

# The Effect of Bundled Interventions on Prevention of Hospital Acquired Clostridium Difficile Infection: An Integrative Review

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## Abstract

Hospitalized patients are at an increased risk for acquiring Clostridium Difficile Infection (CDI). Increased virulence of *C. difficile* strains and increased use of antimicrobials have led to an increase of CDI cases that are more difficult to treat (CDC, 2013). Proper hand hygiene techniques, room cleaning, and equipment cleaning are not consistently being followed by healthcare workers, leading to an increased spread of CDI between hospitalized patients. The purpose of this integrative review was to determine the best evidence-based methods to reduce hospital-acquired CDI rates. The evidence reviewed supports the implementation of a multifaceted approach including: (a) proper hand hygiene practices, (b) adequate and appropriate surface cleaning practices, (c) compliance to contact isolation procedures, and (d) strengthening of an existing antimicrobial stewardship committee to reduce hospital-acquired CDI rates.

**Keywords:** Clostridium difficile Infection (CDI); Hospital-acquired; *C. difficile*; Hand hygiene

## Introduction

Clostridium difficile infection (CDI) rates have steadily increased in hospitalized patients and have contributed to increased length of hospital stay, adverse patient outcomes, and increased health care costs [1]. CDI is the leading cause of antibiotic-associated diarrhea and is a highly problematic healthcare-associated infection (HAI) due to the difficulty in treating CDI and the risk of contamination [1]. According to the CDC, one of every 10-20 hospitalized patients in the United States develops a hospital-associated infection [2]. Approximately 13 of every 1,000 inpatients are either infected or colonized with *C. difficile* [2]. *C. difficile* is a gram-positive, anaerobic, spore-forming bacterium that causes a spectrum of disease severity. Severity of *C. difficile* illnesses ranges from mild infection, self-limiting diarrhea, serious diarrhea, pseudomembranous colitis, to life-threatening fulminant colitis; sometimes so severe the infection can lead to death [3]. The average total cost for a single inpatient CDI is more than \$35,000, and the estimated annual cost burden for the healthcare system exceeds \$3 billion [4].

*C. difficile* infection occurs by ingestion of spores as a result of contaminated patient environment, shared equipment, or via the hands of healthcare personnel [5]. *C. difficile* can be spread by touching surfaces contaminated with *C. difficile* or coming into contact with a CDI infected individual. The major risk factors for CDI are exposure to antibiotics, hospitalization, and advanced age [2]. Evidence suggests that the incubation period for *C. difficile* following ingestion of spores is 2-3 days, but patients remain at elevated risk for contracting CDI for 3 or more months after they have stopped antibiotic treatment [6]. In recent years, the epidemiology of CDI has changed dramatically, with increases in incidence and severity of cases being reported across the United States, Canada and Europe [7]. The change in epidemiology of CDI has been attributed to the emergence of a hyper-virulent epidemic strain of *C. difficile* [7].

The two most common reservoirs of *C. difficile* in the healthcare setting are infected humans (symptomatic or asymptomatic) and inanimate objects [8]. Patient care items such as electronic devices, thermometers, and contaminated commodes have been implicated in the transmission of CDI between hospitalized patients [2]. Many patient care activities can provide an opportunity for transmission of CDI. Some common activities performed in the hospital include sharing of electronic thermometers, oral care or oral suctioning with contaminated hands, administration of feedings or medication, emergency procedures, poor hand hygiene practices, sharing of patient care items without appropriate disinfectant, and ineffective environmental cleaning [8]. The chief risk factor for CDI is prior to exposure to antimicrobials [3]. In the hospital setting, the majority of cases are associated with

antibiotics. Nearly all antimicrobials have been associated with CDI [3]. CDI rates continue to increase due to increased number of carriers, increased virulence of CDI, inadequate hand hygiene of healthcare workers, improper cleansing of room and equipment, and increased use of antimicrobials. The purpose of this integrative review was to determine the best evidence-based methods to reduce hospital-acquired CDI rates.

