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Primary Prevention of *Clostridium difficile*-Associated Diarrhea: Current Controversies and Future Tools

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Abstract

Purpose of Review *Clostridium difficile* infection (CDI) is a major cause of morbidity and mortality in hospitalized patients and rates in most places have not decreased significantly despite broad efforts by both hospitals and public health entities. This review aims to provide readers with a better understanding of the limitations of current prevention strategies. We also review potential future tools that may be available for the primary prevention of CDI in the next decade.

Recent Findings Research over the last decade has expanded our appreciation of the role of asymptomatic shedding in the healthcare setting and in the community. This review demonstrates that poor quality data underlies even well-established guidance from national authorities on basic topics such as contact precautions, avoidance of alcohol-based hand hygiene products, CDI testing, supplemental cleaning modalities, and the use of bleach solutions. Additionally, we review research on novel preventative interventions such as identification of asymptomatic carriers, supplemental environmental cleaning technologies, vaccines, and the manipulation of the intestinal microbiome. While there is preliminary data that supports further research in all of these areas, the research is not yet robust enough on which to base local or national policy recommendations, though late-phase human clinical trials of CDI vaccine trials are ongoing.

Summary Over the last decade, researchers have begun to reassess the traditional infection prevention model for CDI. Data suggesting a greater role for asymptomatic shedders has increased our understanding of current vertical prevention techniques and is forcing researchers to look more at new processes and technologies to decrease disease incidence.

Keywords *Clostridium difficile* · Review · Prevention

Introduction

Clostridium difficile (CD) is an anaerobic, spore-forming gram-negative bacillus that is ingested and causes a spectrum of diarrheal infections, most commonly in patients with perturbed intestinal microbiomes after antibiotic exposure. *C. difficile* infections (CDI) are important causes of morbidity and mortality. A study of 10 geographical areas estimated the overall burden of CDIs in the USA as more than 80,000 cases and 29,000 associated deaths in the year 2011 alone [1]. Unfortunately, the high estimates in 2011 are the result of a steady increase in the incidence of CDI over the last two decades. From 2000 to 2010, mortality rates due to CDI roughly doubled in the adult and elderly populations in hospitals in the USA [2, 3]. The emergence of a new, possibly more virulent strain of CD, the B1/NAP1/027 strain, may explain some of the increasing severity of CDI, though this association is still somewhat controversial [4–6]. Nevertheless, increasing CDI rates over the last decade are especially troubling when you consider the concerted effort and resources that public health providers and hospitals have already expended to prevent these infections [7–10].

In this review, authors searched the English language literature, emphasizing publications since 2012, aiming to outline some of the current controversies surrounding the prevention of CDI in the healthcare setting.

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Current Controversies: Asymptomatic CD Carriage and Its Impact on Contact Precautions

Traditional CDI prevention strategies have largely centered on the use of vertical infection control interventions, including identification of symptomatic CDI, prompt initiation of contact precautions, hand hygiene, and sporicidal environmental disinfectants. These interventions are outlined in national guidelines and widely employed by hospitals [8••, 9, 10]. This approach is based largely on the assumption that most nosocomial transmission is due to shedding by symptomatic patients in healthcare facilities [11]. In this model, symptomatic patients with CDI shed large quantities of spores and vegetative bacteria into the environment. Interestingly, recent literature suggests that asymptomatic CD carriers may play a larger role than previously appreciated in the transmission of endemic CDI.

Recent research demonstrates that asymptomatic carriers play a significant role in CD transmission within healthcare facilities [12]. A review by Donskey et al. [13••] cited the rate of asymptomatic CD carriage in healthcare facilities between 7 and 18% in acute care hospitals and even higher rates in long-term care facilities. The main risk factors across studies included patients with longer hospital stays (especially over 4 weeks), chemotherapy, and stomach acid-suppressing medications.

Though many hospitals discontinue contact precautions for patients with CDI shortly after diarrhea resolves, there is evidence that shedding persists for weeks and may be a source of transmission both in hospitals and long-term care facilities [14–16]. Additionally, asymptomatic carriage in the community is increasingly being noted as a potential cause of pre-hospital transmission and may fuel hospital-onset CDI [17•, 18•]. Studies using molecular typing to measure the relatedness of CD strains to each other found that between 55 and 83% of endemic CD strains causing CDI in the healthcare setting could not be directly linked to other symptomatic patients in healthcare facilities [18•, 19, 20]. This suggests that either acquisition of CD prior to hospital admission or that hospital transmission from asymptomatic shedders may be responsible for a majority of healthcare-acquired CDI cases. While each of these studies had methodological drawbacks, these studies nevertheless demonstrate that current prevention efforts focused only on CD transmission from symptomatic patients is unlikely to prevent CDI in a significant segment of patients.

