Measures to Control and Prevent *Clostridium difficile* Infection

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Control of *Clostridium difficile* infection (CDI) outbreaks in health care facilities presents significant challenges to infection control specialists and other health care workers. *C. difficile* spores survive routine environmental cleaning with detergents and hand hygiene with alcohol-based gels. Enhanced cleaning of all potentially contaminated surfaces with 10% sodium hypochlorite reduces the environmental burden of *C. difficile,* and use of barrier precautions reduces *C. difficile* transmission. Thorough handwashing with chlorhexidine or with soap and water has been shown to be effective in removing *C. difficile* spores from hands. Achieving high-level compliance with these measures is a major challenge for infection control programs. Good antimicrobial stewardship complements infection control efforts and environmental interventions to provide a comprehensive strategy to prevent and control outbreaks of CDI. The efficacy of metronidazole or vancomycin prophylaxis to prevent CDI in patients who are receiving other antimicrobials is unproven, and treatment with these agents is ineffective against *C. difficile* in asymptomatic carriers.

Clostridium difficile infection (CDI) rates in the United States have tripled from 2000 to 2005, and disease morbidity and mortality have increased, particularly among elderly persons. Clearly, there is a need for more-effective infection control and prevention measures to reduce CDI incidence and disease severity. Infection control measures for *C. difficile* involve 2 major approaches: preventing ingestion of the organism and its spores by patients and reducing the chance of developing CDI in the event of such ingestion. Strategies to achieve the former approach consist of traditional infection control strategies that target the environment, personnel hygiene, and barrier methods, whereas strategies for reducing disease are mainly focused on minimizing or eliminating antimicrobial exposure, particularly when use of these agents is unnecessary. The latter approach is often termed "good antimicrobial stewardship."

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ENVIRONMENTAL CONTROL, PERSONNEL HYGIENE, AND BARRIER METHODS

All hospitals should actively monitor the severity and rate of hospital-acquired CDI as part of their infection control programs, so they can determine whether the rate is acceptable and quickly detect any increases in the CDI incidence, CDI-associated mortality rate, and colectomy rate. Comparison of rates within a hospital to rates at other hospitals for benchmarking is complicated by the variety of measures used to monitor CDI "rates," including laboratory findings (i.e., positive results of *C. difficile* toxin tests), *International Classification of Diseases, Ninth Revision* codes for CDI, and laboratory findings combined with clinical symptoms (i.e., positive results of a *C. difficile* toxin test in conjunction with defined clinical symptoms), which is the most accurate method. Even when prospective surveillance is done, different case definitions and denominators are often used, making the creation of case comparators impossible. Two interventions have been shown to be effective at interrupting disease transmission during CDI outbreaks: disinfection with hypo-

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chlorite to minimize environmental contamination, and use of effective barrier precautions (particularly gloves) during patient contact to prevent transmission.

Environmental disinfection and hand hygiene. Patients housed in rooms previously occupied by patients with a drug-resistant organism have been shown to be at risk for acquiring drug-resistant organisms. This demonstrates that the environment is a critical source of contamination and that it enhances the potential for the spread of infection [1]. The environment is even more important for spore-forming organisms such as *C. difficile* that are capable of persisting on hard surfaces for prolonged periods [2]. Because *C. difficile* is shed in feces, any surface or device that becomes contaminated with feces can serve as a reservoir for *C. difficile* spores [3–5]. *C. difficile* spores resist desiccation for months and can persist on hard surfaces for as long as 5 months [2, 6, 7]. In hospital wards and intensive care units, *C. difficile* contamination has been found on 49% of sites in rooms occupied by patients with CDI and on 29% of sites in rooms occupied by asymptomatic carriers [8, 9]. The heaviest contamination is found on floors and bedrails; other sites frequently found to be contaminated include windowsills, commodes, toilets, bedsheets, call buttons, scales, blood pressure cuffs, electronic thermometers, flow-control devices for intravenous catheters, and feeding tube equipment [4, 6, 8, 9].

The importance of environmental contamination cannot be sufficiently emphasized, because it has been shown that as levels of environmental contamination increase, so does the prevalence of *C. difficile* hand carriage among health care workers [9]. Thus, the health care worker becomes an important vector for transmission of *C. difficile* to patients [3–5, 8].