## Methods

To obtain relevant evidence for the best practice intervention for *C. difficile* prevention, a computer-based search of five different databases was conducted. A hand search of reference lists, a review of expert practice recommendations and review of the World Health Organization (WHO) website was also performed. Searched databases included CINAHL, Medline via EBSCO Interface, ProQuest Nursing and Allied Health Source, Cochrane Collaboration and Library, Joanna Briggs Institute Evidence Based Practice, and National Guideline Clearinghouse. Searches were conducted for peer-reviewed literature published between the years 2011-2016 within CINAHL, Medline, ProQuest, Cochrane Library, and Joanna Briggs Institute using the below described subject headings. Searched key words included “Clostridium difficile prevention” AND “control” in CINAHL yielding 29 articles and in Medline yielding 55 articles. Searched key words included “*C. difficile*” AND “prevention” OR “control” in ProQuest yielding 65 articles. Searched key words included “Clostridium difficile” in Cochrane Library yielding 8 articles. Searched key words included “Clostridium difficile prevention” in Joanna Briggs Institute EBP Database yielding 25 articles. The results of this search are shown in Table 1.

Database	Results	Included Article(s)
CINAHL	29	3
Cochrane	8	0
JBI	25	0
Medline	55	0
ProQuest	65	2
Citation Chasing	2	1

**Table 1:** Database Search Results

Strict inclusion and exclusion criteria were developed to focus the search for relevant evidence. Inclusion criteria included the following: (a) published in a scholarly, peer-reviewed journal, (b) published after 2011, (c) printed in English language, and (d) included adult patients over the age of eighteen years of age. Exclusion criteria included: (a) exclusive outpatient treatment, (b) age less than 18 years of age, and (c) interventions not focused on bundled interventions. Search results from the databases were reviewed and all duplicate studies were eliminated. Each article abstract was reviewed. In addition, the WHO recommendations, the United States Preventative Task Force (USPSTF), and the National Guideline Clearinghouse were reviewed to ensure all relevant literature was included. Eighteen references were identified for potential inclusion and the full texts of the articles were printed and reviewed. Of the 18 articles, 6 were included in the final literature review based upon the inclusion and exclusion criteria. These articles were analyzed and critically appraised.

A hand search of reference lists resulted in two additional articles Search results from the databases were reviewed and all duplicate studies were eliminated. Each article abstract was reviewed. In addition, the WHO recommendations, the USPSTF and the National Guideline Clearinghouse were reviewed to ensure all relevant literature was included. Eighteen references were identified for potential inclusion and the full texts of the articles were printed and reviewed. The final literature review included 6 articles that were analyzed and critically appraised.

## Analysis and Interpretation

*Clostridium difficile* prevention has been examined in multiple clinical settings and with various interventions. Six articles were obtained for analysis of the best evidence-based methods to reduce hospital-acquired CDI rates. After appraisal of evidence, each was rated using Melnyk & Fineout-Overholt's (2011) rating system for hierarchy of evidence (Table 2). In the hierarchy, Level I evidence is from a systematic review or meta-analysis of randomized control trials (RCT). Level II evidence is from single RCTs that are well-designed. Level III evidence is from non-randomized control trails. Level IV evidence is from single case-control and cohort studies. Level V evidence is from systematic reviews of descriptive or qualitative studies. Level VI evidence is from single descriptive studies. Level VII evidence is from expert opinions [9]. The evidence was reviewed and met the quality criteria to be included in the supporting evidence for this EBP project. Within the literature which provided the supportive evidence for this project, one article was Level II evidence, three articles were Level III evidence, one article was Level V evidence and one article was Level VII evidence. Results of the leveling are shown in Table 3.

Author (s)	Level of Evidence
APIC (2013)	VII
Koll <i>et al.</i> (2013)	III
Pokrywka <i>et al.</i> (2014)	III
Rubin <i>et al.</i> (2013)	II
Waqar <i>et al.</i> (2016)	III
You, Song, Cho & Lee (2014)	V