While multiple studies have demonstrated benefits of contact precautions and enhanced environmental cleaning in the outbreak setting [21–23], these measures seem to have a lower efficacy in curbing endemic CDI. Newer mathematical models [24, 25] and early clinical studies suggest that intensification of contact precautions through identification and isolation of asymptomatic carriers may be beneficial to decreasing hospital-onset CDI. In the quasi-experimental study by Longtin et al., patients were screened for CD carriage on admission using rectal swabs and PCR [26•]. The screening test was positive in about 5% of asymptomatic patients, who were then placed in contact precautions for the duration of their hospital stay. Compared to the pre-intervention period, the expected number of cases decreased by 63% over the study period, though the benefit was greater over time. While this data suggests a role for screening and isolation, better quality studies are needed, since the cost of the intervention is likely to be high, both financially and in the disruption to clinical practice.

Current Controversies: Soap and Water Versus Alcohol-Based Hand Rubs for Hand Hygiene

Researchers have known that contaminated healthcare workers are potent vectors for transmission of CD spores, but there is still no evidence-based consensus on the best mode of hand hygiene to decrease this risk. Currently, the WHO recommends the use of hand hygiene with soap and water, in addition to gown and glove use, given the concern that alcohol-based hand rubs do not kill CD spores [27]. While this has become common practice, the *Society for Healthcare Epidemiology of America* (SHEA) and the CDC currently only recommend the use of soap and water for hand hygiene in CDI outbreak settings and recommend routine use of alcohol-based hand rubs during routine patient care [8••]. According to the 2017 guidelines, even though alcohol-based hand rubs are unable to inactivate CD spores, no clinical study has demonstrated superiority of CDI prevention with preferential use of soap and water [10].

Multiple studies have shown that alcohol-based hand rubs are not effective in removing CD spores from healthcare worker hands. Oughton et al. compared the effectiveness of multiple hand hygiene modalities for CD using healthy volunteers and non-toxigenic CD [10]. The most effective modalities were plain soap and warm water, and alcohol hand rubs were equivalent to no intervention. Jabbar et al. also found that soap and water was significantly more effective in removing non-toxigenic CD from the hands of healthy volunteers [28]. The study went further to show that volunteers using alcohol transferred CD spores to others 30% of the time via handshakes. Kundrapu et al. (2014) also demonstrated lack of efficacy for alcohol-based hand rubs for CD when they evaluated patient hand hygiene [29]. Though experimental data suggests the increased efficacy of soap and water, no large clinical studies have demonstrated significant rate changes between the approaches [30]. Further clinical data are necessary on the overall impact of soap and waters versus alcohol-based hand rubs in non-outbreak settings. Nevertheless, most hospitals have elected to use soap and water for CDI cases.

To improve efficacy of traditional hand hygiene methods, researchers are evaluating new processes and products to improve CD removal. Novel hand washes, including oil-based products and sand, seemed to perform better than traditional soap and water—likely due to increasing the sheer forces on CD spores through friction [31]. Other promising strategies to enhance sporicidal killing of CD is to supplement alcohol rubs with peracetic acid [32]. However, it is unclear if this product is safe for long-term repeat use or whether it could lead to skin breakdown. Simple measures like optimizing hospital layout and placement of sinks for ease of use may also improve hand hygiene [33]. Further research is needed to develop hand hygiene strategies that are not only effective but also easy to integrate into routine patient care.

Current Controversies: Environmental Cleaning with Bleach Versus Standard Cleaners

SHEA has highlighted the need for adequate room cleaning and disinfection as a means of controlling the spread of CD in acute care hospitals [8••, 10]. CD poses a challenge in the hospital environment because it forms spores that can last for several months and are difficult to kill with standard disinfectants [34]. Based on SHEA/IDSA guidelines, acute care hospitals should use EPA-approved sporicidal disinfectants, "if necessary," to control CDI [8••, 10]. Many hospitals have started cleaning protocols with bleach, given its sporicidal properties, as either daily cleaning or terminal cleaning for patients with CDI [35].

Multiple studies have shown that switching to bleach disinfection protocols decreases CDI incidence. Kaatz et al. found that surface contamination with CD decreased and an institutional outbreak resolved after instituting a disinfection protocol with bleach [36]. Hacek et al. found a 48% reduction in the prevalence density of CD after switching from a quaternary ammonia compound to bleach for terminal cleaning [23]. The study by Mayfield et al., however, found conflicting results [37]. In their bone marrow transplant unit, their CDI rate decreased from 8.6 to 3.3 cases per 1000 patient-days after switching from quaternary ammonia compound to bleach for routine cleaning in the patients' rooms with CDI. The cleaning protocol was similarly switched to bleach in two other units with lower baseline rates of CDI, but there was no improvement in CDI rates after the change. While data on cleaning with hypochlorite to control outbreaks and in hyper-endemic settings is encouraging, it is unclear if routine cleaning is beneficial given limited data supporting use in facilities with low baseline rates.

Although use of bleach for daily or terminal disinfection in patients with CDI is commonly followed in hospitals, there are additional concerns given potential toxicity to the staff, patients, and the environment. Bleach can be corrosive and damage patient care materials and equipment [8••, 10] and is associated with increased bronchospasm and asthma [23, 38]. While new bleach products may mitigate some of the negative effects, benefits need to be balanced against potential harm to equipment and personnel.

Current controversies: Enhanced Disinfection Strategies

In an effort to enhance environmental disinfection strategies against CD, multiple hospitals are utilizing "no-touch disinfection technologies," including ultraviolet light (UV) and hydrogen peroxide vapor [39]. These enhanced disinfection methods are meant to be adjuncts to standard cleaning and disinfection with an approved disinfectant.

