Hospital Infection Control: *Clostridioides difficile*

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Abstract

Clostridioides difficile remains a leading cause of healthcare-associated infection. Efforts at *C. difficile* prevention have been hampered by an increasingly complex understanding of transmission patterns and a high degree of heterogeneity among existing studies. Effective prevention of *C. difficile* infection requires multimodal interventions, including contact precautions, hand hygiene with soap and water, effective environmental cleaning, use of sporicidal cleaning agents, and antimicrobial stewardship. Roles for probiotics, avoidance of proton pump inhibitors, and isolation of asymptomatic carriers remain poorly defined.

Keywords
- *Clostridioides difficile*
- infection control
- infection prevention

Clostridioides difficile (previously named *Clostridium difficile*) causes nearly 500,000 infections and 29,000 associated deaths in the United States each year, making it the leading cause of healthcare-associated infection and gastroenteritis-associated mortality.[1] While *C. difficile* first emerged as a hospital-associated infection and remains predominantly healthcare-associated, its epidemiology continues to evolve. Nearly one-third of *C. difficile* cases are now acquired in the community.[2] Whether this shift of *C. difficile* into the community reflects an escape from the hospital environment, spread via outpatient healthcare contact, or perhaps even a community source for infection remains poorly understood. Genomic epidemiology has shown *C. difficile* transmission to be more complex than initially assumed, confirming acquisition from unexpectedly diverse sources.[3] As a robust, survivable, and genetically diverse pathogen, *C. difficile* poses a difficult challenge for infection prevention efforts. This review summarizes the current evidence base for *C. difficile* infection (CDI) prevention with particular attention to the inpatient, surgical, and perioperative settings.

Basic Pathophysiology

C. difficile is an anaerobic, spore-forming, gram-positive bacillus. The spores are highly durable, resistant to many disinfectants (including ethanol), and capable of long-term environmental persistence. Violating Koch's postulates, the mere acquisition of *C. difficile* is insufficient to cause disease. True infection results from the production of two toxins, *TcdA* and *TcdB*, which damage intestinal epithelial and cytoskeletal structure, leading to severe diarrhea, toxic megacolon, and even death. A healthy and diverse gut microbiota inhibits germination and toxin production, whereas disruption of the normal flora facilitates toxin production, resulting in disease. Antibiotic exposure is the most common trigger for disrupted flora, though other risk factors for developing CDI include advanced age, chronic disease, and gastric acid suppression.[4] In the absence of such triggers, asymptomatic *C. difficile* carriage has been reported in as many as 45% of neonates and 10% of hospitalized adults.[5,6]

Epidemiology of Healthcare-Associated *C. difficile* Infection

Healthcare-associated CDI rates increased dramatically in the early 2000s, driven largely by the rapid emergence of a hypervirulent strain known as NAP1 (North American pulsed-field gel electrophoresis (PFGE) type 1)/027 (polymerase chain reaction (PCR) ribotype 027). The NAP1/027 strain's fitness has been attributed in part to high-level fluoroquinolone resistance, while virulence may stem from increased toxin production and enhanced toxin binding affinity.[7–9] Although still strongly associated with the healthcare setting, NAP1/027 prevalence has begun to decline in some regions.[10,11] Even as the NAP1 wave may have reached its crest, overall rates of CDI show no sign of slowing.[12] Currently,

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C. difficile surpasses even *Staphylococcus aureus* as the most prevalent healthcare-associated pathogen in the United States.[13,14] Hospital-onset CDI occurs at a rate of 2.8 to 9.3 cases per 10,000 patient days and may complicate as many as 1% of all hospitalizations.

Epidemiologic studies estimate postoperative CDI rates between 0.5 and 1.5%, though this rate has been increasing over time.[15,16] Patient-specific risk factors specifically associated with perioperative CDI include age, procedure type, and receipt of perioperative antibiotics.[17–19] When CDI occurs postoperatively, it is associated with significantly increased mortality rates as high as 30% for CDI complicated by sepsis.[20]

Environmental contamination by patients with *C. difficile* infection is nearly universal. Microbiologic surveys of the homes and hospital rooms of patients with *C. difficile* infection recover *C. difficile* nearly 100% of the time, with toilets, sinks, and high-touch surfaces carrying the highest organism burden.[21,22] Additionally, shedding of spores persists for weeks after treatment.[23] Asymptomatic carriage occurs at rates thrice that of true disease, and carriers may still shed *C. difficile* spores.[24] Similar to symptomatic patients, high rates of skin surface and environmental contamination have been observed with carriers.[25] As the role of asymptomatic carriers in the spread of *C. difficile* remains an area of active study, how to appropriately manage this potentially large reservoir for *C. difficile* transmission remains unclear.

Methods for Prevention of *C. difficile* Infection

Given the multiple risk factors for developing CDI, diverse sources of acquisition, and high survivability of the organism itself, CDI prevention requires multimodal interventions.

Hand Hygiene

With its propensity for resistance to disinfectants and long-term environmental persistence, hand hygiene is fundamental for minimizing CDI transmission. *C. difficile* can be recovered from the hands of healthcare providers caring for patients with CDI nearly 60% of the time and from environmental surfaces 30 to 50% of the time.[23,26–28] Widely used alcohol based hand sanitizers are ineffective against *C. difficile* spores. Studies have repeatedly confirmed that washing with soap and water more effectively reduces the spore burden on hands than alcohol-based sanitizers.[28–31] Importantly, soap and water do not kill *C. difficile* spores, they simply facilitate removal from the hands. Although hand washing with soap and water for 15 to 30 seconds clearly reduces spore burden, the benefits of hand hygiene have been harder to demonstrate at the facility level, perhaps reflecting the difficulty of achieving sustained compliance on a large scale. Studies show mixed results; some confirm reductions in facility-wide CDI rates following improvements in usage of soap and water, while others fail to confirm the anticipated difference between soap and water versus alcohol-based hand sanitizer use.[32–36] Probably the largest evidence base comes from the "*Cleanyourhands*" campaign in England and Wales, where procurement rates for soap (considered a proxy for proper hand hygiene compliance) correlated with reduced CDI rates.[37] Recent guidelines emphasize the use of soap and water specifically in settings with high-CDI incidence, while permitting hand hygiene with either soap and water or alcohol-based cleansers in routine settings with low-CDI incidence. However, the majority of hospitals continue to recommend hand hygiene with soap and water for any patients with CDI, regardless of local incidence rates, given the lack of efficacy of alcohol-based sanitizers.

