CDI. This article

Box 1. The six elements of CDC's program for *Clostridium difficile* infection prevention.

- Antibiotic stewardship. Since 50% of all antibiotics given are unnecessary.
- Test for *Clostridium difficile* in patients who have diarrhea who have recently (within 6 weeks) received antibiotics.
- Proper use of transmission-based precautions – early contact isolation for CDI.
- Proper protective equipment use. Gloves and gowns when in contact with the patient or the room environment. Soap and water rather than alcohol hand gel for hand hygiene.
- Room decontamination. Clean surfaces with bleach or hydrogen peroxide, the only two US FDA-approved spore-killing cleaning and disinfecting agents for CDI.
- Information transfer. When a patient transfers, notify the new facility of CDI patients as soon as possible [181].

CDI: *C. difficile* infection.

reviews and proposes a collaborative multidisciplinary approach to preventing CDI in healthcare settings.

Transmission/acquisition

The risk of acquiring CDI occurs from environmental exposure to the organism and from the use of broad-spectrum antibiotics. Environmental transmission occurs primarily in healthcare facilities, where exposure to environmental contamination by spores is most common [11]. Environmental contamination stems from the fecal-oral transfer of *C. difficile* spores from the patient to the healthcare workers' hands and medical equipment to the ingestion of spores by other patients. Since CDI has been the cause of many large outbreaks in hospital settings [12], frequent hand washing by healthcare personnel and frequent cleaning and disinfecting of the patient's environment are of utmost importance in preventing transmission. This is because *C. difficile* spores can live in the environment for up to 5 months and can resist most cleaning and disinfection measures [13]. Animals, domestic and farm, can also acquire CDI, which raises the potential of bi-directional animal to human transmission [14–16]. Additionally, *C. difficile* has been isolated

from various meat foods making one wonder about the possibility of unknown acquisition from the food supply [17].

Defining community onset versus nosocomial acquisition of CDI has become more complex in recent years due to the changing epidemiology of CDI. In 2010, SHEA/IDSA updated clinical practice guidelines to reflect these epidemiological changes with three types of CDI acquisition: community onset, community onset with healthcare facility association and healthcare onset as illustrated in TABLE 1 [18]. Healthcare facilities included in this definition are: acute care hospitals, hemodialysis centers, day surgery centers, chemotherapy centers and long-term care facilities. Any exposure to one of these types of healthcare facilities can increase a patient's risk to acquire CDI. Some facilities have implemented programs to screen at-risk patients for CDI on admission in order to implement more timely contact precautions and obtain baseline data about prevalence. Ultimately, culture and whole genome sequencing may better define sources of acquisition and transmission of CDI.

Risk factors

Risk factors for which there is evidence suggestive of an association with CDI are shown in TABLE 2: increasing age (>65 years old), obesity, irritable bowel disease (IBD), chemotherapy, severity of underlying diseases, non-surgical gastrointestinal procedures, presence of a nasogastric tube, anti-ulcer medications, stay on ICU, duration of hospital stay, duration of antibiotic course and administration of multiple antibiotics [19]. Recognizing the presence of these risk factors is an important initial step in determining appropriate prevention strategies. Although all of these issues can lead to an increased risk of CDI acquisition, disruption of the normal gut flora is necessary for *C. difficile* exposure to result in infection.

Role of the microbiome

With the advent of techniques to perform metagenomic studies, there is increased attention being paid to the role of the normal microbiome in health maintenance and disease [20]. Fecal colonization of potentially virulent pathogens have increased the potential risk for developing infection from emergent pathogens such as *E. coli* ST 131 H30Rx, carbapenem-resistant *Enterobacteriaceae* and *C. difficile*. Alterations of the microbiome are particularly relevant as a necessary risk factor for developing CDI. A majority of infants and neonates become colonized with *C. difficile* during the first year of life, including pathogenic strains and yet do not manifest infection [21]. There are 10^{13} cfu/bacteria per gm of feces, many of which are not currently cultivable. Studies have shown that with the administration of common antibiotics there is a change in the richness, goodness and diversity of the fecal microbiome population [22]. The components of firmicutes and other types of bacteria have been noted to be altered in patients who develop CDI, and those who have relapses of CDI when compared with control populations [23]. A major principal for the prevention of CDI is the maintenance of a 'balanced' fecal

Table 1. Definitions of types of *Clostridium difficile* infection acquisition.

Type of <i>Clostridium difficile</i> infection	Timeframe of occurrence
Community onset	No healthcare exposure for >30 days
Community onset with healthcare facility association	Recent healthcare exposure within <30 days
Healthcare onset	Healthcare onset >48 h post-admission to a healthcare facility

microbiome ranging from avoiding unnecessary antimicrobial use, use of narrower spectrum, targeted antimicrobial therapy and repopulation biotherapy. The use of fecal transplants/biotherapy for relapsing CDI cases highlights the importance of the 'balanced' microbiome [24]. It has even been suggested that analogous to saving some neonate cord cells for future stem cell use that one save samples of fecal flora prior to first antibiotic utilization for future microbiome reconstitution.