Multiple studies have been published recently examining the impact of ultraviolet light technologies using either pulsed xenon ultra violet light (PX-UV) and UV-C radiation. Anderson et al. published a 28-month duration cluster randomized, multicenter, crossover study comparing four terminal disinfection interventions: control, bleach, UV-C, and bleach plus UV-C [40]. The primary outcome was the incidence of patient acquisition of a target organism after staying in a room previously occupied by a patient with that organism. They found that adding UV-C to bleach did not significantly decrease the incidence of CDI in exposed patients. There have been multiple pre-post studies that have also examined the impact of UV light disinfection, and these studies have found decreased or a trend toward decreased CDI rates in various hospital settings and long-term acute care facilities [41•, 42•, 43–47]. Given the mixed results, Marra et al. published a meta-analysis of pooled data from multiple trials and pre-post studies that demonstrated a significant reduction in healthcare-associated CDI rates [41•]. Efficacy appears to be greatest in facilities with higher baseline rates of CD but similarly effective in both academic and community hospital settings. While this data is encouraging, hospitals should consider the significant initial acquisition costs and the need for added labor to operate the machines efficiently prior to implementation. We have used UV light disinfection at UCLA since 2013. Though we believe this technology has theoretical benefits, it has proven logistically challenging. To realistically use this technology to its fullest potential, clinical areas probably should have dedicated UV units and staff to run them at maximum capacity.

Hydrogen peroxide vapor is another potential adjunctive technology. The vapor is sporicidal, inactivates a range of hospital-acquired pathogens, and can disinfect locations within the room that may be hard to manually clean or reach with line of site UV. Passaretti et al. performed a prospective cohort study comparing three wards using standard cleaning with hydrogen peroxide vapor to three wards with standard cleaning. The study found a reduction in a composite endpoint of

multidrug-resistant organisms acquired by the next patient in the room [48]. The outcome was largely driven by acquisition of vancomycin-resistant *Enterococcus*, and the study found a non-significant trend toward decrease in CD in the vapor arm. Other quasi-experimental studies have found improvements in or trends toward improvement in hospital-onset CDI using vapor [49–52]. The previously mentioned meta-analysis by Marra et al. of pooled data from the prospective cohort and multiple pre-post studies demonstrated a non-significant reduction in CDI rates [39]. While early data is encouraging, further prospective controlled trials are necessary to determine if hydrogen peroxide vapor is beneficial in reducing hospital-onset CDI given the high cost of implementation.

Current Controversies: Testing Methodology

Diagnosis of CDI requires clinical suspicion—typically diarrhea—combined with supportive diagnostic testing. Given the variability in sensitivity and specificity among available testing methods, the optimal choice of diagnostic test or combination of tests remains a matter of debate [53–55].

Two gold standard reference methods exist for diagnosis of CDI, although neither is widely used in clinical practice due to impracticality. The first, the cell cytotoxicity assay, relies on detection of cytopathic effects in cell culture after 24–48 h observation when stool filtrate is cultured in the presence or absence of antitoxin antibodies. The second method, cytotoxigenic culture, employs anaerobic culturing of the bacteria and monitoring for production of toxin, which may take up to 5 days. The cell cytotoxicity assay detects 15–40% fewer cases than cytotoxigenic culture [56]. A prospective study of 6522 inpatient episodes found that toxin positivity (positive cytotoxicity assay) correlated with clinical outcomes, whereas detection of toxigenic CD alone did not, suggesting that this reference method may better define true cases of CDI [57].

Many commercial tests exist for diagnosis of CDI with sensitivity and specificity dependent on both the type of test and the reference method used for comparison. Available tests fall into three main targets: toxin immunoassays (EIA), glutamate dehydrogenase (GDH), and nucleic acid amplification tests (NAATs) [53, 56]. From these tests, there are three possible diagnoses: CD colonization, CDI, and CD negative. The choice of test by a hospital or laboratory depends on available resources, cost, volume, and population served [58]. Laboratory rejection of formed stool helps reduce detection of asymptomatic carriers [53].

EIA lack sensitivity (29–86%), raising concerns about false-negative results [53, 54], though the specificity of these tests is up to 99%. Test performance varies widely depending on the manufacturer and the reference method used (i.e., the sensitivity will be lower when compared to cytotoxigenic culture) [56]. The performance of the toxin EIA does not appear to correlate with disease severity [59].

GDH is a highly conserved metabolic enzyme in CD [60]. Assays for this enzyme using EIA methodology are relatively inexpensive, easy to run, and have high sensitivity (approximately 94.5%) but low specificity (approximately 94.5%) when compared to cytotoxigenic culture [55, 56]. Since they detect the presence of all CD strains and not just the toxigenic ones, GDH tests are recommended only as screening tests in combination with other assays, such as toxin EIA [54–56].