As the efficacy of hand hygiene depends on compliance, multiple studies have sought to identify successful techniques for improving hand washing rates among providers. Though no techniques have proven completely effective individually, several have led to modestly improved hand washing compliance. Potentially effective interventions include teaching providers a structured hand-washing technique, using an audit and feedback approach, and relocating sinks to convenient locations near the patient.[38,39]

Given the convenience of alcohol-based hand sanitizers, there have been several recent attempts at chemically modifying hand sanitizers to improve efficacy against *C. difficile* spores. Sporicidal effect may be improved by acidification and warming of ethanol-based sanitizers; however, clinical benefit from such modifications remains to be assessed.[40,41]

Contact Precautions

Contact precautions include donning of gown and gloves upon entry to the room of any patient with suspected or confirmed CDI. Whenever possible, patients with CDI should be placed in private rooms with private commodes. If private facilities are unavailable, cohorting by CDI status is a reasonable alternative. The duration of contact precautions recommended by the Infectious Diseases Society of America (IDSA) varies by local CDI incidence rates. At a minimum, isolation is recommended for 48 hours after symptom resolution, however, in high-incidence settings isolation may be extended up until discharge. The latter recommendation for prolonged isolation is based upon evidence that *C. difficile* shedding may continue for at least 1 to 4 weeks after treatment.[23,26]

Patients with *C. difficile* infection typically contaminate multiple body sites (chest, abdomen, hands, and arms), environmental surfaces (bed rails, tables, telephones, and call buttons), and hospital equipments.[42–44] The use of contact precautions with gown and gloves is intended to reduce the transfer of *C. difficile* to healthcare provider's hands, clothing, and equipment through contact with these surfaces. Despite microbiologic plausibility, evidence for clinical efficacy at reducing CDI rates is less certain.

Recent genomic studies of CDI transmission demonstrate extremely diverse sources. In a landmark study from the Oxford health system, 45% of CDI cases were genetically distinct from all hospital contacts, suggesting a relatively limited role for direct transmission within the hospital.[3] At the very least, the use of private rooms or commodes reduces CDI rates.[45] The additional benefits of contact precautions have been further challenged by a recent prospective cohort study in which discontinuation of routine contact precautions for all CDI patients had no effect on overall CDI rates.[46] Notably, this study was highly selective regarding which

Table 1 Antibiotic class-specific risk for *C. difficile* infection

Antibiotic class	Range of reported odds or hazard ratios
Cephalosporins (1st—2nd generations)	2.4
Cephalosporins (3rd–4th generations)	3.1–4.7
Cephalosporins/ carbapenems (combined)	5.7
Clindamycin	1.9–20.4
Macrolides	1.5–2.7
Penicillin	1.9–3.3
Beta-lactamase inhibitor combinations	2.3
Fluoroquinolones	4.0–5.7
Sulfonilamides	1.8–1.9
Tetracyclines	0.92
Vancomycin	2.6

patients could forego isolation, patients still had private commodes, had to be fully continent, and could not be infected with a hypervirulent strain (e.g., NAP1). Additionally, CDI rates were low throughout the study period. Until more definitive studies become available, IDSA recommendations continue to support contact precautions as a useful strategy for CDI prevention.

Antimicrobial Stewardship

While receipt of nearly any antibiotic increases CDI risk, two recent meta-analyses confirmed that risk varies significantly by antibiotic class (►**Table 1**). Clindamycin (odds ratio [OR] = 16.8), fluoroquinolones (OR = 5.50), cephalosporins, and carbapenems (OR = 5.68) consistently confer the highest risk of CDI. Macrolides, penicillin, and sulfonamides confer a lower but still statistically significant risk, while doxycycline is the only antimicrobial which does not appear to increase CDI risk.[48] Emerging evidence suggests that piperacillin–tazobactam may also inhibit *C. difficile* growth, conferring a lower risk of CDI relative to other broad-spectrum antibiotics. At least one survey-based study found lower rates of *C. difficile* carriage among patients receiving piperacillin–tazobactam compared with those receiving cephalosporins or fluoroquinolones.[49]

The same risks still apply to short-term perioperative antibiotic usage. Even the short-term use of ertapenem (OR = 3.13) or cefoxitin (OR = 2.7) significantly increases the risk of CDI relative to narrow-spectrum agents (e.g., cefazolin).[15,50] Efforts to minimize antibiotic exposure or select the lowest risk agent reduce subsequent risk of CDI.

Antimicrobial stewardship has proven to be one of the most effective means of reducing CDI rates. Multiple studies in the hospital setting have confirmed that implementation of an antimicrobial stewardship program can reduce CDI incidence by as much as 24 to 60%.[51–55] The same significant reductions in CDI rates have been observed with antimicrobial stewardship efforts targeting perioperative antibiotic prophylaxis. Although most existing studies have been retrospective, stewardship interventions targeting perioperative prophylaxis reduce CDI rates as much as 60 to 71%.[56–58]

The goal of an effective antimicrobial stewardship program is to optimize antibiotic choice, timing of administration, and duration to maximize the intended antibiotic effect, while minimizing adverse effects (including risk of CDI or other multidrug resistance pathogens). Key interventions include (1) selection of antibiotics that are effective for the intended purpose without being unnecessarily broad-spectrum, (2) avoidance of prolonged antimicrobial prophylaxis or longer than recommended treatment courses, and (3) avoidance of unnecessary antibiotic administration (e.g., for treatment of asymptomatic bacteriuria or viral respiratory infections).

Especially relevant for the surgical setting, the IDSA provides guidelines on selection, dosing, and duration of perioperative prophylactic antibiotics.[59] While a complete discussion of recommendations is beyond the scope of this review, cefazolin is frequently the first-line choice for nonallergic patients. Options for procedures with higher risk of gram-negative or anaerobic organisms (e.g., colorectal operations) expand to include cefazolin plus metronidazole, ceftriaxone plus metronidazole, or ertapenem, though ertapenem leads to higher risk of CDI. Avoiding carbapenems, fluoroquinolones, or clindamycin wherever possible may help to reduce risk of CDI, as these agents confer the highest overall risk. Duration of prophylaxis should almost never exceed 24 hours; in fact, the most recent guidelines of Centers for Disease Control (CDC) specifically recommend avoiding additional doses for antimicrobial prophylaxis, following closure of the surgical wound.

Another important aspect of antimicrobial stewardship includes accurate allergy assessment. Nearly 10% of patients report a β-lactam allergy, and reported β-lactam allergy frequently leads to the use of alternative prophylaxis agents. Alternative agents, such as clindamycin carry a higher risk of CDI; patients receiving alternative agents due to reported penicillin allergy are up to 23% more likely to develop CDI.[60] Consequently, obtaining an accurate allergy history, coupled with penicillin allergy testing or allergy consultation where available, may reduce the risk of CDI.