Table 2: Levels of Evidence

STUDY/ LEVEL	PARTICIPANTS	PURPOSE/METHODS	INTERVENTION	RESULTS
Carrico <i>et al.</i> , (2013) [17] Level VII	Adult patients diagnosed with <i>C. difficile</i> infection	To develop and implement a guide to prevent <i>C. difficile</i> infection. Prevention interventions include diagnosis, hand hygiene, contact isolation precautions, environmental infection prevention, antimicrobial stewardship, and fecal bacteriotherapy.		Formal guideline for <i>C. difficile</i> prevention using early diagnosis and identification of potential <i>C. difficile</i> patients, proper hand hygiene procedures with soap and water, contact isolation precautions for all patients suspected of CDI, environmental and surface cleaning with an EPA-approved spore killing hypochlorite solution, implementation of an antimicrobial stewardship committee to monitor antibiotic use and de-escalation of antibiotics, and fecal bacteriotherapy offered as treatment option.
Koll <i>et al.</i> , (2014) [15] Level III	Used collaborative model. Local hospitals created collaborative steering committees including infectious disease physicians, infection preventionist, hospital epidemiologists, nurses, and additional staff.	Reduce the incidence of hospital-onset CDI. 2 bundles were implemented (1) infection prevention bundle (2) environmental cleaning protocol	In first 6 months of Collaborative group implemented an infection prevention bundle including (a) contact precautions instituted immediately for patients with diarrhea, (b) sign placement for patients with confirmed or suspected CDI, (c) personal protective equipment readily available and used, (d) adherence to hand hygiene protocols, (e) dedicated rectal thermometers, (f) patient placement, (g) private room for CDI patients (confirmed or suspected), (h) cohorting of CDI patients, if private room unavailable, and (i) as a last option, dedicated bathroom for CDI patients in a shared room with non-CDI patient. Implementation of an environmental cleaning protocol including standardized cleaning with a hypochlorite-based disinfectant for routine and terminal cleaning and a 48-item checklist to assess compliance.	35 hospitals were included in the analysis. Hospital onset-CDI accounted for 44% of all cases. Hospital onset CDI cases mean length of stay more than twice as long (26 days) and all-cause mortality rate almost twice as high (mean= 18%), nonhospital-associated length of stay was 11 days and all-cause mortality rate (mean=10%) or community-onset, hospital-associated CDI length of stay 12 days and all-cause mortality rate (mean=13%). The mean compliance with the prevention bundle was 95% and the mean compliance with the environmental cleaning protocol was 96%. A pronounced downward trend in the mean hospital-onset CDI rate from 12 to 8 per 10,000 patient-days. The predicted hospital-onset reduction over time was significant over the course of the project ( $p<.001$ ). The expected number of hospital-onset CDI cases was 6,461 and the actual number of cases was 5,377.
Pokrywka <i>et al.</i> , (2014) [12] Level III	Admitted patient to hospital with new onset of unexplained diarrhea for at least 12 hours occurring more than 48 hours after admission, and having a positive <i>C. difficile</i> toxins test.	Determine the effect of an expanded bundle, including patient hand hygiene, on the rate of <i>C. difficile</i> disease in hospitalized patients.	The intervention of patient hand hygiene was added to the current <i>C. difficile</i> prevention bundle. Patient hand hygiene was promoted prior to meals using soap and water or with a commercially available alcohol wipe placed on patient trays by dietary staff. The current bundle included (a) early detection of <i>C. difficile</i> cases by toxin testing of any patient with onset of unexplained diarrhea, (b) electronic alerts on positive toxin results to nursing units to initiate barrier precautions with glove and gown use, (c) staff hand hygiene with soap and water, (d) extended duration of isolation for entire hospital stay, (e) staff and patient education on <i>C. difficile</i> disease, and (f) cleaning of all patient rooms with sodium hypochlorite solution.	From July 2009 to Jun 2010, 336 positive results and rate of CDI incidence was 6.95 per 10,000 patient-days. In comparison, the previous year's incidence of <i>C. difficile</i> infection was 10.45 per 10,000 patient-days. The inclusion of patient hand hygiene to the prevention bundle was found to be statistically significant ( $p=0.0009$ ).