Commonly used hospital cleaning agents, such as quaternary ammonium–based (and other surfactant-based) detergents, are not sporicidal and may in fact encourage sporulation [7, 10–12]. In addition, the BI/NAP1 (restriction-endonuclease analysis group BI/North American PFGE type 1) epidemic strain of *C. difficile* that is plaguing many facilities in North America and parts of Europe is known to hypersporulate, unlike non-outbreak strains [11, 12]. Hypersporulation has been shown to be a virulence-associated characteristic of other "outbreak" strains of *C. difficile* [11]. Fecal soiling of the environment is likely to occur for patients with CDI, and spore forms predominate after the disease-associated strains are exposed to air (which vegetative *C. difficile* does not tolerate) [13]. Although a variety of cleaning agents are effective in killing vegetative forms of *C. difficile,* only chlorine-based disinfectants and high-concentration, vaporized hydrogen peroxide are sporicidal [14, 15]. Because published data are lacking for several expensive, proprietary, commercially available combination products with sporicidal claims (i.e., products containing chlorine plus surfactant detergent), careful attention should be paid when selecting hospital cleaning agents, if the intention is to impact rates of CDI transmission [12].

Disinfection with a 1:10 dilution of concentrated sodium hypochlorite (i.e., bleach) has been shown to be effective in reducing environmental contamination in patient rooms and in reducing CDI rates in hospital units where the rate of CDI is high [10, 16–18]. In a study with a ward crossover design, Wilcox et al. [17] observed that a significant reduction ($P<.05$) in the rate of CDI was correlated with the use of a hypochlorite-based disinfectant, rather with the use of a detergent-based solution. Mayfield et al. [10] evaluated the effectiveness of 10% sodium hypochlorite, mixed fresh daily, versus that of a quaternary ammonium–based solution in rooms of patients with a positive result of a *C. difficile* toxin test. In units where CDI rates were high (defined as >3 cases per 1000 patient-days), use of sodium hypochlorite resulted in a substantial reduction in the rate of CDI. Of interest, when the protocol was reversed and quaternary ammonium–based cleaning agents were reintroduced to those units, rates returned to the high baseline level of 8.1 cases per 1000 patient-days [10]. A few years later at the same institution, the rate of CDI increased from 3.9 cases per 1000 patient-days in 2001 to 5.8 cases per 1000 patient-days during the first 6 months of 2002 in the medical intensive care unit and from 6.7 to 8 cases per 1000 patient-days over the same period in the bone marrow transplantation unit [18]. This time, interventions included infection control (i.e., educating staff about isolation of patients, gowning, and gloving, as well as posting handwashing signs as reminders) and environmental interventions (i.e., daily cleaning and disinfection of patient rooms and staff lounge areas, including carpeted areas, with 10% sodium hypochlorite). In both units, a 50% reduction of CDI cases occurred and was sustained for the 12-month follow-up period. Of note, no changes in antimicrobial use or policy occurred during the intervention and follow-up period.

Sodium hypochlorite at higher concentrations (including 10% solutions) is malodorous, can cause corrosion and pitting on equipment and other inanimate surfaces over the long term, and may trigger respiratory difficulties, especially in the workers doing the cleaning. It is appealing to avoid or limit the use bleach when possible. Fortunately, use of bleach only in the rooms of patients with CDI has been effective in reducing CDI rates [10]. The use of bleach is recommended by the Centers for Disease Control and Prevention (CDC) during outbreaks of CDI [3]. From an environmental control perspective, it is important not only to consider a sporicidal cleaning agent but also to adequately clean surfaces that commonly harbor *C. difficile* spores (e.g., bedrails, call buttons, telephones, and floors). Because of unfortunate staffing deficiencies faced by some hospitals today, workers from the environmental services department may, unbeknownst to the practicing clinician, hos-

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pital epidemiologist, and infection control practitioner, mistakenly alter vitally important cleaning practices. Failure to clean frequently touched surfaces with the appropriate cleaning agent may lead to increased transmission within an institution. During an outbreak or even as a preventive measure, multidisciplinary discussions that include leaders from the hospitals' environmental services department should take place to determine what cleaning products are being used, what surfaces are being cleaned, and how often cleaning is performed.