A detailed drug allergy history alone can resolve reported β-lactam allergy in >30% of cases.[61] For example, distinguishing true immunoglobulin (Ig) E-mediated allergy versus nonallergic adverse events, such as nausea or diarrhea, can be easily incorporated into a standardized drug allergy history tool delivered by pharmacists or physicians.[62] Notably, even in penicillin-allergic patients the crossreactivity with cephalosporins is overall low (<2%). As such, patients with nonsevere reactions to penicillin (e.g., rash alone) may be safely given cephalosporins for antimicrobial prophylaxis. For patients with uncertain or severe but distant past reactions to penicillin; penicillin skin testing can reliably determine which individuals may safely receive β-lactams. The negative predictive value of a properly conducted penicillin skin test exceeds 99%.[63,64] Penicillin skin testing has been incorporated into several perioperative clinics, as well as inpatient hospital wards, with significant improvements in rates of first-line

antibiotic use and no increase in adverse drug events.[65,66] The importance of clarifying allergies among surgical patients was further solidified by a cohort recent study of 8,385 undergoing colon surgery, hip or knee arthroplasty, hysterectomy, or coronary artery bypass grafting.[67] Patients with a reported penicillin allergy had a 50% higher risk of surgical site infection compared with patients without an allergy (adjusted OR $=1.51$, 95% confidence interval [CI]: 1.02–2.22) due to decreased use of cefazolin (12 vs. 92%, $p < 0.001$) and increased use of clindamycin, vancomycin, and gentamicin.

Environmental Decontamination

With high rates of contamination on multiple surfaces in the patient care environment and a propensity for persistence, admission to a room in which the preceding occupant had CDI is an independent risk factor for CDI.[68] *C. difficile* can be recovered from environmental samples in nearly all rooms previously occupied by a patient with CDI, and has been recovered in greater than 25% of rooms even after cleaning.[22,69] Although high rates of environmental contamination are thought to increase risk of CDI, the strain causing disease is frequently different than the strain isolated from the patient's immediate surroundings. Molecular epidemiologic surveys have shown greater than expected genetic diversity among CDI isolates, suggesting that only a minority of CDI cases are attributable to direct acquisition within the hospital environment.[3,70]

Beyond observational and epidemiologic data, several studies have assessed the effect of various cleaning protocols on rates of CDI with conflicting results. Some of the inconsistency in assessing the impact of environmental transmission on CDI rates may be explained by variation in study methodologies. Most studies that demonstrated significant reductions in CDI rates after changes in cleaning protocols were undertaken in high-incidence settings, whereas negative trials appear correlated with lower incidence settings where effect would be inherently more difficult to detect.[71–73] As such, environmental decontamination retains an important role in high-incidence settings, including the hospital environment (►**Table 2**).

There are multiple facets to environmental decontamination, including (1) quality control of cleaning adequacy, (2) use of appropriate sporicidal cleaning agents, and (3) consideration of adjunct decontamination methods (e.g., ultraviolet (UV) light or hydrogen peroxide aerosols). First, *C. difficile* decontamination depends upon thoroughness of room cleaning. Cleaning methods (including chemical or UV light based) lose efficacy if gross contamination is present.[74,75] In addition, even in the absence of chemical cleaning, physical cleaning may result in as much as a three-log reduction in spore burden.[76] Various quality-improvement trials aimed to improve room cleaning methods have shown modest but sometimes statistically significant reductions in either *C. difficile* environmental contamination or facility-specific nosocomial CDI rates.[77,78] Successful interventions include improved training for environmental service workers, audits of cleaning adequacy (using either *C. difficile* environmental cultures, fluorescent, or bioluminescent markers) and use of specially trained terminal decontamination teams dedicated to cleaning the rooms of patients on contact precautions.[79–81]

Selection of appropriate sporicidal cleaning agents is also important, as studies have shown that neutral detergents or quaternary ammonium compounds are insufficient to kill *C. difficile* spores. In fact, some detergents may actually promote sporulation and survival.[82] In contrast, studies assessing efficacy of sporicidal cleaning agents have shown the greatest benefit in high-incidence settings and when used in conjunction with other CDI prevention measures.[71] Glutaraldehyde, peracetyl, and peroxide based agents are effective against *C. difficile*; however, direct comparisons of products using uniform microbiologic methods have demonstrated wide variability in performance.[36,83–86] In general, hypochlorite- or bleach-based solutions have the most consistent benefit across studies, including effectiveness studies measuring reductions in CDI rates following the incorporation of hypochlorite solutions into cleaning protocols.[87]

More recently, several no-touch adjunct measures have shown promise, particularly those based on UV light or hydrogen peroxide vapors or aerosols.[88–92] While all enhanced strategies require specialized equipment and cannot be conducted with the patient in the room, hydrogen peroxide vapor and aerosol-based systems also require that the room be sealed during treatment. In contrast, UV light systems are easier to deploy and are supported by one of the largest cluster-randomized trials to assess terminal room cleaning methods, to date. The Benefits of Enhanced Terminal Room Disinfection Study (BETR-D) demonstrated a statistically significant reduction in incidence of *C. difficile* and multidrug resistant organisms following the addition of UV light treatment to standard cleaning procedures, with a relative risk ratio of 0.7 ($p = 0.036$).[93] A recently completed secondary analysis confirmed that enhanced disinfection of high-risk rooms (e.g., those housing patients with CDI) reduces hospital-wide *C. difficile* incidence through an indirect impact on all hospitalized patients.[94]

Prevention Measures with Uncertain Value

Screening and Isolation of Asymptomatic Carriers

Asymptomatic carriers of *C. difficile* pose a particular challenge. Carriers are known to shed spores even when asymptomatic, resulting in environmental contamination rates similar to those with active disease.[95] Mathematical modeling studies suggest that isolation of colonized patients upon admission has the potential to significantly reduce CDI transmission rates; however real-world studies are lacking to date.[96] Molecular epidemiologic studies have found evidence of CDI acquired by transmission from asymptomatic carriers, though these events appear to account for only a minority of actual CDI cases.[97,98] At least one large, controlled quasiexperimental study has been conducted to determine whether screening for *C. difficile* carriage followed by isolation precautions of carriers can reduce CDI rates. This single-center study estimated a reduction in CDI cases of roughly 7 per 10,000 patient days, which was sufficient to reach statistical significance.[99] Despite these encouraging initial findings, replication

Table 2 Summary of selected high-impact studies published between 2008 and 2018, categorized by topic