Patients with advanced age >65 years

CDI has been associated with advanced age [25–27]. A meta-analysis found CDI type B1/NAP1/027 to be associated with older age (>65 years) and fluoroquinolone use [27]. A case-control study in the Netherlands conducted in a 980-bed teaching hospital from 2005 to 2007 found two types of *C. difficile*, 017 and 027, during an outbreak. Risk factors were compared among CDI patients (cases) and non-CDI patients with diarrhea (controls). Older age (65 and older), inflammatory bowel disease and abdominal surgery were found to be adjusted and crude risk factors for both types of *C. difficile*. Patients with non-CDI diarrhea (19%) were found to be younger than CDI patients (36% older than 80 years). Ribotype 027 was statistically significant for 65–80 years of age (adjusted odds ratio [OR]: 4.56; 95% CI: 1.36–15.4). However, type 017 was not statistically significant (adjusted OR: 1.96; 95% CI: 0.74–5.12) [25]. While studies have focused on chronological age, it seems that physiological age and the presence of co-morbidities and alterations of immune status may play a greater role than perceived. As patients age, there is thymic involution effecting cellular and humoral immunity. Thymic involution and immunocompromised patients including those who have a decrease in T cells are at an increased risk for CDI [28].

Obesity

Obesity plays a role in the risk of acquiring CDI [25,26]. A retrospective analysis was performed to better understand the role of obesity as a risk factor for CDI. Medical records were reviewed for 132 patients with CDI at Boston Medical Center, a 508-bed academic medical center, from November 2011 until April 2012. Following the SHEA/IDSA guidelines for type of CDI acquisition, 43% (91) had community onset (CO) and 30% (41) had healthcare facility onset (HO). Among the 91 CO patients, 32 had community onset after healthcare facility exposure (CO-HCFA). Among the CO-HCFA patients, other significant risk factors determined were prior hospitalization, stay in a long-term care facility, recent surgery, hemodialysis and outpatient chemotherapy. Using univariate analysis, more patients with IBD were determined to have CO CDI ($p = 0.018$) than HO or CO-HCFA CDI and more patients were determined to be obese ($p = 0.08$). Patients with CO CDI were four-times more likely to be obese when compared with patients who experienced CO-HCFA. General community onset of CDI seems more likely for obese and IBD patients than for patients who have had recent healthcare facility exposure [29]. Interestingly, recent data

Table 2. Clostridium difficile infection risk factors references.

Risk factors	Ref.
Advanced age (>65 years old)	[25–28]
Obesity	[25,26,29,30]
Irritable bowel disease	[25,32,33,35,36]
Chemotherapy	[37,38]
Imbalance of the fecal microbiome	[21–24,30]
Thymic involution	[28]
Proton pump inhibitors	[100–122]
Duration of antibiotic course	[48–53]
Administration of multiple antibiotics	[48–53]

in an animal model have suggested that antibiotics not only affect the goodness, richness and diversity of the fecal flora, but also that alterations in fecal flora can lead to weight gain, which is transmissible [30].

Of note, a retrospective case-control study was conducted among 6300 hospital patients in 2011 in two internal medicine departments in two different hospitals. The study analyzed 148 CDI patients in comparison to 148 hospital patients who did not have diarrhea. Mean BMI was higher in the CDI patients (33.6) in comparison to the controls (28.9). High body mass index (OR: 1.196; 95% CI: 1.12–1.27) and history of intra-abdominal surgery (OR: 2.865; 95% CI: 1.26–6.52) were the only risk factors that were associated with CDI. The study findings showed that CDI is correlated with obesity and intra-abdominal surgery [31].

Irritable bowel disease

Changes in fecal microbiome have been linked to obesity and IBD [25]. A retrospective, observational study was conducted from 2000 to 2005 in the Medical College of Wisconsin at the Inflammatory Bowel Disease Center to better understand the impact of CDI in IBD patients. Patients with positive toxin for CDI were included in the study. The study included admitted patients with CDI from Froedtert Hospital, Medical College of Wisconsin's teaching hospital. The rate of CDI increased among IBD patients from 2003 when no CDI cases were detected to 14 cases in 2004, 9 (rate of 1.8%) and 46 cases in 2005 (rate of 4.6%). Increases occurred among hospital patients during this time, as well (207 cases in 2004, 487 cases in 2005). The study found that patients with IBD had a higher risk of developing CDI compared with the non-IBD patients [32].

Of special note, Rodemann *et al.* [33] analyzed hospital admissions from the Barnes Jewish Christian clinical data repository for CDI patients from 1998 to 2004 to learn about IBD in CDI patients. They analyzed CDI incidence for patients with IBD, non-IBD, CDI and ulcerative colitis. CDI

Table 3. Risk stratification of antibiotics for development of *Clostridium difficile* infection [182–187].

High risk	Intermediate	Low risk
Cephalosporins	Macrolides	Doxycycline
Clindamycin	β -lactam/ β -lactamase inhibitors	Tigecycline
Carbapenems		Azithromycin
Fluoroquinolones		Metronidazole
		Aztreonam
		Penicillin
		Clarithromycin
		Vancomycin
		Trimethoprim
		Nitrofurantoin

was higher in IBD and ulcerative colitis patients than in non-IBD patients ($p < 0.001$). As the relationship of CDI and IBD is evolving, data show that most IBD patients will contract CDI as outpatients. IBD patients treated with immunomodulators or corticosteroids combined with antibiotics have a higher rate of CDI acquisition than IBD patients who are treated with antibiotics alone [34]. Some research has shown that genetic and microbiotic factors in IBD are influenced by the enteric microbiota [35]. The human microbiome plays a tremendous role in the development of CDI for IBD and obese patients. Gene-level and network-level topologic differences have been connected to IBD patients and obese patients [36].