As mentioned above, it has been shown that as the environmental burden of *C. difficile* increases, so does the prevalence of *C. difficile* hand carriage among health care workers [9]. Thus, it is important to not only consider environmental interventions but also to simultaneously evaluate adherence to good hand hygiene practices. Alcohol-based hand sanitizers are highly effective against non–spore-forming organisms, but they do not kill *C. difficile* spores or remove *C. difficile* from the hands [7, 19]. A recent study found that the reduction in spore counts after applying any of 3 alcohol-based hand gels was significantly lower than after handwashing with chlorhexidine gluconate ($P < .009$). A mean of 30% of the inoculum of *C. difficile* spores remaining on contaminated hands after the use of alcohol-based gel was transferred to a second volunteer by handshaking [20]. A recent study at a US hospital found that, although there was a progressive increase from 10% to 85% in the use of alcohol-based hand rubs over a 3-year period ($P < .001$), there was no evidence of an increase in the incidence of CDI [21]. This finding suggests that routine hand hygiene with an alcohol-based hand rub before and after patient contact does not increase the risk of CDI during a nonoutbreak period. Acquisition of CDI is multifactorial, and the results of this study are not surprising. Compliance with hand hygiene practices has dramatically improved since the introduction of alcohol-based hand sanitizers, which effectively decontaminate health care workers' hands by eliminating non–spore-forming bacteria. For this reason, use of alcohol-based hand rubs should be widely promoted. However, it is well-known that *C. difficile* spores are not killed by alcohol, and the most effective way to remove them from hands is through handwashing. Therefore, when caring for patients with CDI in an outbreak situation, caregivers and family members alike should perform hand hygiene with soap and water rather than with alcohol-based sanitizers, a practice that is also recommended by the CDC [3]. Clearly, glove use is the precaution proven to be most effective in preventing the transmission of *C. difficile* during care of a patient with CDI [22]. After removal of gloves worn during care of patients with CDI, we prefer handwashing with soap and water. Although the efficacy of gown use during routine care of patients with CDI has not been adequately studied, intuition suggests that it is a viable precaution, because it prevents contamination of clothing. The CDC recommends that gowns be used during the care of patients with CDI.

Because patients are often discharged during the course of therapy for CDI, the principles discussed to this point should apply to the home and other venues to which patients are discharged, especially long-term care or rehabilitation facilities where other susceptible patients may reside. Fortunately, the risk of environmental contamination is markedly reduced once diarrhea has stopped. Additionally, the likelihood that other household inhabitants are taking antimicrobials—a major risk factor for CDI—is low. Although it may be more difficult to implement in the home, cleaning bathroom surfaces with diluted hypochlorite and washing hands with soap and water may help reduce the likelihood of recurrent disease as a result of reinfection of the patient.

Additional measures. Although randomized trials are lacking, endoscopes and other reusable devices must be disinfected; disinfection should follow the manufacturer's recommendations and usually involves alkaline glutaraldehyde or ethylene oxide, both of which are sporicidal [23]. Switching from reusable rectal thermometers or electronic thermometers with disposable sheaths to single-use disposable thermometers has been shown to considerably decrease the incidence of CDI [4]. Other common equipment, such as stethoscopes, bed scales, intravenous equipment (i.e., the pole assembly), and pumps, should be cleaned after use or dedicated to individual patients when possible. With regard to contact precautions, use of gloves when providing care to patients with CDI and handling their bodily substances has been shown to significantly reduce the rate of CDI [22]. Although gown use has not been definitively shown to reduce CDI rates, it is recommended as part of contact precautions [4, 7, 23].

Prompt identification of patients with symptomatic CDI is essential so that isolation precautions can be put into effect and treatment can be initiated, thus decreasing the environmental bioburden associated with diarrhea. One strategy that has been implemented to decrease the time to recognition of CDI is to allow nurses to order *C. difficile* toxin testing. Additional electronic alerts can be generated that communicate *C. difficile* positivity and the need for barrier precautions. Whenever possible, patients with known or suspected CDI should be placed in a private room to prevent transmission. If private rooms are not available, patients with CDI should be cohorted [24]. In one study, patients who were roommates or neighbors of a patient with CDI, as well as patients who were housed in a room previously occupied by a patient with CDI, had a 12% attributable risk of nosocomial acquisition of CDI [25]. The CDC also recommends that equipment be dedicated to individual patients when possible and that all contact precautions be continued until the cessation of diarrhea [3].