Most NAATs detect highly conserved regions within the gene encoding toxin B production (*tcd*B), although assays for other targets have also been developed including for *tcd*A, *tcd*C (a negative regulator of toxin A/B production), and *cdt* (binary toxin gene) [54, 61]. In their review, Crobach et al. report pooled sensitivity of 96% and specificity of 94% compared to the cell cytotoxicity assay, 95% sensitivity and 98% specificity compared to toxigenic culture [54]. The high sensitivity of NAATs raises concerns about false-positive results in asymptomatic carriers without CDI. A prospective study by Polage et al. demonstrated that virtually all complications and deaths from CDI occurred in patients with positive toxin immunoassays but not in those who were NAAT positive and toxin negative, arguing that relying exclusively on NAATs may result in overdiagnosis and treatment [62].

Given the relatively low sensitivity of some toxin EIA products combined with the overdetection of asymptomatic carriers by the highly sensitive NAATs (and GDH), some experts recommend combining tests into two- or three-step algorithms to improve both negative and positive predictive values [54–56, 61]. Within these algorithms, step 1 is to test with a highly sensitive GDH EIA or NAAT. Step 2 is to test with a highly specific toxin A/B EIA. Step 3 is an optional toxigenic culture or NAAT if clinical suspicion remains despite a negative toxin EIA. Alternatively, simultaneous use of GDH and toxin A/B EIA may be used [54].

Because hospitals in many states that publicly report CDI are incentivized to decrease their hospital-acquired rates, there has been an increasing move away from NAAT testing alone and toward multi-step algorithms. The most recent CDC guidance for reporting recommended that hospitals be stratified by test type. With this shift away from NAAT, there is a concern that the low sensitivity of EIA may lead to false-negative tests that could increase the risk of poor outcome for patients due to delayed treatment and could increase the level of environmental contamination by CD spores through lack of contact precautions or specific cleaning for CDI cases. Conversely, reliance on NAAT could increase the rate of detection of asymptomatic CD carriers and lead to overdiagnosis and overtreatment, though asymptomatic patients may be excluded using computer algorithms to reject specimens of patients on laxatives or who have solid stool. For institutions looking to revise their CD diagnosis strategy, they must decide philosophically

which misclassification they can tolerate and implement strategies to mitigate the potential negative impacts.

Future Area: CD Vaccine

The scientific basis for developing a vaccine for the prevention of CDI is predicated on serologic studies demonstrating higher antitoxin antibodies in CD carriers compared to patients who develop CDI. However, a recent review shows that the most well-studied antibodies against CD, immonoglobulins *tcd*A and *tcd*B, may not tell the whole story as there are multiple studies with discrepant results [63]. Nevertheless, researchers and pharmaceutical companies have pressed forward with the development of both passive immunotherapies such as bezlotoxumab (Zinplava, Merck Sharp Dohme) and vaccines that target CD toxins. Randomized, placebo-controlled studies found that bezlotoxumab decreased CDI recurrence by 40%, though the absolute decrease in recurrence rate was about 10% in both studies [64•]. Based upon these studies, the FDA approved the use of injectable bezlotoxumab for patients with CDI recurrence but not for primary prevention of CDI. CD vaccines now in development for primary prevention also focus on antibodies to *tcd*A and *tcdB*. In phase 2 studies, at least two vaccines elicited adequate neutralizing antibody levels in patients [65, 66]. Phase 3 trials are now ongoing to determine how effective the vaccines will be for primary prevention. Additional studies are investigating other potential vaccine target proteins but are still in early stage development [63].

Although development of a vaccine for CD primary prevention is exciting, there are some potential limitations and concerns. Unfortunately, the group most likely to benefit from the prevention of CDI, immunocompromised patients (such as patients on hemodialysis or with metastatic malignancies), are excluded from the clinical trials, and there is reason to believe that these groups may not be able to generate protective antibody levels to prevent disease. Additionally, it is not yet clear whether the current vaccines targeting *tcd*A and *tcdB* will be as effective as vaccines against other CD components. A more theoretical concern is that vaccinated patients may be less likely to develop CDI but could be more likely to be colonized with CD and therefore to shed CD into the environment [67].

Future Area: Intestinal Microflora Manipulation to Prevent CDI

Because perturbation of the intestinal microflora contributes so heavily to development of CDI, researchers have looked to manipulate intestinal microflora for primary prevention of CDI. Infecting patients with non-toxigenic strains of CD, probiotics, and fecal microbiota transplants are potential tools for prevention of CDI in the future, though research is still in early stages.

In a murine model, one study arm was pre-treated with multiple antibiotics and then given 10^7 dose of non-toxigenic strain of CD, CD37, twice daily for 2 days. The animals were then exposed to a 10^6 dose of toxigenic CD (B1/NAP1/027). The experimental group was compared to a control arm that was not exposed to CD37. Thirty percent of the animals in the experimental group developed diarrhea compared to 100% of the controls. Eighty percent of the experimental animals survived in the experimental group compared to 20% of the controls [68]. Similar studies performed in hamsters have also demonstrated protection against diarrhea and mortality from the NAP1 strain of CD [69, 70]. A human trial demonstrated that infection with non-toxigenic CD strains is feasible and well tolerated, but additional human prevention trials are yet to be published [71]. We believe this approach could be extremely powerful on an institutional level, because non-toxigenic strains could replace pathogenic organisms in the patient population and in the environment, decreasing the major drivers of CDI.