Topic	Study	Methods	Design/features	Conclusion
1. Hand hygiene	Kundrapu et al[30]	Prospective randomized trial	Microbiologic assessment of hand contamination following wash with soap/water vs. alcohol-based hand sanitizer	Handwashing with soap and water reduced spore burden while alcohol-based hand sanitizers had no effect
	Stone et al[37]	Multicenter prospective interrupted time series	Interrupted time series analysis	Increased soap procurement independently correlated with reduced CDI rates
2. Cleaning agents	Boyce et al[36]	Prospective, cluster-controlled crossover trial	Microbiologic survey of high-touch surfaces, quaternary ammonium compounds (QAC) vs. improved hydrogen peroxide (IHP)	• *C. difficile* recovery was significantly lower with IHP than QAC • Non-significant reduction in composite incidence of nosocomial pathogens (IRR 0.58–1.029)
	Doan et al[85]	Prospective randomized trial	Microbiologic survey comparing effects of hydrogen peroxide vapor, dry ozone, chlorine releasing agent (Actichlor Plus), microfiber cloth	Hydrogen peroxide, chlorine releasing agents and peracetic acid wipes all achieved >2 log reductions in *C difficile* spores
3. Environmental cleaning	Ray et al[117]	Multicenter randomized trial	Fluorescent markers plus microbiology survey comparing standard vs. enhanced cleaning	Decreased recovery of *C. difficile* from rooms, but no significant change in overall CDI incidence
	Sitzlar et al[80]	Prospective study of sequential interventions	Microbiologic survey	Use of fluorescent markers, standardized cleaning processes and creation of a dedicated disinfection team were associated with reductions in *C. difficile* burden in the environment
	Guerrero et al[78]	Prospective sequential intervention	Microbiologic survey	Education, passive observation, and real-time feedback all reduced *C. difficile* spore burdens in cleaned rooms
4. Antimicrobial stewardship	Baur et al[54]	Systematic review and meta-analysis	32 studies, 9,056,241 total patients	Stewardship programs reduce CDI incidence by 32% (IRR = 0.35–0.68)
	Feazel et al[55]	Systematic review and meta-analysis	78 studies	Stewardship programs reduce CDI incidence by 52% (IRR = 0.38–0.62)
	Shea et al[118]	Before/after comparison	Assessment of CDI rates before and after restriction of respiratory fluoroquinolones	50% reduction in CDI incidence following restriction of fluoroquinolones ($p = 0.04$)
5. No-touch cleaning methods	Ali et al[119]	Before/after comparison	Microbiologic survey using environmental samples	• UV light achieve 0.1–4.8 log reductions in CDI spores • Efficacy reduced by environmental soilage
	Anderson et al[93]	Cluster-randomized, multicenter crossover	Incidence of infection or colonization rates among exposed patients (those in a cleaned room previously occupied by a CDI patient)	• Adding UV to standard cleaning procedures significantly reduced composite rates of CDI or MDROs • No significant difference in CDI rates between bleach with or without UV light
6. Proton pump inhibitor use	Azab et al[120]	Systematic review and meta-analysis	12 studies, 74,132 patients	• PPI use OR = 1.15–1.67 relative to H2 blockers • Low quality of evidence overall
	Arriola et al[121]	Systematic review and meta-analysis	23 studies, 186,033 patients	Pooled OR of 1.52–2.14 for CDI after PPI use

Table 2 (*Continued*)

Topic	Study	Methods	Design/features	Conclusion
7. Probiotics	Goldenberg et al[105]	Systematic review and meta-analysis	Clinical outcomes (CDI rates) compiled from 31 RCTs with 8,672 patients	• CDI RR 0.67–1.10, probiotics vs placebo • Many included trials industry funded • Heterogeneous formulations • Benefit may be limited to those with >5% CDI risk per subgroup analysis
	Johnston et al[103]	Systematic review and meta-analysis	20 trials, 3,818 patients comparing probiotics to placebo or no treatment	• Probiotics reduce CDI risk, RR = 0.24–0.49 • Inconsistent controls • Missing data in 5–45% of patients
	Pozzoni et al[122]	Randomized placebo-controlled trial	Single center, elderly inpatient population ($n = 204$)	No reduction in risk of CDI
8. Isolation	Longtin et al[99]	Quasiexperimental controlled study	Segmented regression analysis comparing CDI rates after initiation of screening + isolation for asymptomatic carriers	• Carriage rate of 4.8% • Screening and isolation predicted to prevent up to 60% of expected cases

Abbreviations: CDI, *Clostridioides difficile* infection; IRR, incident rate ratio; MDRO, multi-drug resistant organisms; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial; RR, risk ratio; UV, ultraviolet.

beyond a single center and assurance against confounding factors are still necessary before this potentially costly intervention can be more widely recommended. As such, current IDSA guidelines do not endorse screening or isolation of asymptomatic carriers.

Proton Pump Inhibitor Stewardship

Multiple epidemiologic studies have suggested an increased risk of CDI with proton pump inhibitor use, particularly in healthcare-associated CDI.[2,100,101] The role of proton pump inhibitors in risk of community-acquired CDI is less clear.[102] To date no studies confirm that proton pump inhibitor discontinuation reduces CDI risk. Given recent recognition of proton pump inhibitor overuse, it is prudent to assess whether the medication is still indicated and consider discontinuation when, clinically appropriate.

Probiotics

Numerous studies have sought to assess the effect of probiotics on CDI risk. Unfortunately, most are hampered by widely varying formulations and significant industry involvement in many extant trials. Multiple meta-analyses have summarized the multiple trials performed to determine the efficacy of probiotics for CDI prevention. Highlighting substantial heterogeneity in both studies and analytic methodology, effect estimates for probiotics range from OR of 0.35 to 0.61.[103–106] Studies that assessed particular formulations confirmed similarly wide heterogeneity, though combination formulations were in general slightly superior. Whether probiotics have any role in prevention of perioperative CDI prevention remains largely untested, except for a single-prospective randomized trial which found no effect.[107]

CDI Prevention Bundles

With multiple methods for CDI prevention available, there have been several attempts to create *C. difficile* prevention bundles. Most studies of CDI prevention bundles demonstrated an associated decline in CDI rates after implementation, yet these studies are hampered by variability in methods and bundle components. Several meta-analyses have attempted to synthesize currently available data to identify particularly effective components of CDI prevention, though study heterogeneity limited conclusions to qualitative assessments only. Individual bundle components achieving at least a moderate level of support across studies include contact precautions with gloves, antimicrobial stewardship, and terminal cleaning of rooms with chlorine-based agents.[108,109]

Novel Approaches for the Future

A wide range of additional strategies for minimizing the risk of *C. difficile* infection are in various stages of development and assessment. Though none are currently ready for clinical use, a few novel approaches that may play a role in future CDI prevention are briefly highlighted here.

Antibodies to toxin B are protective against recurrent *C. difficile* infection, prompting efforts to create toxoid vaccines for *C. difficile*.[110] There are currently several candidate vaccines in early phases of clinical trials.[111–113] While some studies have shown evidence of immunogenicity, assessment of clinical outcomes awaits phase-III trial data.

Colonization with a nontoxigenic strain of *C. difficile* (which are incapable of causing diarrhea) appears to be protective against CDI in animal models. One such strain (NTCD-M3) was found to be well-tolerated and similarly

protective in a small phase-II human trial for the prevention of recurrent CDI.[114] Phase-III trials are still needed, and it remains to be seen whether the protective effect is mitigated by antibiotic receipt that may still result in significant disruption of the remainder of the gut microbiota.