Chemotherapy & immunocompromised conditions

Chemotherapy-associated CDI was first reported in 1981 for a patient who had embryonal cell cancer. This first reported patient had recurrent CDI with each chemotherapy treatment, but was asymptomatic between chemotherapy treatments [37]. It is difficult to distinguish between chemotherapy-associated and antibiotic-associated diarrhea. This is because chemotherapeutic agents cause diarrhea and CDI without any use of antibiotics. However, most cancer patients receiving long-term chemotherapy also receive antibiotics. Hematopoietic stem cell transplant patients experience most of the associated risks that CDI patients experience: prolonged hospitalization, antibiotic prophylaxis and gastrointestinal mucosal damage [38].

Antimicrobial stewardship

A person's fecal microflora provides a host defense by inhibition of colonization and overgrowth of *C. difficile* [39–41]. A healthy adult's colon contains 10–100 trillion cfu/bacteria per gm of feces with obligate anaerobic species outnumbering aerobic organisms by a ratio between 10 and 100:1. Antimicrobial agents vary in their ability to disrupt this host defense (TABLE 3), increasing the risk of colonization by potentially pathogenic microorganisms [42]. This colonization increases the risk of *C. difficile* colonization of the colon and toxin production [43–45]. It is estimated that 15–25% of cases of antibiotic-associated diarrhea are due to the overgrowth of *C. difficile* [46]. Disruption of the microflora in the colon

requires days to weeks to return to normal levels, if ever [40]. A major risk factor for CDI is prior antibiotic use [47]. Therefore, differences in specific antimicrobial selection, the use of multiple antimicrobial agents and prolonged use of antimicrobial agents increase the risk of CDI [48–53]. A strategy to decrease the risk of CDI is to limit the duration of antimicrobial therapy and minimize the number of agents. Antimicrobial agents with anaerobic activity have a higher likelihood of being associated with *C. difficile*-associated diarrhea due to disruption of colonic flora [39–41,54], especially due to the emergent epidemic strains [55–58].

Cephalosporins (high risk)

C. difficile isolates are resistant to most cephalosporins and second- and third-generation cephalosporins create a high risk for CDI. Studies associate cephalosporins as major risk factors for CDI with greater OR compared with fluoroquinolones [48,49]. In a Canadian epidemic outbreak of CDI, the risk factors were use of fluoroquinolones (OR: 3.22; $p = 0.04$) and cephalosporins (OR: 5.19; $p = 0.006$) [59].

Clindamycin (high risk)

In the late 1970s, a disease called 'clindamycin colitis', later identified as CDI, came to medical attention [60]. There has been an emergence of clindamycin-resistant strains of *C. difficile* that were associated with large outbreak (minimum inhibitory concentration [MIC] $>256 \mu\text{g/ml}$) [61,62]. Clindamycin impact on the intestinal flora over a prolonged period of time increases the risk of CDI even after clindamycin is discontinued [63,64]. Restriction of the use of clindamycin has been reported to decrease rates CDI rates [65,66].

Fluoroquinolones (high risk)

Fluoroquinolones have poor *in vitro* activity against *C. difficile* and has been associated with an increased risk of CDI [67,68]. The reported OR and relative risks have ranged from 2.0 to 12.7 [48,69]. An increased incidence in CDI occurred with a higher morbidity and mortality rate due to a fluoroquinolone-resistant strain of *C. difficile* [49]. *C. difficile* strains resistant to the fluoroquinolones (ciprofloxacin, moxifloxacin, gatifloxacin and levofloxacin) had MICs of at least $32 \mu\text{g/ml}$, but were susceptible to clindamycin. Levofloxacin had a lower incidence (OR: 0.5) compared with other fluoroquinolones. However, the association with levofloxacin can be inaccurate because it was not used in most of the study hospitals. Other studies have associated levofloxacin as a risk factor for CDI [48].

Tigecycline (low risk)

Tigecycline is a glycylcycline antibiotic with broad-spectrum activity. Tigecycline is also active against anaerobic bacteria such as *C. difficile* and *Bacteroides fragilis* [70,71]. Tigecycline has MIC₉₀ of 0.032–0.12 $\mu\text{g/ml}$ against *C. difficile* strains [72–74]. In contrast, cefotaxime, ciprofloxacin and meropenem have MIC₉₀ of >64 , 32 and 4 $\mu\text{g/ml}$, respectively [75,76]. The antibiotic concentrations exceed the MIC of tigecycline in the large

bowel, which suggests that tigecycline is less likely to alter the gut flora. In an *in vitro* study, tigecycline suggested that it inhibits the sporulation of *C. difficile* at sub-MIC levels [77]. In a human gut model, tigecycline has shown to have inhibitory activity on *C. difficile* [78,79]. Toxin production in the gut model occurs with subtherapeutic MIC for *C. difficile* [80]. Antibiotic concentrations were below the limits of detection after stopping tigecycline, there was no late toxin production [78]. Tigecycline has been reported to be effective in a few cases of recalcitrant CDI [81]. This potential therapeutic option is limited due to lack of clinical trial data for its use in prevention of CDI.