Probiotics, largely *Lactobacillus* sp., have been studied for more than a decade for primary and secondary prevention of CDI. A Cochrane review published in 2017 identified 31 randomized controlled trials that met inclusion criteria [72]. The review concluded that there was moderate quality evidence suggesting probiotics are both safe and effective for preventing CDI. The pooled results of the studies demonstrated a 60% reduction in CDI incidence in patients taking probiotics, though the review authors suggest that the results may be skewed toward benefit. Another review of meta-analyses found that despite the heterogeneity of included studies in terms of study design and probiotic formulation, all showed decreased incidence of CDI when used for primary prevention [73]. In our institution, we have used *Lactobacillus* probiotics for more than 5 years in some populations and have found them to be safe, though CD rates have not decreased in these populations significantly.

Fecal microbiota transplants have been studied widely and demonstrate benefit for the prevention of CDI recurrence, but there is currently no data for primary prevention of CDI. Some additional studies have looked at donor-derived fecal organisms, short of full transplants, and non-microbiota stool, but these studies have thus far looked primarily at secondary prevention [74, 75]. Another study tested the efficacy of a sterile fecal filtrate transfer and demonstrated resolution of CDI symptoms in a small group suggesting that non-microbiota stool transfer may be effective in prevention CDI recurrence. While researchers have yet to test these measures in primary prevention, they may prove to be efficacious in high-risk patient populations. Newer oral delivery of these products may make them more attractive for primary prevention, though the FDA has tightly regulated them in the past making cost and availability a limiting factor.

Future Area: Bacteriophage Therapy

Bacteriophages are viruses that target bacteria. Since bacteriophages are active against specific CD strains, treating patients with a combination of phages may eradicate CD carriage in the primary or secondary prevention setting. Although only tested in animal models to prevent relapse of CDI [76–78], bacteriophage therapy holds promise as a potential tool for CDI prevention in the future. Bacteriophage therapy could be a potent tool in the future against CD and other drug-resistant organisms and is an area currently being hotly researched, though no products are currently in human testing.

Future Area: Chemoprophylaxis in High-Risk Patients

Limited prospective data exist regarding chemoprophylaxis of high-risk patients though current guidelines do not recommend this approach based on lack of evidence [55]. Although there are no compelling data to support antimicrobial primary prophylaxis, secondary prophylaxis with oral vancomycin and probiotics is increasing. The high cost of currently available drugs, such as fidaxomicin and oral vancomycin, renders this approach currently uneconomical.

Conclusion

The importance of CDI has grown over the last decade despite significant efforts by both public health and the healthcare industry to curb its spread. As we learn more about the complexity of CD transmission and the role of asymptomatic carriers and persistent environmental contamination, the older prevention paradigms are likely to change. While many of the future prevention interventions, such as therapeutic manipulation of the intestinal microbiome, are still in early stages of research, some new, though controversial technologies for environmental disinfection are available now, though require additional research to optimize their use. Additionally, the first-generation CD vaccines are in phase 3 trials and may be available for use soon. The ultimate hope is that our growing knowledge of CD and the increasing availability of new technology to curb the spread of CD and prevent illness will protect patients from the frustrating and serious problem of CDI.

Compliance with Ethical Standards

Conflict of Interest Zachary Rubin and Elise Martin are receiving research funding from Pfizer for an ongoing clinical trial on a CDI vaccine. Paul Allyn owns stock in Pfizer.

Human and Animal Rights and Informed Consent This article cites one study with human subjects performed by Zachary Rubin, which previously was reviewed and approved by the local IRB. All other studies cited with human or animal subjects were not performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. New Engl J Med. 2015;372:825–34.
2. Zilberg MD, Shorr AF, Koleff MH. Increase in adult Clostridium difficile-related hospitalizations and case fatality rate, United States, 2000-2005. Emerg Infect Dis. 2008;14:929–31.
3. Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in Clostridium difficile infection incidence among hospitalized adults in the United States: 2001-2010. Am J Infect Dis. 2014;42:1028–32.
4. See I, Mu Y, Cohen J, Beldavs ZG, Winston LG, Dumyati G, et al. NAP1 strain type predicts outcomes from Clostridium difficile infection. Clin Infectious Dis. 2014;58:1394–400.
5. Scardina T, Labuszewski L, Pacheco SM, Adams W, Schreckenberger P, Johnson S. Clostridium difficile infection (CDI) severity and outcome among patients infected with the Nap1/B1/027 strain in non-epidemic setting. Infect Control Hosp Epidemiol. 2015;36:280–6.
6. Bauer KA, Johnston JEW, Wenzler E, Goff DA, Cook CH, Balada-Llasat JM, et al. Impact of the NAP-1 strain on disease severity, mortality and recurrence of healthcare-associated Clostridium difficile infection. Anaerobe. 2017;48:1–6.
7. CDC. Antimicrobial resistance threats. https://www.cdc.gov/drugresistance/biggest_threats.html.
8. •• McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018. **This article provides the most up to date guidance from public health.**
9. Dubberke ER, Carling P, Carrico R, Donskey CJ, Loo VG, McDonald LC, et al. Strategies to prevent Clostridium difficile infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35:S48–65.
10. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines: guidelines for Clostridium difficile infection in adults: 2010 update by the Society of Healthcare Epidemiology of America (SHEA) and in the Infectious Diseases Society of America. Infect Control Hosp Epidemiol. 2010;31:431–55.
11. McFarland LV, Mulligan ME, Kwok RYY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection. N Engl J Med. 1989;320:204–10.
12. Curry SR, Muto CA, Schlackman JL, Pasculle AW, Shutt KA, Marsh JW, et al. Use of multilocus variable number of tandem repeats analysis genotyping to determine the role of asymptomatic carriers in Clostridium difficile transmission. Clin Infect Dis. 2013;57:1094–102.
13. •• Donskey CJ, Kundrapa S, Despande A. Colonization versus carriage of Clostridium difficile. Infect Dis Clin N Am. 2015;29:13–28. **Well researched review of the evidence surrounding asymptomatic carriage of CD.**