Ribaxamase is an oral β-lactamase intended to minimize the effects of intravenous (IV) broad-spectrum antibiotics on the gut microbiota. By degrading any residual β-lactam antibiotics secreted into the gut after hepatobiliary clearance, ribaxamase may reduce exposure of the gut microbiota to systemically administered antibiotics. Phase-I and -IIa trials support the intended mechanism of action; however, clinical effect remains to be assessed.[115,116]

Conclusion

Despite being a wide-spread and consequential healthcare-associated infection, efforts at *C. difficile* prevention have been hindered by complex transmission patterns, a limited number of available high-quality studies, and moderate efficacy of current measures. While ongoing research is needed to answer many of the remaining questions in CDI epidemiology and prevention, there are a few interventions that have proven particularly effective in high-incidence settings. Generally supported interventions for reducing CDI transmission include contact precautions, hand hygiene with soap and water, quality control of environmental cleaning, use of chlorine-based sporicidal agents, and adjunctive treatment with UV light or peroxide aerosols. Roles for probiotics, limitation of proton-pump inhibitor usage, and isolation of asymptomatic carriers remain to be defined. Efforts to develop an effective toxoid vaccine or to mitigate the harms of systemic antibiotics on the gut microbiota offer some promise for the more distant future.

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Conflict of Interest

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References

1 Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372(09): 825–834
2 Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. JAMA Intern Med 2013;173(14):1359–1367
3 Eyre DW, Cule ML, Wilson DJ, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. N Engl J Med 2013;369(13):1195–1205
4 Dubberke E. Strategies for prevention of *Clostridium difficile* infection. J Hosp Med 2012;7(Suppl 3):S14–S17
5 Zacharioudakis IM, Zervou FN, Pliakos EE, Ziakas PD, Mylonakis E. Colonization with toxinogenic *C. difficile* upon hospital admission, and risk of infection: a systematic review and meta-analysis. Am J Gastroenterol 2015;110(03):381–390, quiz 391
6 Kubota H, Makino H, Gawad A, et al. Longitudinal investigation of carriage rates, counts, and genotypes of toxigenic *Clostridium difficile* in early infancy. Appl Environ Microbiol 2016;82(19): 5806–5814
7 He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemic healthcare-associated *Clostridium difficile*. Nat Genet 2013;45(01):109–113
8 McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 2005; 353(23):2433–2441
9 Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet 2005;366 (9491):1079–1084
10 Freeman J, Bauer MP, Baines SD, et al. The changing epidemiology of *Clostridium difficile* infections. Clin Microbiol Rev 2010;23 (03):529–549
11 Bauer MP, Notermans DW, van Benthem BH, et al; ECDIS Study Group. *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet 2011;377(9759):63–73
12 Evans CT, Safdar N. Current trends in the epidemiology and outcomes of *Clostridium difficile* infection. Clin Infect Dis 2015; 60(Suppl 2):S66–S71
13 Magill SS, Edwards JR, Bamberg W, et al; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370 (13):1198–1208
14 Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the burdens of hospital-onset, healthcare facility-associated *Clostridium difficile* infection and of healthcare-associated infection due to methicillin-resistant *Staphylococcus aureus* in community hospitals. Infect Control Hosp Epidemiol 2011;32(04):387–390
15 Carignan A, Allard C, Pépin J, Cossette B, Nault V, Valiquette L. Risk of *Clostridium difficile* infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. Clin Infect Dis 2008;46(12):1838–1843
16 Zerey M, Paton BL, Lincourt AE, Gersin KS, Kercher KW, Heniford BT. The burden of *Clostridium difficile* in surgical patients in the United States. Surg Infect (Larchmt) 2007;8(06):557–566
17 Li X, Wilson M, Nylander W, Smith T, Lynn M, Gunnar W. Analysis of morbidity and mortality outcomes in postoperative *Clostridium difficile* infection in the veterans health administration. JAMA Surg 2016;151(04):314–322
18 Poeran J, Mazumdar M, Rasul R, et al. Antibiotic prophylaxis and risk of *Clostridium difficile* infection after coronary artery bypass graft surgery. J Thorac Cardiovasc Surg 2016;151(02):589–97.e2
19 Abdelsattar ZM, Krapohl G, Alrahmani L, et al. Postoperative burden of hospital-acquired *Clostridium difficile* infection. Infect Control Hosp Epidemiol 2015;36(01):40–46
20 Vogel TR, Dombrovskiy VY, Lowry SF. Impact of infectious complications after elective surgery on hospital readmission and late deaths in the U.S. Medicare population. Surg Infect (Larchmt) 2012;13(05):307–311
21 Shaughnessy MK, Bobr A, Kuskowski MA, et al. Environmental contamination in households of patients with recurrent *Clostridium difficile* infection. Appl Environ Microbiol 2016;82(09): 2686–2692
22 Dubberke ER, Reske KA, Noble-Wang J, et al. Prevalence of *Clostridium difficile* environmental contamination and strain variability in multiple health care facilities. Am J Infect Control 2007;35(05):315–318

23 Sethi AK, Al-Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of *Clostridium difficile* during and after treatment of *C. difficile* infection. Infect Control Hosp Epidemiol 2010;31(01):21–27

24 Guerrero DM, Becker JC, Eckstein EC, et al. Asymptomatic carriage of toxigenic *Clostridium difficile* by hospitalized patients. J Hosp Infect 2013;85(02):155–158

25 Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RL, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. Clin Infect Dis 2007;45(08): 992–998

26 Shrestha SK, Sunkesula VC, Kundrapu S, Tomas ME, Nerandzic MM, Donskey CJ. Acquisition of *Clostridium difficile* on hands of healthcare personnel caring for patients with resolved *C. difficile* infection. Infect Control Hosp Epidemiol 2016;37(04):475–477

27 Jullian-Desayes I, Landelle C, Mallaret MR, Brun-Buisson C, Barbut F. *Clostridium difficile* contamination of health care workers' hands and its potential contribution to the spread of infection: review of the literature. Am J Infect Control 2017;45(01): 51–58

28 Landelle C, Verachten M, Legrand P, Girou E, Barbut F, Brun-Buisson C. Contamination of healthcare workers' hands with *Clostridium difficile* spores after caring for patients with *C. difficile* infection. Infect Control Hosp Epidemiol 2014;35(01):10–15

29 Oughton MT, Loo VG, Dendukuri N, Fenn S, Libman MD. Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of *Clostridium difficile*. Infect Control Hosp Epidemiol 2009;30(10):939–944

30 Kundrapu S, Sunkesula V, Jury I, Deshpande A, Donskey CJ. A randomized trial of soap and water hand wash versus alcohol hand rub for removal of *Clostridium difficile* spores from hands of patients. Infect Control Hosp Epidemiol 2014;35(02):204–206

31 Jabbar U, Leischner J, Kasper D, et al. Effectiveness of alcohol-based hand rubs for removal of *Clostridium difficile* spores from hands. Infect Control Hosp Epidemiol 2010;31(06):565–570