Doxycycline (low risk)

Doxycycline is a broad-spectrum antibiotic that is considered in the low-risk group for the development of CDI. Despite tetracycline resistance of some isolates, doxycycline at therapeutic levels inhibits *C. difficile in vitro* [82,83]. Absorption of doxycycline occurs in the upper gastrointestinal tract and excreted renally, which minimizes the effects on the gut flora. In a retrospective study, doxycycline and tetracycline were associated with a decreased risk of community-acquired CDI (RR: 0.0; 95% CI: 0.0–0.9) [84]. In historical cohort study, patients were followed for the development of CDI 30 days after receiving ceftriaxone, a high-risk cephalosporin. Only 5/1066 patients receiving doxycycline developed CDI, for an incidence rate of 1.67 per 10,000 patient-days [85]. The comparator group had an increased incidence rate of 5.60 per 10,000 patient-days. A large, retrospective, case–control study demonstrated doxycycline had a protective effect in CDI [86].

Restriction of antibiotics

Antimicrobial stewardship includes selection, dosing, de-escalation and reducing the duration of therapy of antibiotics [87]. Several studies have demonstrated that changes in antimicrobial prescribing practices can affect the incidence of CDI [88]. The combination of antimicrobial stewardship program and infection prevention measures reduced the incidence of CDI ($p = 0.007$) in the outbreak of the epidemic strain of RT027 [89]. Once antibiotic usage decreased by 46%, the incidence of CDI decreased by 60%. For example, despite infection control measures, CDI incidence decreased once the use of clindamycin was restricted [90–92]. Additionally, a restrictive policy on ciprofloxacin and ceftriaxone reduced the rates of CDI by 77% [93]. An outbreak of CDI coincided with a formulary change from levofloxacin to gatifloxacin in a long-term care facility and hospital [94]. During the levofloxacin use, 17% (10 out of 58) patients who received a mean of 13 days of levofloxacin developed CDI. After the formulary switch to gatifloxacin, 30% (14 out of 47) patients with a mean therapy duration of 13.5 days of gatifloxacin developed CDI. Once the formulary switched back to levofloxacin, there was a lower incidence of CDI (0.5 cases of *C. difficile* associated disease per 1000 patient-days), but the number of patients was not specified.

An interventional, retrospective study evaluating the restriction of high-risk antibiotics such as second-generation

cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin over a period of 6.5 years demonstrated a reduction in the incidence of CDI ($p = 0.0081$) [95]. In addition to a decrease in CDI rates, antimicrobial stewardship can decrease the rates of vancomycin-resistant *enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) [96,97]. However, in a prospective controlled interrupted times series study with each being 21 months, there was no change in the MRSA rates after implementing a narrow-spectrum antibiotic policy [98]. The combination approach of antimicrobial stewardship and infection prevention is effective in decreasing the incidence of CDI [99].

Proton pump inhibitors

Gastric acid is effective in killing vegetative *C. difficile* and neutralizing the toxins in human and animal studies [100,101]. However, its spores, which are acid resistant, pass through the stomach and germinate in the small bowel once exposed to bile acids [102–104]. Proton pump inhibitors (PPIs) decrease the gastric acidity, which disrupts the gut flora and increases the risk of colonization [105,106]. PPIs have a negative effect on leukocyte activity, which contributes to the defense against *C. difficile* [107–109].

There have been conflicting data on the association between PPI and risk of CDI. Several meta-analyses have shown an association with PPI and CDI [110–112]. One study showed that 63% of PPI users who had CDI did not have an indication for PPI therapy [112]. For example, in a meta-analysis of 40 observational studies, there was a positive association with PPI and CDI (OR: 1.74; 95% CI: 1.47–2.05; $p < 0.001$) [110]. Several editorials provide a critique that these meta-analyses included low-quality studies and have heterogeneity in the study population, which makes it difficult to associate PPIs with CDI [113–115]. A retrospective, single-center, medical record review demonstrated that there was a statistically significant risk of development of CDI (2.8% in PPI group vs 0.4% in non-PPI group; $p < 0.001$) [116]. Another retrospective, cohort study found that PPIs did not increase the risk of recurrence of CDI [117]. The US FDA has issued a warning of increased risk of CDI with PPIs [118]. Systematic reviews also show that patients receiving PPIs had more comorbidities compared with the non-PPI group, which may be a confounding factor [119]. In retrospective studies, PPIs were associated with recurrence of CDI [120,121]. In a retrospective case–control study, the duration of PPI therapy was found to be a risk factor (OR: 1.14; 95% CI: 1.02–1.27; $p = 0.018$) [122]. As a result, the role of PPI in the development of CDI is still controversial, despite the association shown in observational studies; however, awareness of proper indications for use of PPIs should be reviewed for patients and overuse avoided.