Comprehensive strategy for CDI outbreaks. An overall

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treatment-team approach may improve treatment outcome and reduce mortality and the frequency of colectomy in severe hospital outbreaks of CDI. During an outbreak in Pittsburgh, Pennsylvania, control measures included implementation of an educational program and measures to facilitate rapid identification and isolation of patients with CDI, use of verbal and electronic alerts that specify the patients with suspected disease as well as the type of isolation precautions (i.e., cohorting vs. placing patients in private rooms) and contact precautions (i.e., donning gowns and gloves and performing hand hygiene before and after all patient or environmental contact), insertion of an isolation code in the electronic medical records of patients to prevent placement of patients with and patients without suspected CDI in the same room, and enhanced disinfection with hypochlorite. In the Pittsburgh outbreak, the duration of patient isolation was extended from beyond the time of diarrhea resolution to the time of hospital discharge [19]. This was likely an optimal approach, because asymptomatic patients with *C. difficile* continue to shed the organism into the environment, albeit at a much lower rate than patients with diarrhea. Perhaps this precaution is more important when strains are hypersporulators. Unfortunately, in many institutions, including the University of Pittsburgh, patient census is high, and there are simply not enough private rooms in which to isolate all patients with suspected CDI. Under these conditions, it becomes imperative to appropriately cohort patients to ensure that isolation precautions are accommodated. Cessation of isolation precautions 2 days after diarrhea stops has been suggested as an alternative method. The CDC still recommends removal of isolation and contact precautions when patients return to "their normal stooling pattern" [3].

In the Pittsburgh outbreak, traditional infection control measures were initially thought to be ineffective in limiting the spread of CDI, because compliance with infection control measures was imperfect (62% of caregivers were compliant with the hand hygiene protocol, and 60% used appropriate garb during contact with patients under isolation precautions) and because effective environmental cleaning was lacking [19]. Use of alcohol-based hand sanitizers was introduced at this hospital 7 months after the start of the outbreak and therefore could not have been initially associated with the increased CDI rates. Further analysis found that the rate of nosocomial CDI was reduced by 50% via implementation of infection control measures alone. Use of a new case definition that expanded the number of CDI cases considered to be hospital acquired was responsible for the perceived increase in the CDI rate [19].

ANTIMICROBIAL STEWARDSHIP

To complement specific environmental and infection control interventions, investment in programmatic strategies to enhance antimicrobial stewardship is optimal to supplement the other multifaceted interventions. Antimicrobial stewardship, as well as antimicrobial-associated risk factors, are addressed in detail in an accompanying article in this supplement [26]. For institutions interested in developing and implementing an antimicrobial stewardship program, joint guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have recently been published to assist with this project [27]. Some of the best examples of the effect of selective management and control of antimicrobial use, particularly for clindamycin and second- and third-generation cephalosporins, have involved the incidence of CDI [28–31]. Programmatic approaches to optimize antimicrobial use can be viewed as a function of augmenting patient safety. An antimicrobial stewardship program in concert with the activities of infection control practitioners, a hospital epidemiologist, and members of the environmental services department provide a multifaceted method to address the prevention of CDI during outbreaks and periods of endemicity.

CDI prophylaxis. In an attempt to prevent the development of CDI, some clinicians administer metronidazole or oral vancomycin prophylactically to patients without diarrhea and/or signs of CDI who are receiving antimicrobial therapy for an underlying infection [7]. However, for all patients, exposure to any antimicrobial increases the risk for CDI, and for patients with established *C. difficile* infection, antimicrobial exposure increases the likelihood of future relapse [32]. Prophylaxis in this situation is illogical because use of vancomycin or metronidazole may cause harm by increasing the patient's risk for CDI and because use of vancomycin has the potential to promote the development of vancomycin resistance in other bacteria [6, 7, 33].

Treatment of carriers. Asymptomatic carriers do not have a higher risk than noncarriers of developing CDI, and colonization paradoxically has a protective effect and is associated with a decreased risk of CDI [34–36]. However, asymptomatic carriers of *C. difficile* constitute a potential source of nosocomial transmission [8, 34, 37]. Four studies evaluated whether treatment of asymptomatic carriers would control the spread of CDI [33, 38–41]. Only 1 prospective study in a leukemia unit showed that the frequency of CDI was reduced (from 16.6% to 3.6%) after treatment of all symptomatic and asymptomatic *C. difficile* carriers with vancomycin, which occurred after renovation and decontamination of the environment [38]. Two other uncontrolled studies found that treatment of asymptomatic *C. difficile* carriers did not reduce the frequency of CDI [33, 39, 40]. In the only randomized, placebo-controlled study among these 4 investigations, 30 patients excreting *C. difficile* without diarrhea or abdominal symptoms were randomized to receive oral vancomycin (125 mg 4 times per day), oral metronidazole (500 mg 2 times per day), or placebo (3 times per day) for 10 days [41]. Immediately after the completion of