32 Pokrywka M, Buraczewski M, Frank D, et al. Can improving patient hand hygiene impact *Clostridium difficile infection* events at an academic medical center? Am J Infect Control 2017;45(09): 959–963

33 Barker AK, Zellmer C, Tischendorf J, et al. On the hands of patients with Clostridium difficile: a study of spore prevalence and the effect of hand hygiene on *C. difficile* removal. Am J Infect Control 2017;45(10):1154–1156

34 Kaier K, Hagist C, Frank U, Conrad A, Meyer E. Two time-series analyses of the impact of antibiotic consumption and alcohol-based hand disinfection on the incidences of nosocomial methicillin-resistant Staphylococcus aureus infection and *Clostridium difficile* infection. Infect Control Hosp Epidemiol 2009;30(04): 346–353

35 Vernaz N, Sax H, Pittet D, Bonnabry P, Schrenzel J, Harbarth S. Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA and *Clostridium difficile*. J Antimicrob Chemother 2008;62(03):601–607

36 Boyce JM, Guercia KA, Sullivan L, et al. Prospective cluster controlled crossover trial to compare the impact of an improved hydrogen peroxide disinfectant and a quaternary ammonium-based disinfectant on surface contamination and health care outcomes. Am J Infect Control 2017;45(09):1006–1010

37 Stone SP, Fuller C, Savage J, et al. Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and *Clostridium difficile* infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. BMJ 2012;344:e3005

38 Deyneko A, Cordeiro F, Berlin L, Ben-David D, Perna S, Longtin Y. Impact of sink location on hand hygiene compliance after care of patients with *Clostridium difficile* infection: a cross-sectional study. BMC Infect Dis 2016;16:203

39 Deschênes P, Chano F, Dionne LL, Pittet D, Longtin Y. Efficacy of the World Health Organization-recommended handwashing technique and a modified washing technique to remove *Clostridium difficile* from hands. Am J Infect Control 2017;45(08):844–848

40 Tomas ME, Nerandzic MM, Cadnum JL, et al. A novel, sporicidal formulation of ethanol for glove decontamination to prevent *Clostridium difficile* hand contamination during glove removal. Infect Control Hosp Epidemiol 2016;37(03):337–339

41 Nerandzic MM, Sunkesula VC, C TS, Setlow P, Donskey CJ. Unlocking the sporicidal potential of ethanol: induced sporicidal activity of ethanol against *Clostridium difficile* and *Bacillus* spores under altered physical and chemical conditions. PLoS One 2015; 10(07):e0132805

42 Guerrero DM, Nerandzic MM, Jury LA, Jinno S, Chang S, Donskey CJ. Acquisition of spores on gloved hands after contact with the skin of patients with *Clostridium difficile* infection and with environmental surfaces in their rooms. Am J Infect Control 2012;40(06):556–558

43 Weber DJ, Rutala WA, Miller MB, Huslage K, Sickbert-Bennett E. Role of hospital surfaces in the transmission of emerging health care-associated pathogens: norovirus, *Clostridium difficile*, and *Acinetobacter species*. Am J Infect Control 2010;38(05, Suppl 1): S25–S33

44 Bobulsky GS, Al-Nassir WN, Riggs MM, Sethi AK, Donskey CJ. Clostridium difficile skin contamination in patients with *C. difficile*-associated disease. Clin Infect Dis 2008;46(03):447–450

45 Teltsch DY, Hanley J, Loo V, Goldberg P, Gursahaney A, Buckeridge DL. Infection acquisition following intensive care unit room privatization. Arch Intern Med 2011;171(01):32–38

46 Widmer AF, Frei R, Erb S, et al. Transmissibility of *Clostridium difficile* without contact isolation: results from a prospective observational study with 451 patients. Clin Infect Dis 2017;64 (04):393–400

47 Brown K, Valenta K, Fisman D, Simor A, Daneman N. Hospital ward antibiotic prescribing and the risks of *Clostridium difficile* infection. JAMA Intern Med 2015;175(04):626–633

48 Deshpande A, Pasupuleti V, Thota P, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. J Antimicrob Chemother 2013;68(09):1951–1961

49 Kundrapu S, Sunkesula VC, Jury LA, et al. Do piperacillin/tazobactam and other antibiotics with inhibitory activity against *Clostridium difficile* reduce the risk for acquisition of *C. difficile* colonization? BMC Infect Dis 2016;16:159

50 Balch A, Wendelboe AM, Vesely SK, Bratzler DW. Antibiotic prophylaxis for surgical site infections as a risk factor for infection with *Clostridium difficile*. PLoS One 2017;12(06):e0179117

51 Wenisch C, Parschalk B, Hasenhündl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. Clin Infect Dis 1996;22(05):813–818

52 DiDiodato G, McArthur L. Evaluating the effectiveness of an antimicrobial stewardship program on reducing the incidence rate of healthcare-associated *Clostridium difficile* infection: a non-randomized, stepped wedge, single-site, observational study. PLoS One 2016;11(06):e0157671

53 Patton A, Davey P, Harbarth S, Nathwani D, Sneddon J, Marwick CA. Impact of antimicrobial stewardship interventions on *Clostridium difficile* infection and clinical outcomes: segmented regression analyses. J Antimicrob Chemother 2018;73(02):517–526

54 Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. Lancet Infect Dis 2017;17(09):990–1001

55 Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69(07):1748–1754

56 Walker H, Patton A, Bayne G, et al. Reduction in post-operative acute kidney injury following a change in antibiotic prophylaxis policy for orthopaedic surgery: an observational study. J Antimicrob Chemother 2016;71(09):2598–2605

57 Blocker O, Abdulkadir U, Roberts P. *Clostridium difficile*-associated diarrhoea in primary joint arthroplasty in Aneurin Bevan University Health Board South. Ann R Coll Surg Engl 2016;98 (03):222–225

58 Al-Obaydi W, Smith CD, Foguet P. Changing prophylactic antibiotic protocol for reducing *Clostridium difficile*-associated diarrhoeal infections. J Orthop Surg (Hong Kong) 2010;18(03): 320–323

59 Bratzler DW, Dellinger EP, Olsen KM, et al; American Society of Health-System Pharmacists (ASHP); Infectious Diseases Society of America (IDSA); Surgical Infection Society (SIS); Society for Healthcare Epidemiology of America (SHEA). Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 2013;14(01):73–156

60 Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol 2014;133(03): 790–796

61 Vaisman A, McCready J, Hicks S, Powis J. Optimizing preoperative prophylaxis in patients with reported β-lactam allergy: a novel extension of antimicrobial stewardship. J Antimicrob Chemother 2017;72(09):2657–2660

62 Sigona NS, Steele JM, Miller CD. Impact of a pharmacist-driven beta-lactam allergy interview on inpatient antimicrobial therapy: a pilot project. J Am Pharm Assoc (2003) 2016;56(06): 665–669