Probiotics

Probiotics are microorganisms that are believed to reduce the risk of colonization by counteracting the disturbances in intestinal flora [123]. The administration of probiotics introduces

microorganisms into the indigenous microflora [124,125]. Probiotics are an option as adjunctive therapy to prevent CDI. A Phase III, quasi-experimental, prospective cohort study using probiotics as part of a bundle approach in addition to antimicrobial stewardship demonstrated a decrease in CDI (73% $p < 0.001$) [126]. A meta-analysis of 20 randomized controlled studies with 3818 participants found a reduced incidence of *C. difficile* antibiotic-associated diarrhea (placebo = 5.9%, probiotics = 2.0%, absolute risk reduction = 3.9%) [127]. The limitations are that 13 trials did not provide actual CDI rates and there is a potential bias with studies conducted by the probiotic manufacturers. Other systematic reviews had similar results to this one [128,129]. Other trials demonstrated a reduction in CDI rates when adding probiotics [130–132]. In a single-center, randomized, double-blind, placebo-controlled dose-ranging study, the group receiving 100 billion CFU of *Lactobacillus acidophilus* CL1285® + *Lactobacillus casei* LBC80R® Bio-K- + CL1285 provided superior outcomes and fewer gastrointestinal events compared with the group receiving 50 billion CFU formulation [133]. A double-blind, placebo-controlled study that randomized patients in receiving a probiotic containing both *Lactobacillus* and *Bifidobacterium* or placebo for 20 days found 2.9% *C. difficile*-associated toxin in the probiotic group versus 7.25% in placebo-controlled group [134]. In a multicenter, randomized, double-blind trial, patients who were older than 65 years who were on antibiotics took a multistrain preparation of lactobacilli and bifidobacteria or a placebo [135]. A weakness is that patients were allowed to receive antibiotics for up to 7 days before randomization instead of at the beginning of antibiotic therapy. CDI occurred in 12 participants (0.8%) in probiotic group and 17 participants (1.2%) in placebo group ($p = 0.35$). The current IDSA treatment guidelines for *C. difficile* do not endorse probiotics [136]. There have been reports of fungemia and bacteremia in immunocompromised patients who have used probiotics, but the overall rates of adverse events are similar to placebo [137,138]. An evaluation of randomized, placebo-controlled studies using probiotics found that the studies were underpowered and had potential flaws [139]. As a result, there needs to be additional studies that are adequately powered and well designed to demonstrate a benefit of probiotics for prevention of CDI. Still many patients either take probiotics on their own without consulting their physicians or request them during hospitalization.

Vaccination

Toxins A and B, which are inflammatory exotoxins, are released by *C. difficile* [140–142]. High concentration of serum IgG against toxin A was found in asymptomatic patients who were carriers of *C. difficile* [143]. Healthy patients who responded to the first episode of CDI were able to mount a systematic immunity, which was demonstrated by higher concentration of IgG antibody concentration against toxin A and thus, reduced the likelihood of CDI recurrence [144]. The ideal candidates for potential CDI vaccinations would be elderly or immunocompromised patients who have a higher risk of CDI

with severity ranging mild diarrhea to fulminant pseudomembranous colitis [145].

An oral *Lactococcus lactis* preparation was given to hamsters that had *C. difficile*. It demonstrated potential in preventing CDI [146]. *C. difficile* vaccine that contained inactivated toxoids A and B caused antibody response in healthy adults [147,148]. The vaccination elicited serum anti-toxin A antibody responses in healthy adults, but it still needs to demonstrate its effect on preventing CDI.

A Phase II trial evaluated the immunogenicity, dosage and immunization schedule in adults at risk of CDI to assess primary prevention [149] and estimate prevention of recurrence in infected patients [150]. Sanofi-Pasteur began recruitment for a randomized, observer-blind, placebo-controlled, multicenter, multinational Phase III trial in August 2013 to evaluate the safety and immunogenicity of toxoid vaccine to prevent symptomatic CDI [151]. There is potential for the use of a *C. difficile* vaccine to aid in the prevention of CDI, but more clinical trials are needed to demonstrate the efficacy.

Statins

Statins may have a potential role in the prevention of CDI. Statins, which inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase, have shown to have anti-inflammatory effects, which are independent of lipid lowering [152–154]. In a matched case–control study, there was a lower incidence of CDI in the statin group compared with the non-statin group (adjusted OR: 0.78; 95% CI: 0.76–0.84) [155]. A retrospective case–control study of patients with CDI demonstrated that there was a lower incidence of CDI in the statin group (64/197 32.5%) compared with the non-statin group (87/169 51.5%) [156]. A retrospective study found lower recurrence in CDI rates for patients in the statin group compared with the non-statin group [157]. Even though it is not statistically significant, severe complications occurred in 14.6% of the statin users and 16.7% in the non-statin group ($p = 0.853$). A multicenter case–control study demonstrated that statins had a negative association with the development of community-associated CDI [158]. However, there are conflicting data refuting the potential positive effect of statins on CDI. In a retrospective cohort study, statins were shown to decrease mortality in patients with sepsis. However, there was a significant increase of CDI in the statin group ($n = 60$) compared with the non-statin group ($n = 128$) (20 vs 5.5%; $p < 0.05$) [159]. The investigators from this cohort study hypothesize that statin use may potentiate the toxic effects of CDI [160]. With the current limitations in data, statins may have potential in preventing the development of CDI, but large, prospective studies are needed.

Infection prevention practices

Infection prevention and hospital epidemiology are key to the prevention of CDI in healthcare settings [161]. Yet what those processes entail exactly and who should be involved is an ongoing discussion. The American Journal of Gastroenterology's

Table 4. Infection prevention recommendations for *Clostridium difficile* infection [188].