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therapy, rates of *C. difficile* carriage were 10% in the vancomycin group, 70% in the metronidazole group, and 80% in the placebo group. However, in the vancomycin group, elimination of *C. difficile* carriage was temporary: of 9 patients with stool specimens negative for *C. difficile* at the end of therapy, excretion recurred in 8 a mean duration ($\pm$SD) of 20 $\pm$ 8 days after completion of the treatment regimen [41]. At the end of the 2-month follow-up period, 6 of 9 patients treated with vancomycin remained culture positive for *C. difficile,* compared with only 2 of 10 patients who received placebo ($P < .05$) [41]. In addition, 1 asymptomatic patient treated with vancomycin who was originally colonized with a nontoxigenic *C. difficile* strain became reinfected with a toxigenic strain and developed CDI. On the basis of the limited evidence provided by these trials, treatment of asymptomatic carriers of *C. difficile* is not warranted.

OTHER MANAGEMENT ISSUES

Gastric-acid suppression. Fordtran [6] characterized acidic gastric juice as "nature's disinfectant" for the gastrointestinal tract because it kills vegetative forms of *C. difficile* and other pathogens, such as *Salmonella* species, *Shigella* species, and *Vibrio cholerae* [42]. Consequently, reduction of gastric acid secretion because of clinical conditions, such as atrophic gastritis, which is common in elderly individuals, and during treatment with proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (HRAs) enables ingested pathogens to survive and reach the intestinal tract, which increases the risk of infection [6]. Many patients who enter the hospital are already taking PPIs, and these are the preferred agents for stress ulcer prophylaxis for virtually all patients admitted to intensive care units [6]. The steady increase in the use of PPIs has coincided with an increase in the incidence of CDI [43]. At a hospital in Canada, nearly 50% of patients receiving antimicrobials were also receiving a PPI, and 10% were receiving HRAs [43]. However, the increased use of PPIs was apparent several years before the now widely reported increased incidence of CDI was observed. There is concern regarding the overuse of acid-suppressive therapy in hospitalized patients, and a recent study found that prescriptions for PPIs and HRAs, mainly for stress ulcer prophylaxis, were inappropriate in 68% of hospitalized patients. In addition, 56% of patients for whom prophylactic treatment was considered unnecessary were discharged receiving therapy, and 46% were still using acid-suppressive agents 3 months later [44]. *C. difficile* spores, however, are resistant to acid and are thought to be able to pass through the normally acidic gastric environment unscathed. Whether use of these agents increases the risk for CDI remains controversial, with some reports showing an increased risk [43, 45, 46] and others showing no added risk [47–49].

Feeding tube use. A prospective cohort study of 76 consecutive hospitalized patients who were and 76 who were not using a feeding tube found that tube feeding was an independent risk factor for the acquisition of CDI (OR, 3.1; 95% CI, 1.1–8.7; $P = .03$) [50]. The investigators suggested that tube-fed patients may have acquired *C. difficile* from the hands of health care workers during routine handling of the feeding tube system; that formulas and delivery systems might have been contaminated with *C. difficile;* that formulas might have lacked dietary fiber, resulting an intestinal environment favorable to the growth of *C. difficile;* and that delivery of formulas below the gastric acid barrier might have promoted the introduction and survival of *C. difficile* [50]. Although the composition of formula is not readily modifiable, glove use by health care workers during handling of feeding tube systems may reduce the CDI risk; however, no studies are available to confirm the efficacy of such a precaution.

CONCLUSION

Control of CDI outbreaks presents substantial challenges to hospital infectious diseases specialists, epidemiologists, infection control practitioners, frontline clinicians, environmental services departments, and hospital administrators, as well as to patients and their families. Effective measures are available to reduce environmental contamination with *C. difficile* and to prevent the spread of this pathogen by workers and equipment. However, compliance with enhanced environmental cleaning and contact precautions must be closely monitored if these measures are to have an impact during outbreaks of CDI. Programmatic approaches to enhance antimicrobial stewardship are part of the multifaceted interventions to prevent CDI. Close collaboration among the aforementioned individuals and departments is necessary to combat the escalating challenges provided by *C. difficile*. Education of all personnel involved in the care of patients with CDI is essential.

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