STUDY/ LEVEL	PARTICIPANTS	PURPOSE/METHODS	INTERVENTION	RESULTS
Rubin <i>et al.</i> , (2013) [13] Level II	Computer simulation model – agent-based modeling (ABM)	To simulate a typical hospital environment and the spread of <i>C. difficile</i> between patients by contaminated environmental surfaces and health care worker hands.	5 sub-models were created (1) the patient flow sub-model governed processes of patient admission, transfer and discharge (2) the virtual hospital represented a medium-sized facility with nine 30-bed acute care floors and two 15-bed intensive care units (3) The response and intervention sub-model governed policies for managing infected patients and preventing transmission (4) The contact event sub-model governed processes of contamination of environmental surfaces within the room, transfer of organisms to health care worker hands and acquisition of organisms by susceptible patients (5) The contact network sub-model represented the connections between patients, nurses and doctors.	The bundle interventions during the typical intervention scenario improved for actual CDI rates and reported CDI rates of 40 events per 10,000 patient-days with a base-case scenario of 140 events per 10,000 patient-days actual CDI rates and 80 events per 10,000 patient-days reported CDI rates. The impact of each single component at the typical intervention scenario was greatest for hand hygiene (7 events per 10,000 patient-days), empiric isolation (9 events per 10,000 patient-days), and testing (13 events per 10,000 patient-days).
Waqar <i>et al.</i> , (2016) [14] Level III	All patients admitted to the tertiary care center with suspected CDI.	To reduce the rates of HCA CDI at a tertiary care center	Implementation of a modified contact isolation sign for all CDI patients to only use soap and water for hand washing, the sign was a visual alert to environmental service to use 1:10 dilution of bleach for terminal cleaning. Training and feedback of proper room cleaning for CDI patients was conducted with environmental service staff. All CDI patients were kept in contact isolation. A computer-based learning module was created and required to be reviewed by all health care providers including nursing, physicians, and ancillary staff members. Monitoring high-touch surface cleanliness during terminal cleaning with use of Clean-Trace Hygiene Management System. An antimicrobial stewardship committee was created to reduce Fluoroquinolones use in addition to existing goals.	CDI rate decreased from 15.38 to 6.94 per 10,000 patient-days (The average monthly rate of CDI decreased per 10,000 patient-days from 12.5 to 7.8 (p=.001). The mean rate of hand hygiene adherence was 63% and did not change during the study period. The percent of cleanliness if high-touch surfaces improved from 62.7 to 91 and Fluoroquinolones use decreased from 65 defined daily dose per 1,000 patient-days to 31 defined daily dose per 1,000 patient-days.
You E, Song H, Cho J & Lee J (2014) [11] Level V	Patients admitted to the unit with presence of symptoms (diarrhea or fever and unexplained leukocytosis) and a positive stool test for <i>C. difficile</i> toxins.	To prevent CDI in hospitalized patients admitted to the medical intensive care unit	Infection control interventions that were implemented in the medical intensive care unit consisted of (a) education, (b) isolation, (c) hand hygiene, (d) contact precautions, and (e) environmental cleaning. Prior to intervention, hand hygiene was the only <i>C. difficile</i> prevention procedure. Educational interventions consisted of a lecture which was presented to all medical staff and attending physicians. Information included: survey results, baseline data, proper isolation, hand hygiene, contact precautions and environmental disinfection. Patients with CDI were placed in a private isolation zone and separate hand-washing sinks were positioned near each bed. Isolation was maintained until the patient had remained free of diarrhea symptoms for 48 hours.	The overall incidence rate of CDI increased within the hospital from 0.93 to 1.17 per 1,000 patient-days, but the incidence of CDI in the medical intensive care unit decreased significantly from 4.70 to 1.53 cases per 1,000 patient-days (p=0.012, OR 0.36, 95% CI 0.13-0.85). The medical intensive care unit had a reduction in CDI incidence by approximately 67%.

Table 3: Summary of Appraised Literature

## Synthesis

The evidence clearly demonstrated the significance of four bundled strategies to prevent *C. difficile* infection in an acute care setting (a) hand hygiene that includes soap and water in patients, healthcare workers, families and visitors, (b) isolation and contact precautions including gloves and gown, (c) environmental cleaning using a sodium hypochlorite solution, and (d) antibiotic stewardship committee. The evidence from the literature appraisal was synthesized using these strategies.

