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SUPPLEMENT ARTICLE

Prevention of Healthcare-Associated *Clostridium difficile* Infection: What Works?

Erik R. Dubberke, MD, MSPH

Prevention of *Clostridium difficile* infection has become extremely important because of increases in its incidence and severity. Unfortunately, efforts at *C. difficile* infection prevention are hampered by lack of data to support optimal prevention methods, especially for endemic *C. difficile* infection. Studies are needed to define the optimal prevention practices and to investigate novel prevention methods.

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Increases in the incidence and severity of *Clostridium difficile* infection (CDI) have highlighted the need for proven methods to prevent CDI. Unfortunately, the current state of literature on CDI prevention is limited. There continue to be many unanswered questions about how to best prevent CDI. Most data come from single centers where multiple interventions are conducted in response to a CDI outbreak. These bundled interventions in response to outbreaks can lead to significant biases in the interpretation of the results and make it difficult to know which interventions were truly effective. In addition, some interventions that may prevent CDI in settings where there is an outbreak appear to be less efficacious in settings where it is endemic. The recent changes in CDI epidemiology indicate the need for more-effective methods to prevent CDI in both situations. Despite the many unknowns regarding optimal methods for CDI prevention, the increases in CDI incidence and severity require that all acute care facilities must have a CDI prevention program.

There are several key components to a successful CDI prevention program.¹ There must be good communication between all healthcare workers who play a role in CDI prevention and treatment, so that patients with CDI can be identified rapidly for initiation of infection prevention measures and CDI-specific treatment. Healthcare workers who play a role in the prevention and treatment of CDI include infection prevention specialists, hospital epidemiologists, physicians, nurses, laboratory personnel, housekeeping staff, pharmacy personnel, and hospital administrators.¹ These individuals all must know what their responsibilities are and must be held accountable for their behavior, to ensure adherence to the hospital's CDI prevention policies and procedures. As the group responsible for directing the CDI prevention program, infection prevention and control specialists must be familiar with the limitations in the CDI prevention literature. This is

particularly important if the healthcare facility is experiencing a problem with CDI and it is necessary to determine which "special approaches" for preventing CDI will most likely be beneficial on the basis of local CDI epidemiology and healthcare worker adherence to CDI prevention measures.¹

WHAT WORKS

The Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals² grades all recommended practices to prevent healthcare-associated infections on the basis of the strength of the recommendation and the quality of evidence to support that recommendation (recommendations require a minimum strength of "B" to be included). There are 16 recommended practices in the *C. difficile* component of the Compendium.¹ Twelve of the practices have a grade of "B-III," or moderate strength of evidence to support the recommendation and evidence from opinions of respected authorities, clinical experience, or descriptive studies. Two practices have a grade of "B-II," or moderate strength of evidence to support the recommendation and evidence from nonrandomized trials, cohort or case-control studies, multiple time series, or dramatic results of uncontrolled experiments. There are only 2 practices with a strength of "A," or good evidence to support the recommendation. One has a grade of "A-II." The other is the only recommended practice to prevent CDI that has evidence from a randomized trial and therefore has a grade of "A-I."

The single recommended practice to prevent CDI that is graded "A-I" is to wear gloves when caring for a patient with CDI. A study conducted prior to the advent of universal and standard precautions randomized 4 wards with similar baseline rates of CDI to provide standard of care or to conduct an educational intervention.³ The intervention consisted of an educational campaign instructing nurses to wear gloves

when handling body fluids, especially stool. Boxes of gloves were placed at each patient's bedside on the intervention wards. There was a statistically significant decrease in CDI incidence on the intervention wards, from 7.7 to 1.5 cases per 1,000 patient-days ($P = .015$), and no significant change in CDI incidence on the control wards (from 5.7 to 4.2 cases per 1,000 patient-days). Point prevalence assessments of asymptomatic *C. difficile* carriage were conducted before and after the intervention. There was a statistically significant decrease in the proportion of patients colonized with *C. difficile* on the intervention wards (from 27% to 9% of patients; $P = .029$), but no significant difference on the control wards (from 17% to 10% of patients).

The recommended practice graded "A-II" is antimicrobial stewardship. There are 2 primary approaches to using antimicrobial stewardship to prevent CDI: restricting the use of a single antimicrobial associated with a high risk of CDI, and a more comprehensive approach focused on improving overall antimicrobial prescribing practices and reducing unnecessary antimicrobial exposures. Both approaches have been successful during outbreaks, and improved antimicrobial prescribing practices have been successful at decreasing the number of cases in settings where CDI is endemic, as well.⁴⁻⁶

CDI PREVENTION AND BUNDLES

The current trend to apply recommended practices for healthcare-associated infection prevention is the "bundle approach." The Keystone ICU Project demonstrated that an easy-to-follow "bundle" of recommended practices can result in dramatic decreases in the number of catheter-associated bloodstream infections occurring in intensive care units.⁷ All 5 of the evidence-based practices selected for the bundle had a "I-A" level of supporting evidence (the grading criteria used in the 2002 Guidelines for the Prevention of Intravascular Catheter-Related Infections and in the 2008 Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals are similar but not identical) and have low barriers to implementation.^{7,8} In addition, the bundle used for the Keystone ICU Project had previously been demonstrated to be successful in multiple healthcare settings.^{9,10} In contrast, there are no existing validated bundles for the prevention of CDI, the only recommendation graded "A-I" (to wear gloves when handling feces) is already the standard of care, and the other recommended CDI prevention practices can be difficult to implement and monitor. In addition, because of the low quality of evidence to support most CDI prevention practices, the costs of implementing and maintaining a recommendation that may have minimal impact on CDI prevention must be considered when designing a bundle of CDI-related prevention practices.