63 del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. Ann Allergy Asthma Immunol 2007;98(04):355–359

64 Penicillin Allergy in Antibiotic Resistance Workgroup. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. J Allergy Clin Immunol Pract 2017;5(02):333–334

65 Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. Ann Allergy Asthma Immunol 2006;97(05):681–687

66 Rimawi RH, Cook PP, Gooch M, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. J Hosp Med 2013;8(06):341–345

67 Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. Clin Infect Dis 2018;66(03):329–336

68 Shaughnessy MK, Micielli RL, DePestel DD, et al. Evaluation of hospital room assignment and acquisition of *Clostridium difficile* infection. Infect Control Hosp Epidemiol 2011;32(03):201–206

69 Verity P, Wilcox MH, Fawley W, Parnell P. Prospective evaluation of environmental contamination by *Clostridium difficile* in isolation side rooms. J Hosp Infect 2001;49(03):204–209

70 Warrack S, Duster M, Van Hoof S, Schmitz M, Safdar N. *Clostridium difficile* in a children's hospital: assessment of environmental contamination. Am J Infect Control 2014;42(07):802–804

71 Orenstein R, Aronhalt KC, McManus JE Jr, Fedraw LA. A targeted strategy to wipe out *Clostridium difficile*. Infect Control Hosp Epidemiol 2011;32(11):1137–1139

72 Kaatz GW, Gitlin SD, Schaberg DR, et al. Acquisition of *Clostridium difficile* from the hospital environment. Am J Epidemiol 1988; 127(06):1289–1294

73 McMullen KM, Zack J, Coopersmith CM, Kollef M, Dubberke E, Warren DK. Use of hypochlorite solution to decrease rates of *Clostridium difficile*-associated diarrhea. Infect Control Hosp Epidemiol 2007;28(02):205–207

74 Zhang A, Nerandzic MM, Kundrapu S, Donskey CJ. Does organic material on hospital surfaces reduce the effectiveness of hypochlorite and UV radiation for disinfection of *Clostridium difficile*? Infect Control Hosp Epidemiol 2013;34(10):1106–1108

75 Cadnum JL, Tomas ME, Sankar T, et al. Effect of variation in test methods on performance of ultraviolet-C radiation room decontamination. Infect Control Hosp Epidemiol 2016;37(05):555–560

76 Rutala WA, Gergen MF, Weber DJ. Efficacy of different cleaning and disinfection methods against *Clostridium difficile* spores: importance of physical removal versus sporicidal inactivation. Infect Control Hosp Epidemiol 2012;33(12):1255–1258

77 Semret M, Dyachenko A, Ramman-Haddad L, Belzile E, McCusker J. Cleaning the grey zones of hospitals: a prospective, crossover, interventional study. Am J Infect Control 2016;44(12):1582–1588

78 Guerrero DM, Carling PC, Jury LA, Ponnada S, Nerandzic MM, Donskey CJ. Beyond the Hawthorne effect: reduction of *Clostridium difficile* environmental contamination through active intervention to improve cleaning practices. Infect Control Hosp Epidemiol 2013;34(05):524–526

79 Eckstein BC, Adams DA, Eckstein EC, et al. Reduction of *Clostridium difficile* and vancomycin-resistant *Enterococcus* contamination of environmental surfaces after an intervention to improve cleaning methods. BMC Infect Dis 2007;7:61

80 Sitzlar B, Deshpande A, Fertelli D, Kundrapu S, Sethi AK, Donskey CJ. An environmental disinfection odyssey: evaluation of sequential interventions to improve disinfection of *Clostridium difficile* isolation rooms. Infect Control Hosp Epidemiol 2013;34 (05):459–465

81 Best EL, Parnell P, Thirkell G, et al. Effectiveness of deep cleaning followed by hydrogen peroxide decontamination during high *Clostridium difficile* infection incidence. J Hosp Infect 2014;87 (01):25–33

82 Fawley WN, Underwood S, Freeman J, et al. Efficacy of hospital cleaning agents and germicides against epidemic *Clostridium difficile* strains. Infect Control Hosp Epidemiol 2007;28(08): 920–925

83 Siani H, Cooper C, Maillard JY. Efficacy of "sporicidal" wipes against *Clostridium difficile*. Am J Infect Control 2011;39(03): 212–218

84 Barbut F, Menuet D, Verachten M, Girou E. Comparison of the efficacy of a hydrogen peroxide dry-mist disinfection system and sodium hypochlorite solution for eradication of *Clostridium difficile* spores. Infect Control Hosp Epidemiol 2009;30(06):507–514

85 Doan L, Forrest H, Fakis A, Craig J, Claxton L, Khare M. Clinical and cost effectiveness of eight disinfection methods for terminal disinfection of hospital isolation rooms contaminated with *Clostridium difficile* 027. J Hosp Infect 2012;82(02):114–121

86 Wullt M, Odenholt I, Walder M. Activity of three disinfectants and acidified nitrite against *Clostridium difficile* spores. Infect Control Hosp Epidemiol 2003;24(10):765–768

87 Hacek DM, Ogle AM, Fisher A, Robicsek A, Peterson LR. Significant impact of terminal room cleaning with bleach on reducing nosocomial *Clostridium difficile*. Am J Infect Control 2010;38 (05):350–353

88 Pegues DA, Han J, Gilmar C, McDonnell B, Gaynes S. Impact of ultraviolet germicidal irradiation for no-touch terminal room disinfection on *Clostridium difficile* infection incidence among hematology-oncology patients. Infect Control Hosp Epidemiol 2017;38(01):39–44

89 McCord J, Prewitt M, Dyakova E, Mookerjee S, Otter JA. Reduction in *Clostridium difficile* infection associated with the introduction of hydrogen peroxide vapour automated room disinfection. J Hosp Infect 2016;94(02):185–187

90 Wong T, Woznow T, Petrie M, et al. Postdischarge decontamination of MRSA, VRE, and *Clostridium difficile* isolation rooms using 2 commercially available automated ultraviolet-C-emitting devices. Am J Infect Control 2016;44(04):416–420