Summary of recommendation	Strength of recommendation; level of evidence
Hospital-based infection control programs can help to reduce the incidence of CDI	Conditional; moderate
Routine screening for CDI in hospital patients without diarrhea is not recommended and asymptomatic carriers should not be treated	Strong; low
Antibiotic stewardship is recommended to reduce the risk of CDI	Strong; high
Contact precautions for a patient with CDI should be maintained at a minimum until the resolution of diarrhea	Strong; high
Patients with known or suspected CDI should be placed in a private room or in a room with another patient with documented CDI	Strong; high
Hand hygiene and barrier precautions, including gowns and gloves, should be used by all healthcare workers and visitors entering the room of any patient with known or suspected CDI	Strong; moderate
Single-use disposable equipment should be used for prevention of CDI transmission. Non-disposable medical equipment should be dedicated to the patient's room and other equipment should be thoroughly cleaned after use in a patient with CDI	Strong; moderate
Disinfection of environmental surfaces is recommended using a Environmental Protection Agency registered disinfectant <i>Clostridium difficile</i> sporicidal claim or 5000 ppm chlorine-containing cleaning agents in areas of potential contamination by <i>C. difficile</i>	Strong; high
Although there is moderate evidence that two probiotics (<i>Lactobacillus rhamnosus</i> GG and <i>Saccharomyces boulardii</i>) decrease the incidence of antibiotic-associated diarrhea, there is insufficient evidence that probiotics prevent CDI	Strong; low

CDI: *C. difficile* infection.

Guidelines for Diagnosis, Treatment and Prevention of CDIs published in 2013 provide the following summary of recommendations (TABLE 4) for infection prevention in CDI patient care.

Isolation precautions

The CDC's 'Appendix A, Type and Duration of Precautions Recommended for Selected Infections and Conditions', recommends that contact precautions be followed for CDI patients for duration of the illness with the following notes:

'Discontinue antibiotics if appropriate. Do not share electronic thermometers, ensure consistent environmental cleaning and disinfection. Hypochlorite solutions may be required for cleaning if transmission continues. Hand washing with soap and water preferred because of the absence of sporicidal activity of alcohol in waterless antiseptic handrubs' [162].

This means that the use of gowns and gloves for all contact with CDI patients and equipment should be used to decrease transmission. Yet while the CDC recommends contact precautions for the duration of CDI, little guidance exists on how and when to discontinue contact precautions for CDI patients who no longer have signs and symptoms.

Discontinuation of contact precautions for CDI patients is an area of much debate. While many healthcare facilities maintain contact precautions for the duration of a patient's stay, others focus on isolating only symptomatic CDI patients. However, discontinuing contact precautions once a CDI patient is asymptomatic poses challenges due to the possibility

of asymptomatic shedding of spores. There are no recommendations on what should be done when an inpatient has positive *C. difficile* culture/assay results, receives treatment and then begins to have negative CDI tests during the same admission. Should patients with a history of CDI remain in contact isolation for the duration of their stay? Some hospitals discontinue contact precautions for CDI patients once a patient is continent of stool and has no signs or symptoms. Other hospitals require patients with CDI to remain in contact precautions for the duration of their stay regardless of signs and symptoms.

A survey of Los Angeles area hospitals illustrates anecdotal evidence that a myriad of practices exist in the absence of guidelines for discontinuing contact precautions. Among eight hospitals (teaching and community) in the Los Angeles area, all eight hospitals place patients with active CDI on contact precautions. There is more variety in practices regarding discontinuing contact precautions: three hospitals do not discontinue contact precautions for CDI patients and five hospitals discontinue contact precautions with variable contingencies (i.e., no signs/symptoms for 48 h, no signs/symptoms for 72 h, no signs/symptoms with treatment completed).

CDI patients pass spores both when they are symptomatic and asymptomatic. Thus, if a patient is asymptomatic for 24–48 h, but continues to release spores for an unknown period, it seems that continuing contact precautions for the duration of a CDI patient's stay would be a good measure to prevent further spread of CDI, but there is a paucity of data to support this. Alternatively, when a patient is continent of stool and adheres

to appropriate hand washing, the risk from the patient may be minimal, as long as the environment and medical equipment has been appropriately decontaminated and healthcare providers are performing good hand hygiene. More data are needed to determine the best approach for contact isolation of asymptomatic CDI patients.

Hand hygiene

In the Fall of 2011, Dubberke and Gerding published the 'Rationale for Hand Hygiene Recommendations after Caring for a Patient with CDI' as an update to the SHEA Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals, in which they do not recommend the use of soap and water for hand hygiene for CDI prevention in non-outbreak settings [163]. These recommendations instead focus on the lack of data on hand hygiene in CDI non-outbreak settings. However, Landelle *et al.* conducted a study in 2007 at a French university hospital in a non-outbreak setting. The study found CDI spores on healthcare workers' hands even after rubbing their palms with alcohol just after patient contact [164].

Despite this compelling French study, there is still a paucity of data on hand hygiene practices with CDI patients. Thus, the use of gloves is preferential when caring for CDI patients. Gloves, when removed correctly to minimize hand contamination, provide the best method to prevent the spread of CDI through healthcare worker's hands. Attention must be given to the frequent changing of gloves so that healthcare workers do not spread CDI spores from patient to patient. More data are needed to determine the best hand hygiene methods for CDI patient care providers.