A less formal bundle approach individualized to a healthcare facility can be a helpful tool as part of a CDI prevention program; the bundle can be used to remind healthcare workers of their role in CDI prevention. Abbett et al.¹¹ created a

bundle in response to an increase in CDI incidence and severity at their facility, which primarily reinforced adherence to existing policies. After the education of healthcare staff on their role in preventing CDI and the provision of visual reminders, the CDI incidence decreased from 1.10 to 0.66 cases per 1,000 patient-days ($P < .001$). No data were collected on compliance with components of the bundle before or after the intervention, so it is unclear which component of the bundle may have had the greatest impact. However, there was a significant increase in the number of stool specimens sent to the laboratory for *C. difficile* testing after the intervention, despite the decrease in the number of patients who received a diagnosis of CDI, suggesting that more-rapid case finding and initiation of CDI prevention practices that occur after a patient receives a diagnosis of CDI contributed to a decrease in CDI incidence.

HOW LOW IS LOW ENOUGH?

As previously stated, most data on CDI prevention come from outbreaks. When studied, many of the recommended practices to prevent CDI during outbreaks appear less effective in settings of endemicity.^{12,13} The lack of knowledge on how to further decrease CDI incidence in settings of endemicity is stressed in the current draft of the "Action Plan to Prevent Healthcare-Associated Infections" by the US Department of Health and Human Services; it states that the "preventability of endemic CDI is unknown."^{14(p14)} Therefore, we must consider whether new approaches to CDI prevention are needed. Two areas that need to be investigated further are whether there are unrecognized sources of *C. difficile* transmission or whether there are additional methods that can prevent CDI before the onset of symptoms.

There may be unrecognized sources of *C. difficile* transmission in the hospital and community. Several recent publications have found *C. difficile* contamination of food.¹⁵ *C. difficile* can also contaminate hospital linens.¹⁶ Contaminated linens can then serve as a vector to contaminate other linens during the laundering process.¹⁷ Although past studies have found that the major source of *C. difficile* transmission is from patients with symptomatic CDI, *C. difficile* can be transmitted from asymptomatic carriers.¹⁸ Unfortunately, there are no validated methods to detect asymptomatic *C. difficile* carriers, and existing data indicate that currently available methods are not sufficiently sensitive or specific for the rapid detection of asymptomatic *C. difficile* carriers.¹⁹ Unrecognized sources of *C. difficile* transmission and methods to prevent transmission from these sources need to be investigated.

Most efforts to prevent CDI occur after a patient develops symptomatic infection. Prevention of CDI in settings of endemicity may require emphasis on early prevention efforts—that is, before the onset of CDI. One method being investigated is to identify patients at high risk for CDI through a risk prediction model.²⁰ Interventions could then be designed

to decrease the risk in patients identified as high risk for CDI. Another approach being investigated is the administration of nontoxigenic *C. difficile* to protect against colonization by toxigenic *C. difficile*, thus preventing CDI. In animal models, administration of nontoxigenic *C. difficile* prior to challenge with toxigenic *C. difficile* has been shown to be effective at prevention of both an initial episode of CDI and recurrence of CDI.²¹ A third area that holds promise is immunotherapy. Patients asymptomatically colonized with *C. difficile* have higher titers of antibodies against *C. difficile*, patients who develop an anamnestic antibody after *C. difficile* acquisition are at lower risk to develop CDI, and patients who fail to produce antibodies against *C. difficile* after an episode of CDI are at increased risk for developing recurrent episodes.^{22,23} A recently published phase II trial evaluating anti-*C. difficile* toxin monoclonal antibodies as adjunctive treatment for CDI in addition to standard-of-care antibiotic treatment (with metronidazole or vancomycin) demonstrated that patients who received the monoclonal antibodies were significantly less likely to have a recurrent episode of CDI, compared with patients who received placebo (7% vs 25%; $P < .001$).²⁴ It is unlikely that a biological agent, such as monoclonal antibodies, will be used as primary prophylaxis, because of the typically high cost of such products. However, the results of the trial suggest that CDI may at some point be added to the list of vaccine-preventable diseases.²⁵

CONCLUSION

Currently, CDI prevention efforts are hampered by a lack of high quality data to support most recommended prevention practices, with only 2 practices that have good evidence to support them (wearing gloves and antimicrobial stewardship). This makes the role of infection prevention and control even more important when designing a CDI prevention program or CDI bundles of CDI-related prevention practices, as infection prevention and control must determine which prevention practices to apply on the basis of local patient care practices and CDI epidemiology. Currently, recommended practices appear to be most effective when instituted in response to a CDI outbreak, and the best methods to prevent CDI in settings of endemicity are not known. More research is needed to identify all sources of *C. difficile* transmission and novel CDI prevention practices in order to significantly decrease rates of CDI in hospitals across the United States.

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