14. Sethi AK, Al-Nassir WN, Nerandzic MM, et al. Persistence of skin contamination and environmental shedding of Clostridium difficile during and after treatment of C. difficile infection. Infect Control Hosp Epidem. 2010;32:21–7.
15. Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RLP, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic Clostridium difficile strains among long-term care facility residents. Clin Infect Dis. 2007;45: 992–8.
16. Jinno S, Kundrapu S, Guerrero DM, Jury LA, Nerandzic MM, Donskey CJ. Potential for transmission of Clostridium difficile by asymptomatic acute care patients and long-term care facility residents with prior C. difficile infection. Infect Contr Hosp Epidemiol. 2012;33:638–9.
17.• Fuyura-Kanamori L, Riley TV, Paterson DL, et al. Comparison of Clostridium difficile ribotypes circulating in Australian hospitals and communities. J Clin Microbiol. 2017;55:216–25. **Provocative study looking at the interaction between the community and the hospital CDI suggesting that the community maybe the source of significant hospital-onset CDI.**
18.• Eyre DW, Cule ML, Wilson DJ, Griffiths D, Vaughan A, O'Connor L, et al. Diverse sources of C. difficile infection identified on whole genome sequencing. New England J Med. 2013;369:1195–205. **Despite some methodologic concerns, this is the largest study demonstrating the likely large contribution of asymptomatic CD carriers to endemic CDI incidence.**
19. Walker AS, Eyre DW, Wyllie DH, Dingle KE, Harding RM, O'Connor L, et al. Characterization of Clostridium difficile hospital ward-based transmission using extensive epidemiologic data and molecular typing. PLoS Med. 2012;9:e1001172.
20. Noren T, Akerlund T, Back E, Sjoberg L, Persson I, Alriksson I, et al. Molecular epidemiology of hospital-associated and community-acquired Clostridium difficile infection in a Swedish county. J Clin Microbiol. 2004;42:3635–43.
21. Fisher A, Dembry LLM. Norovirus and Clostridium difficile: squelching the wildfire. Curr Opinion in Infect Dis. 2017;30:440–7.
22. McMullen KM, Zack J, Coopersmith CM, et al. Use of hypochlorite solution to decrease rates of *Clostridium difficile*-associated diarrhea. Infect Control Hosp Epidemiol. 2007;28(2007):205–7.
23. Hacek DM, Ogle AM, Fisher A, Robicsek A, Peterson LR. Significant impact of terminal room cleaning with bleach on reducing nosocomial *Clostridium difficile*. Am J Infect Control. 2010;38: 350–3.
24. Maghdoori S, Moghadas SM. Assessing the effect of patient screening and isolation on curtailing Clostridium difficile infection in hospital settings. BMC Infect Dis. 2017;17:384.
25. Lanzas C, Dubberke ER, Lu Z, Reske KA, Grohn YT. Epidemiologic model for Clostridium difficile transmission in healthcare settings. Infect Control Hosp Epidemiol. 2011;32:553–61.
26.• Longtin Y, Paquet-Bolduc B, Gilca R, Garenc C, Fortin E, Longtin J, et al. Effect of detecting and isolating Clostridium difficile carriers at hospital admission on the incidence of C. difficile infections: a quasi-experimental controlled study. JAMA Intern Med. 2016;176:796–804. **Study demonstrating that CDI incidence decreases with aggressive screening and isolation of CD carriers in addition to symptomatic cases.**
27. WHO guidelines on hand hygiene in health care: first global patient safety challenge clean care is safer care. Geneva: World Health Organization; 2009.
28. 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):939–44.
29. Jabbar U, Leischner J, Kasper D, Gerber R, Sambol SP, Parada JP, et al. Effectiveness of alcohol-based hand rubs for removal of Clostridium difficile spores from hands. Infect Control Hosp Epidemiol. 2010;31(6):565–70.