Cleaning & disinfection

Although there has been great focus on the cleaning and disinfection of CDI patient environments, CDI has been found outside of patient rooms in other areas such as nursing stations, doctors' stations and at the Pyxis[®] machines during outbreaks [165]. These are areas that are not placed in contact isolation and are not as frequently terminally cleaned, nor are they areas where staff only wash their hands with soap and water. Thus, stricter and more frequent cleaning and disinfecting throughout all healthcare areas should occur with products approved to kill spores. In February 2014, the Environmental Protection Agency (EPA), Office of Pesticide Programs, released 'List K: EPA's Registered Antimicrobial Products Effective Against *Clostridium difficile* Spores'. This list includes the brand names of cleaning and disinfecting products that are hypochlorite based or hydrogen peroxide based [166]. While a 1:10 dilution of bleach (sodium hypochlorite) is the best known and most frequently used product to clean and disinfect the CDI environment, products containing hydrogen peroxide are also approved by the EPA as a CDI spore-killing option. Although a liquid dilution of hydrogen peroxide is used most frequently, use of vaporized hydrogen peroxide (HPV) is also available. Ultraviolet light, though not approved by the FDA as a spore-killing option, is

also being used as a supplement to routine cleaning and disinfection of the CDI environment.

New technologies in cleaning & disinfection

Hydrogen peroxide vapor

HPV is used as a disinfection measure by machines placed in CDI environments that spray a vapor for set intervals. These machines are used to disperse HPV in healthcare environments as a supplement to routine cleaning procedures. Use of HPV machines is rare as costs range from US\$50,000 to US\$100,000 per unit [167]. The HPV decontamination process can take up to 3–4 h to clean and disinfect one patient room in a hospital. Thus, one machine can clean and disinfect approximately 6–8 rooms per day. HPV machines have been associated with decreases in hospital-acquired multidrug-resistant organisms including VRE, MRSA, *C. difficile* and *Acinetobacter* [168]. Decreased disinfecting times and lower costs are needed for widespread usage of HPV machines to occur.

Ultraviolet light

Ultraviolet (UV) light is being marketed as another approach to kill *C. difficile* spores. While UV has not yet been approved by the EPA, several machines are marketed to kill *C. difficile* spores that use either pulsed xenon or mercury-based ultraviolet. As a supplement to routine cleaning procedures, UV machines should be placed in 3–4 different locations in patient rooms/healthcare areas at 4–5 min intervals for a total of approximately 12–15 min disinfection time. With a 12–15 min disinfection time, it would take approximately 50 h (or 2 days) to clean 200 patient rooms. The cost of UV machines are estimated at approximately US \$39,000–US\$80,000 each [169,170]. Pulsed xenon UV has been associated with decreases in hospital-acquired VRE [171] and hospital-acquired *C. difficile* [172], as well as with increases in patient satisfaction scores [173]. Even though UV machines have a shorter disinfecting time at 12–15 min than HPV machines at 3–4 h, lower costs are needed for widespread usage of UV machines to occur. Also, more data are needed to understand the use of UV machines in the CDI patient environment.

Future directions: the bundle approach to preventing CDI

Infection prevention and control bundles have been shown to decrease MRSA and *Acinetobacter* transmission [174]. Infection prevention practices and antibiotic stewardship lead the list of approaches that must be used to achieve sustained prevention of CDI [175,176]. Successfully achieving these programs is no simple matter. In order to achieve the bundled approach, multidisciplinary involvement led by healthcare leadership or hospital administration is needed.

Implementing all aspects of the CDI bundle approach cannot occur overnight. Providence Saint John's Health Center in Santa Monica, California began to implement the CDI bundled approach slowly in the early 2000s. The bundled approach strengthened over time as there was a sustained decrease in hospital-acquired *C. difficile* from 2007 (56 cases/66,825

Table 5. Lean Clostridium difficile infection prevention bundle checklist.

15-Step CDI prevention bundle	LEAN stakeholder analysis	Checklist
Patient identification		
1. Does the laboratory have the necessary microbiology equipment to test for CDI? a. The lab implements rapid diagnostics to test for CDI, when possible	M, MS, A	
2. The Emergency Department should be recognizing signs and symptoms for CDI and testing prior to admission, when possible	IP, MS, A	
Infection prevention		
3. The hospital should have a strong, well-respected and supported IP program	IP, MS, A, N, Q	
4. IP should conduct daily microbiology reviews and keep records of all CDI patients with internal benchmarking. a. CDI should be included on the hospital's annual Infection Prevention Risk Assessment. b. Measurable goals aimed at CDI prevention should be included on the hospital's annual Infection Prevention Program Plan	IP, MS, A, N, Q	
5. IP should report significant data and trends to more committees than just the Infection Prevention Committee in order to highlight important events and direct leadership energy. a. These committees include: Quality, EOC, Critical Care, Emergency Medicine, NICU/ Pediatric, Surgery, Medical Executive and the Board of Directors	IP, MS, A, N, Q, EOC	
6. IP should maintain good relationships and regular communication with: a. Neighboring facilities i. This should include hospitals, nursing homes, long-term care facilities and dialysis centers b. Local IPs i. This should include active participation in local, state and national APIC groups c. Local health authority	IP, CM	
7. IP should conduct ongoing education for: a. All disciplines including MD, RN, CNA, RT, RD, PT/OT, EVS, Transport, Volunteers, Case Workers and Clergy i. Special attention and clear direction to EVS regarding thorough daily and terminal cleaning practices of high touch surfaces b. Patients and visitors about good hand hygiene and practices necessary to reduce transmission of CDI in the home environment	IP, EVS, CM	
Antimicrobial stewardship		
8. The Pharmacy should have an Antimicrobial Stewardship Program (ASP). a. The ASP should include regular rounding by a pharmacist with ID training who is supported by medical staff leadership in order to effectuate change with the MD outliers (physicians who are resistant to changing their prescription practices). b. Careful usage of broad-spectrum antibiotics c. Careful usage of proton pump inhibitors d. Consider probiotics usage e. Consider fecal microbiota transplantation, a bowel recolonization procedure, for refractory CDI patients	ASP, MS, A, IP	
Environmental transmission		
9. Contact precautions should be used for care of all CDI patients. a. This means that all staff who care for CDI patients should wear gloves and gowns when caring for and entering the care environment of CDI patients	IP, A, N, MS	
10. Hand hygiene with soap and water should be used by all care providers for all CDI patients. a. This means that hand hygiene with soap and water should be used prior to an outbreak in order to prevent an outbreak	IP, A, N, MS	
A: Administration/Healthcare Leadership; ASP: Antimicrobial Stewardship; CDI: Clostridium difficile infection; CM: Case Management; EOC: Environment of Care; EVS: Environmental Services; IP: Infection Prevention; M: Microbiology; MS: Medical Staff; N: Nursing; Q: Quality.		