91 Mosci D, Marmo GW, Sciolino L, et al. Automatic environmental disinfection with hydrogen peroxide and silver ions versus manual environmental disinfection with sodium hypochlorite:

a multicentre randomized before-and-after trial. J Hosp Infect 2017;97(02):175–179
92 Anderson DJ, Gergen MF, Smathers E, et al. Decontamination of targeted pathogens from patient rooms using an automated ultraviolet-C-emitting device. Infect Control Hosp Epidemiol 2013;34(05):466–471
93 Anderson DJ, Chen LF, Weber DJ, et al; CDC Prevention Epicenters Program. Enhanced terminal room disinfection and acquisition and infection caused by multidrug-resistant organisms and *Clostridium difficile* (the benefits of enhanced terminal room disinfection study): a cluster-randomised, multicentre, crossover study. Lancet 2017;389(10071):805–814
94 Anderson DJ, Moehring RW, Weber DJ, et al; CDC Prevention Epicenters Program. Effectiveness of targeted enhanced terminal room disinfection on hospital-wide acquisition and infection with multidrug-resistant organisms and *Clostridium difficile*: a secondary analysis of a multicentre cluster randomised controlled trial with crossover design (BETR disinfection). Lancet Infect Dis 2018;18(08):845–853
95 Guerrero DM, Chou C, Jury LA, Nerandzic MM, Cadnum JC, Donskey CJ. Clinical and infection control implications of *Clostridium difficile* infection with negative enzyme immunoassay for toxin. Clin Infect Dis 2011;53(03):287–290
96 Grigoras CA, Zervou FN, Zacharioudakis IM, Siettos CI, Mylonakis E. Isolation of *C. difficile* carriers alone and as part of a bundle approach for the prevention of *Clostridium difficile* infection (CDI): a mathematical model based on clinical study data. PLoS One 2016;11(06):e0156577
97 Eyre DW, Griffiths D, Vaughan A, et al. Asymptomatic *Clostridium difficile* colonisation and onward transmission. PLoS One 2013;8 (11):e78445
98 Curry SR, Muto CA, Schlackman JL, et al. Use of multilocus variable number of tandem repeats analysis genotyping to determine the role of asymptomatic carriers in *Clostridium difficile* transmission. Clin Infect Dis 2013;57(08):1094–1102
99 Longtin Y, Paquet-Bolduc B, Gilca R, et al. Effect of detecting and isolating *Clostridium difficile* carriers at hospital admission on the incidence of *C difficile* infections: a quasi-experimental controlled study. JAMA Intern Med 2016;176(06):796–804
100 Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol 2012;107(07):1001–1010
101 Barletta JF, El-Ibiary SY, Davis LE, Nguyen B, Raney CR. Proton pump inhibitors and the risk for hospital-acquired *Clostridium difficile* infection. Mayo Clin Proc 2013;88(10):1085–1090
102 Naggie S, Miller BA, Zuzak KB, et al. A case-control study of community-associated Clostridium difficile infection: no role for proton pump inhibitors. Am J Med 2011;124(03):276.e1–276.e7
103 Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med 2012;157 (12):878–888
104 McFarland LV. Probiotics for the primary and secondary prevention of *C. difficile* infections: a meta-analysis and systematic review. Antibiotics (Basel) 2015;4(02):160–178
105 Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. Cochrane Database Syst Rev 2017;12:CD006095
106 Evans CT, Johnson S. Prevention of *Clostridium difficile* infection with probiotics. Clin Infect Dis 2015;60(Suppl 2):S122–S128
107 Sadahiro S, Suzuki T, Tanaka A, et al. Comparison between oral antibiotics and probiotics as bowel preparation for elective colon cancer surgery to prevent infection: prospective randomized trial. Surgery 2014;155(03):493–503
108 Barker AK, Ngam C, Musuuza JS, Vaughn VM, Safdar N. Reducing *Clostridium difficile* in the inpatient setting: a systematic review of the adherence to and effectiveness of *C. difficile* prevention bundles. Infect Control Hosp Epidemiol 2017;38(06):639–650
109 Louh IK, Greendyke WG, Hermann EA, et al. *Clostridium difficile* infection in acute care hospitals: systematic review and best practices for prevention. Infect Control Hosp Epidemiol 2017;38 (04):476–482
110 Leav BA, Blair B, Leney M, et al. Serum anti-toxin B antibody correlates with protection from recurrent *Clostridium difficile* infection (CDI). Vaccine 2010;28(04):965–969
111 Bézay N, Ayad A, Dubischar K, et al. Safety, immunogenicity and dose response of VLA84, a new vaccine candidate against *Clostridium difficile*, in healthy volunteers. Vaccine 2016;34(23):2585–2592
112 de Bruyn G, Saleh J, Workman D, et al; H-030-012 Clinical Investigator Study Team. Defining the optimal formulation and schedule of a candidate toxoid vaccine against *Clostridium difficile* infection: a randomized Phase 2 clinical trial. Vaccine 2016; 34(19):2170–2178
113 Sheldon E, Kitchin N, Peng Y, et al. A phase 1, placebo-controlled, randomized study of the safety, tolerability, and immunogenicity of a *Clostridium difficile* vaccine administered with or without aluminum hydroxide in healthy adults. Vaccine 2016;34(18): 2082–2091
114 Gerding DN, Meyer T, Lee C, et al. Administration of spores of nontoxigenic Clostridium difficile strain M3 for prevention of recurrent *C. difficile* infection: a randomized clinical trial. JAMA 2015;313(17):1719–1727
115 Roberts T, Kokai-Kun JF, Coughlin O, et al. Tolerability and pharmacokinetics of SYN-004, an orally administered β-lactamase for the prevention of *Clostridium difficile*-associated disease and antibiotic-associated diarrhea, in two phase 1 studies. Clin Drug Investig 2016;36(09):725–734
116 Kokai-Kun JF, Roberts T, Coughlin O, et al. The Oral beta-Lactamase SYN-004 (Ribaxamase) Degrades Ceftriaxone Excreted into the Intestine in Phase 2a Clinical Studies. Antimicrob Ag Chemother 2017;61(03):pii:e02197–e02216
117 Ray AJ, Deshpande A, Fertelli D, et al. A Multicenter Randomized Trial to Determine the Effect of an Environmental Disinfection Intervention on the Incidence of Healthcare-Associated Clostridium difficile Infection. Infect Control Hosp Epidemiol 2017; 38(07):777–783
118 Shea KM, Hobbs ALV, Jaso TC, et al. Effect of a Health Care System Respiratory Fluoroquinolone Restriction Program To Alter Utilization and Impact Rates of *Clostridium difficile* Infection. Antimicrob Agents Chemother 2017;61(06):e00125-17
119 Ali S, Muzslay M, Wilson APR. Comparison of two whole-room ultraviolet irradiation systems for enhanced disinfection of contaminated hospital patient rooms. J Hosp Infect 2017;97 (02):180–184
120 Azab M, Doo L, Elmofti Y et al. Comparison of the Hospital-Acquired *Clostridium difficile* Infection Risk of Using Proton Pump Inhibitors versus Histamine-2 Receptor Antagonists for Prophylaxis and Treatment of Stress Ulcers: A Systematic Review and Meta-Analysis. Gut Liver 2017;11(06):781–788
121 Arriola V, Tischendorf J, Musuuza J, et al. Assessing the Risk of Hospital-Acquired *Clostridium difficile* Infection with Proton Pump Inhibitor Use: A Meta-Analysis. Infect Control Hosp Epidemiol 2016;37(12):1408–1417
122 Pozzoni P, Riva A, Bellatorre AG, et al. Saccharomyces boulardii for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol 2012;107 (06):922–931