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(2):204–6.
31. Knight N, Strait T, Anthony N, Lovell R, Norton HJ, Sautter R, et al. Clostridium difficile colitis: a retrospective study of incidence and severity before and after institution of an alcohol-based hand rub policy. Am J Infect Control. 2010;38(7):523–8.
32. Isaacson D, Haller B, Leslie H, Roemer M, Winston L. Novel handwashes are superior to soap and water in removal of Clostridium difficile spores from the hands. Am J Infect Control. 2015;43(5):530–2.
33. Nerandzic MM, Sankar TC, Setlow P, et al. A cumulative spore killing approach: synergistic sporicidal activity of dilute peracetic acid and ethanol at low pH against Clostridium difficile and Bacillus subtilis spores. Open Forum Infect Dis. 2016;3(1):ofv206.
34. Zellmer C, Blakney R, Van Hoof S, et al. Impact of sink location on hand hygiene compliance for Clostridium difficile infection. Am J Infect Control. 2015;43(4):387–9.
35. Kim KH, Fekety R, Batts DH, Brown D, Cudmore M, Silva J, et al. Isolation of Clostridium difficile from the environment and contacts of patients with antibiotic-associated colitis. J Infect Dis. 1981;143(1):42–50.
36. Barbut F. How to eradicate Clostridium difficile from the environment. J Hosp Infect. 2015;89(4):287–95.
37. Kaatz GW, Gitlin SD, Schaberg DR, et al. Acquisition of Clostridium difficile from the hospital environment. Am J Epidemiol. 1988;127(6):1289–94.
38. Mayfield JL, Leet T, Miller J, Mundy LM. Environmental control to reduce transmission of Clostridium difficile. Clin Infect Dis. 2000;31(4):995–1000.
39. Delclos GL, Gimeno D, Arif AA, Burau KD, Carson A, Lusk C, et al. Occupational risk factors and asthma among health care professionals. Am J Respir Crit Care Med. 2007;175(7):667–75.
40. Sastre J, Madero MF, Fernández-Nieto M, Sastre B, del Pozo V, Potro MGD, et al. Airway response to chlorine inhalation (bleach) among cleaning workers with and without bronchial hyperresponsiveness. Am J Ind Med. 2011;54(4):293–9.
41.• Marra AR, Schweizer ML, Edmond MB. No-touch disinfection methods to decrease multidrug-resistant organism infections: a systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2018;39(1):20–31. **A thoughtful review of newer no-touch disinfection prevention modalities.**
42.• Anderson DJ, Chen LF, Weber DJ, Moehring RW, Lewis SS, Triplett PF, et al. Enhanced terminal room disinfection and acquisition and infection caused by multidrug resistant organisms and Clostridium difficile (the Benefits of Enhanced Terminal Room Disinfection study): a cluster-randomised, multicentre, crossover study. Lancet. 2017;389:805–14. **Interesting, though largely negative, trial of bleach and UV light compared to standard of care. Results may have been hampered by failure to eradicate CD spores shed by asymptomatic patients in addition to reasons cited in paper and accompanying editorial.**
43. Napolitano NA, Mahapatra T, Tang W. The effectiveness of UV-C radiation for facility-wide environmental disinfection to reduce healthcare-acquired infections. Am J Infect Control. 2015;43: 1342–6.
44. Pegues DA, Han J, Gilmar C, McDonnell B, Gaynes S. Impact of ultraviolet germicidal irradiation for no-touch terminal room disinfection on Clostridium difficile infection incidence among hematology-oncology patients. Infect Control Hosp Epidemiol. 2017;38:39–44.
45. Levin J, Riley LS, Parrish C, English D, Ahn S. The effect of portable pulsed xenon ultraviolet light after terminal cleaning on