Table 5. Lean *Clostridium difficile* infection prevention bundle checklist (cont.).

15-Step CDI prevention bundle	LEAN stakeholder analysis	Checklist
Environmental transmission		
11. The hospital should assure that Environmental Protection Agency-approved cleaning products are used to kill CDI spores. a. Careful attention should be paid to the thorough daily and terminal cleaning and disinfecting of CDI patients' rooms	IP, EVS, A, EOC	
12. The hospital should assure the use of disposable equipment, whenever possible, for all CDI patient care. a. When disposable equipment is not available, CDI patients' shared/movable equipment should be cleaned and disinfected with products that have been approved by the Environmental Protection Agency to kill CDI spores	IP, A, EOC	
Multidisciplinary approach		
13. Sustained, long-term prevention of CDI is a multidisciplinary team effort a. It should involve IP, ASP, EVS, Microbiology, Case Management, Nursing, Quality, Medical Staff and Administration	IP, ASP, EVS, M, CM, N, Q, MS, A, EOC	
14. House wide culture of safety and quality with high standards and clear goals a. House wide policies aimed at preventing environmental and antibiotic acquisition of CDI	A, MS, IP, N, Q	
15. Strong support for IP and ASP from Administration and Medical Staff leadership (such as CMO and/or Chief of Staff) a. The hospital should have regularly conducted EOC rounds	A, MS, IP, ASP, EOC	
A: Administration/Healthcare Leadership; ASP: Antimicrobial Stewardship; CDI: <i>Clostridium difficile</i> infection; CM: Case Management; EOC: Environment of Care; EVS: Environmental Services; IP: Infection Prevention; M: Microbiology; MS: Medical Staff; N: Nursing; Q: Quality.		

patient days \times 1000 = rate of 0.84) through 2012 (18 cases/55,596 patient days \times 1000 = rate of 0.32). During this time, the Infection Prevention department experienced staff turnover several times. While staff turnover was occurring, Infection Prevention Committee membership remained largely the same. Sustained committee membership allowed for long-term CDI prevention. This review aims to list all of the CDI bundle components in the following 15-step checklist that are necessary to achieve reduction in CDI and to sustain long-term prevention of CDI in the healthcare setting.

The CDI prevention bundle checklist table (TABLE 5) includes a column on Lean stakeholder analysis using Lean Six Sigma principles [177]. This Lean Six Sigma stakeholder analysis determines each group that should be involved in the multidisciplinary CDI prevention team. The key CDI prevention stakeholders are: Infection Prevention, Antimicrobial Stewardship, Environmental Services, Environment of Care, Microbiology, Case Management, Quality, Medical Staff, Nursing and Administration/Healthcare Leadership. It is important to note that to sustain true long-term CDI prevention, the task cannot be achieved by Infection Prevention and Antimicrobial Stewardship alone. Multidisciplinary involvement from healthcare leadership is necessary to sustain true reductions in CDI and to achieve CDI prevention.

Expert commentary & five-year view

CDI is now more prevalent than MRSA as a healthcare-acquired infection in some community hospitals, coupled with its high morbidity and mortality it is an increasing major

concern for health systems worldwide [178]. As current therapy is imperfect with a 20–30% relapse rate, more attention has been focused on the prevention of CDI [179]. This necessitates the identification of risk factors and the development of measures used to prevent them. Our review attempts to summarize and explicate these risk factors and suggest approaches for remediation. It seems obvious that a multifaceted, multilayered approach is required and must involve out-patient and in-patient antimicrobial stewardship, improved microbiological diagnostics and enhanced infection prevention measures with strong support from healthcare leadership. While the recent 'Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals: 2014 Update' provides clear guidance, further research on the exact mechanisms of disease, appropriate hand hygiene practices and possible discontinuation of contact precautions for asymptomatic CDI patients, as well as information on alternative sources of acquisition is needed [180].

Financial & competing interests disclosure

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Key issues

- What is the source of community-associated and healthcare-associated *Clostridium difficile* spore exposure?
- What components of the microbiome and host immunity are protective for avoidance of *C. difficile* infection (CDI)?
- What are the appropriate hand hygiene practices for CDI patient care?
- Resolution of if/when to discontinue contact precautions for asymptomatic CDI patients.
- Improved environmental decontamination methods for the CDI patient environment.

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