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

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Abstract

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

Introduction

Increases in *Clostridium difficile* infection (CDI) incidence and severity have highlighted the need for proven methods to prevent CDI. Unfortunately the current state of CDI prevention literature is limited. There continues to be many unanswered questions on 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 makes it difficult to know which intervention/s was/were truly effective. In addition, some interventions that may prevent CDI in outbreak settings appear to be less efficacious in endemic settings. The recent changes in CDI epidemiology indicate the need for more effective methods to prevent CDI in both outbreak and endemic settings. Despite the many unknowns regarding optimal methods for CDI prevention, the increases in CDI incidence and severity require all acute care facilities to 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 patients with CDI can be identified rapidly for initiation of infection prevention measures and CDI specific treatment. Healthcare workers that play a role in the prevention and treatment of CDI include Infection Prevention Specialists, Hospital Epidemiologists, physicians, nurses, laboratory personnel, housekeeping, pharmacy and the hospital administration (1). These individuals must all know what their responsibilities are and 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 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 based on the local CDI epidemiology and healthcare worker adherence to CDI prevention measures (1).

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What Works

The Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals grades all recommended practices to prevent healthcare-associated infections based on the strength of the recommendation and quality of evidence to support that recommendation (recommendations required a minimum strength of "B" to be included). There are sixteen recommended practices in the *C. difficile* component of the Compendium (1). Twelve of the practices have a grade of "BIII," or moderate evidence to support the recommendation and evidence from opinions of respected authorities, clinical experience, or descriptive studies. Two practices have a grade of "BII," or moderate evidence to support and evidence from non-randomized trials, cohort or case-control studies, multiple time series, or dramatic result from uncontrolled experiment. There are only two practices with a strength of "A," or good evidence to support. One has a grade of "AII" The other is the only recommended practice to prevent CDI that has evidence from a randomized trial and therefore has a grade of "AI."

The single "AI" recommended practice to prevent CDI is to wear gloves when caring for a patient with CDI. A study conducted prior to the advent of universal/standard precautions randomized four wards with similar baseline CDI rates to standard of care or an educational intervention (2). The intervention consisted of an educational campaign instructing nurses to wear gloves when handling body fluids, especially stool. Boxes of gloves were also placed at each patient's bedside on the intervention wards. There was a statistically significant reduction in CDI incidence from 7.7 cases / 1,000 patient days to 1.5 cases / 1,000 patient days ($p = 0.015$), and no change in CDI incidence on the control wards (5.7 vs. 4.2 / 1,000 patient days). Point prevalence assessments of asymptomatic *C. difficile* carriage were conducted before and after the intervention. There was a statistically significant reduction in the proportion of patients colonized with *C. difficile* on the intervention wards (27% vs. 9%, $p = 0.029$) but no difference on the control wards (17% vs. 10%).

The "AII" recommended practice is antimicrobial stewardship. There are two primary approaches for using antimicrobial stewardship to prevent CDI: restricting 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 in outbreak settings, and improved antimicrobial prescribing practices has been successful at reducing CDI in endemic settings as well (3-5).

CDI Prevention and Bundles

The current trend to apply recommended healthcare-associated infection prevention practices is the "bundle approach." The Keystone ICU Project demonstrated that an easy to follow "bundle" of recommended practices can result in dramatic reductions in catheter-associated bloodstream infections in intensive care units (6). All five of the evidence-based practices selected for the bundle all had an "IA" level of supporting evidence (grading criteria used for the 2002 Guidelines for the Prevention of Intravascular Catheter-Related Infections and 2008 Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals are similar, but not identical), and have low barriers to implement (6;7). In addition, the bundle used for the Keystone ICU Project had previously been demonstrated to be successful in multiple healthcare settings (8;9). In contrast, there are no existing validated bundles for the prevention of CDI, the only "AI" level recommendation (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 CDI bundle.

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 created a CDI bundle in response to an increase in CDI incidence and severity at their facility, which primarily reinforced adherence to existing policies (10). After educating healthcare staff on their roles in preventing CDI and providing visual reminders, the CDI incidence decreased from 1.10 to 0.66 CDI cases / 1,000 patient days ($p<0.001$). 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 for *C. difficile* testing after the intervention despite the reduction in the number of patients diagnosed with CDI, suggesting more rapid case finding and initiation of CDI prevention practices that occur after a patient is diagnosed with CDI contributed to the reduction in CDI.

How Low is Low Enough?

As previously stated, most data on CDI prevention comes from outbreak settings. When studied, many of the recommended practices to prevent CDI in outbreak settings appear less effective in endemic settings (11;12). The lack of knowledge on how to further reduce CDI in endemic settings is stressed in the current draft of the HHS Action Plan to Prevent Healthcare-Associated Infections as it states the “preventability of endemic CDI is unknown.” 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 if 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 (13). *C. difficile* can also contaminate hospital linens (14). Contaminated linens can then serve as a vector to contaminate other linens during the laundering process (15). Although past studies have found the major source of *C. difficile* transmission is from patients with symptomatic CDI, *C. difficile* can be transmitted from asymptomatic carriers (16). Unfortunately there are no validated methods to detect asymptomatic *C. difficile* carriers, and existing data indicate currently available methods are not sufficiently sensitive or specific for the rapid detection of asymptomatic *C. difficile* carriers (17). 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 endemic settings may require emphasizing prevention efforts earlier, 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 (18). Interventions could then be designed to reduce the risk in patients identified as high risk for CDI. Another approach being investigated is the administration of non-toxigenic *C. difficile* to protect against colonization by toxigenic *C. difficile*, thus preventing CDI. Administration of non-toxigenic *C. difficile* prior to challenge with toxigenic *C. difficile* has been shown to be effective at preventing both an initial episode of CDI and CDI recurrences in animal models (19). 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 of CDI (20;21). A recently published phase II trial evaluating anti-*C. difficile* toxin monoclonal antibodies as adjunctive treatment for CDI in addition to standard of care antibiotics (metronidazole or vancomycin) demonstrated that patients who received the monoclonal antibodies were significantly less likely to develop a recurrent episode of CDI compared to patients who received placebo (7% vs. 25%, $p<0.001$) (22). It is unlikely a biological agent such as monoclonal antibodies will be used as primary prophylaxis due to the typical 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 (23).

Conclusion

Currently CDI prevention efforts are hampered by a lack of high quality data to support most recommended prevention practices, with only two 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, as Infection Prevention and Control must determine which prevention practices to apply based on 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 endemic settings are not known. More research is needed to identify all sources of *C. difficile* transmission and novel CDI prevention practices in order to significantly reduce rates of CDI in hospitals across the U.S.

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