hospital-associated Clostridium difficile infection in a community hospital. Am J Infect Control. 2013;41:746–8.
46. Haas JP, Menz J, Dusza S, Montecalvo MA. Implementation and impact of ultraviolet environmental disinfection in acute care setting. Am J Infect Control. 2014;42:586–90.
47. Miller R, Simmons S, Dale C, Stachowiak J, Stibich M. Utilization and impact of a pulsed-xenon ultraviolet room disinfection system and multidisciplinary care team on Clostridium difficile in a long-term acute care facility. Am J Infect Control. 2015;43:1350–3.
48. Vianna PG, Dale CR Jr, Simmons S, Stibich M, Licitra CM. Impact of pulsed xenon ultraviolet light on hospital-acquired infection rates in a community hospital. Am J Infect Control. 2016;44:299–303.
49. Nagaraja A, Visintainer P, Haas JP, Menz J, Wormser GP, Montecalvo MA. Clostridium difficile infections before and during use of ultraviolet disinfection. Am J Infect Control. 2015;43:940–5.
50. Passaretti CL, Otter JA, Reich NG, Myers J, Shepard J, Ross T, et al. An evaluation of environmental decontamination with hydrogen peroxide vapor for reducing the risk of patient acquisition of multidrug-resistant organisms. Clin Infect Dis. 2013;56(1):27–35.
51. Boyce JM, Havill NL, Otter JA, McDonald LC, Adams NMT, Cooper T, et al. Impact of hydrogen peroxide vapor room decontamination on Clostridium difficile environmental contamination and transmission in a healthcare setting. Infect Control Hosp Epidemiol. 2008;29:723–9.
52. Horn K, Otter JA. Hydrogen peroxide vapor room disinfection and hand hygiene improvements reduce Clostridium difficile infection, methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and extended-spectrum β-lactamase. Am J Infect Control. 2015;43:1354–6.
53. Manian FA, Griesnauer S, Bryant A. Implementation of hospital-wide enhanced terminal cleaning of targeted patient rooms and its impact on endemic Clostridium difficile infection rates. Am J Infect Control. 2013;41:537–41.
54. 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;94:185–7.
55. Gateau C, Couturier J, Coia J, Barbut F. How to: diagnose infection caused by Clostridium difficile. Clin Microbiol Infect. 2018; in press.
56. Crobach MJT, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2016;22(Suppl 4):S63–81.
57. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald L, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and in the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431–55.
58. Planche T, Wilcox MH. Diagnostic pitfalls in Clostridium difficile infection. Infect Dis Clin N Am. 2015;29(1):63–82.
59. Planche TD, Davies KA, Coen PG, Finney JM, Monahan IM, Morris KA, et al. Differences in outcome according to Clostridium difficile testing method: a prospective multicentre diagnostic validation study of C. difficile infection. Lancet Infect Dis. 2013;13(11):936–45.
60. Bartlett JG. Clostridium difficile infection. Infect Dis Clin N Am. 2017;31(3):489–95.
61. Humphries RM, Uslan DZ, Rubin Z. Performance of Clostridium difficile toxin enzyme immunoassay and nucleic acid amplification tests stratified by patient disease severity. J Clin Microbiol. 2013;51(3):869–73.
62. Carman RJ, Wickham KN, Chen L, Lawrence AM, Boone JH, Wilkins TD, et al. Glutamate dehydrogenase is highly conserved among Clostridium difficile ribotypes. J Clin Microbiol. 2012;50(4):1425–6.
63. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults. JAMA. 2015;313(4):398–408.
64.• Polage CR, Gyorke CE, Kennedy MA, Leslie JL, Chin DL, Wang S, et al. Overdiagnosis of Clostridium difficile infection in the molecular test era. JAMA Intern Med. 2015;175(11):1792. **Important study used as justification to move away from nucleic acid testing for CDI.**
65. Rees WD, Steiner TS. Adaptive immune response to Clostridium difficile infection: a perspective for prevention and therapy. Eur J Immunol. 2018;00:1–9.
66. Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. N Engl J Med. 2017;376:305–17.
67. De Bruyne G, Saleh J, Workman D, et al. Defining the optimal formulation and schedule of a candidate toxoid vaccine against Clostridium difficile infection: a randomized phase 2 trial. Vaccine. 2016;34:2170–8.
68. Pfizer. Pfizer announces positive top-line results from phase 2 study of investigational clostridium difficile vaccine for the prevention of *C. difficile* infection. 2017. https://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_positive_top_line_results_from_phase_2_study_of_investigational_clostridium_difficile_vaccine_for_the_prevention_of_c_difficile_infection. Accessed 16 Feb 2017.
69. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. N Engl J Med. 2000;342:390–7.
70. Zhang K, Zhao S, Wang Y, Zhu X, Shen H, Chen Y, et al. The non-toxigenic Clostridium difficile strain CD37 protects mice against infection with a B1/NAP1/027 type of C. difficile strain. Anaerobe. 2015;36:49–52.
71. Nagaro KJ, Phillips ST, Cheknis AK, et al. Nontoxigenic Clostridium difficile protects hamsters against challenge with historic and epidemic strains of toxigenic B1/NAP1/027 C. difficile. Animicrob Agents Chemother. 2013;57:5266–70.
72. Merrigan MM, Sambol SP, Johnson S, Gerding DN. New approach to the management of Clostridium difficile infection: colonization with non-toxigenic C. difficile during daily ampicillin or ceftriaxone administration. Int J Antimicrob Agents. 2009;33(suppl 1):s46–50.
73. Villano SA, Seiberling M, Tatarowicz W, Monnot-Chase E, Gerding DN. Evaluation of an oral suspension of VP20621, spores of a nontoxigenic Clostridium difficile strain M3, in healthy subjects. Animicrob Agents Chemother. 2012;56:5224–9.
74. Goldenberg JZ, Yap C, Lytvyn L, Lo CKF, Beardsley J, Mertz D, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Systemat Rev. 2017;12:CD006095.
75. Evans CT, Johnson S. Prevention of Clostridium difficile infection with probiotics. Clin Infect Dis. 2015;60(suppl_2):S122–8.
76. Khanna S, Pardi DS, Kelly CR, Kraft CS, Dhere T, Henn MR, et al. A novel microbiome therapeutic increases gut microbial diversity and prevents recurrent Clostridium difficile infection. J Infect Dis. 2016;214:173–81.
77. Ott SJ, Waetzig GH, Rehman A, Moltzau-Anderson J, Bharti R, Grasis JA, et al. Efficacy of sterile fecal filtrate transfer for treating patients with Clostridium difficile infection. Gastroenterology. 2017;152:799–811.e7.
78. Nale JY, Spencer J, Hargreaves KR, Buckley AM, Trzepiński P, Douce GR, et al. Bacteriophage combinations significantly reduce Clostridium difficile growth in vitro and proliferation in vivo. Antimicrob Agents Chemother. 2016;60:968–81.