## Hand hygiene

According to the CDC (2013), healthcare worker's hands are frequently contaminated with *C. difficile* following patient contact

and contribute to the spread of *C. difficile*. Wearing gloves prior to contact with a suspected CDI patient can reduce the spread of *C. difficile*. All healthcare workers should wash their hands with an antimicrobial soap and water or disinfectant [10]. You, Song, Cho, and Lee (2014) [11] performed a study to monitor the incidence of CDI and how implementation of a bundle can affect incidence of CDI. The bundle consisted of (a) education, (b) isolation, (c) hand hygiene, (d) contact precautions, and (e) environmental disinfection. A study was conducted that added patient hand hygiene in a care bundle by offering hand hygiene to patients with soap and water prior to meals or with sanitation wipes on patient trays [12].

Compliance of the infection prevention bundle should be monitored on a monthly basis with a recommended target sample size. Five observations per week should be performed on suspected or confirmed CDI patients [10]. A checklist should be used when doing to observation to make sure that all observations are conducted the same and the same data is being gathered. An environmental cleaning tracking tool should also be implemented. This form would be used by environmental services when terminally cleaning a room and would be signed off by his/her supervisor once completed [2].

### Isolation and contact precautions

Early identification of patients who are being investigated for or diagnosed with CDI is the first step to preventing spread of the disease. *C. difficile* can be spread by direct or indirect contact with the patient or the patient's environment [10]. Adherence to the components of Contact Precautions will help break the chain of infection. Patient's suspected of or diagnosed with CDI should be placed in a private room if possible to decrease the spread of CDI. Personal protective equipment must be donned before going into the room and discarded before exiting the patient's room [2]. A gown and gloves should be worn for patient's in contact isolation and for all patients's suspected or diagnosed with *C. difficile* infection. Rubin *et al.* (2013) [13] found bundle intervention including hand hygiene and empiric isolation had the largest impact on actual CDI (5 events per 10,000 patient-days). Waqar *et al.* study found that the average monthly rate of CDI decreased per 10,000 patient-days from 12.5 to 7.8 ( $p=.001$ ) using a bundle which included contact isolation [14]. A study conducted by Koll *et al.* found a pronounced downward trend noted in the mean hospital-onset CDI rate from 12 to 8 per 10,000 patient-days [15]. The medical intensive care unit had a reduction in CDI incidence by approximately 67%. This suggests that patient isolation, environmental cleaning, and the use of personal protective equipment can decrease incidence of CDI [11].

### Environmental cleaning

The environment plays a key role in the spread of CDI. Because *C. difficile* is shed in feces, any surface or medical equipment that becomes contaminated with feces can act as a source for spores and be involved in infection transmission [10]. *C. difficile* spores can exist for five months on hard surfaces. The heaviest contamination can be found on floors and in bathrooms. Any removable items from a patient's room can become contaminated including thermometers, blood pressure cuffs, bedrails, call buttons, tube feedings, flow control devices, bed sheets commode, toilets, scales, telephones TV controls, light controls, and stethoscopes. Many disinfectants commonly used in healthcare will not kill the *C. difficile* spores. Only chlorine-based disinfectants and high-concentration hydrogen peroxide formulations kill spores [2]. The use of 10% sodium hypochlorite solution mixed fresh daily should be used with a clean cloth for each use. The contact time of one minute for the hypochlorite solution should provide adequate disinfection and should air dry [10]. Privacy curtains should be changed during terminal cleaning. Waqar *et al.* completed a study using a modified contact sign on the door to signify that hand washing with soap and water was necessary after contact with the patient and their environment. This sign was also a visual alert to environmental services staff to use bleach at a dilution of 1:10 for terminal cleaning instead of the quaternary cleaner used for all other patient rooms at the facility [11,16].

### Antimicrobial stewardship committee

CDI is frequently a complication of antibiotic use, and the development of a healthcare facility program to ensure appropriate antibiotic use is considered an important prevention intervention [10]. The most important protection mechanism against CDI in humans is the normal gut flora. Antimicrobial stewardship programs ensure that appropriate antibiotic use is considered for all patients to prevent CDI. Another important role of the antimicrobial stewardship committee is to achieve optimal medical therapy for treatment of CDI. The main treatment goals are killing *C. difficile*, killing toxin, and restoring normal flora. Waqar *et al.* conducted a study in 2016 using an antimicrobial stewardship committee sought to further the reduction of Fluoroquinolones use in addition to the existing goals. This committee introduced appropriate guidelines for antimicrobial use for urinary tract and intra-abdominal infections. Fluoroquinolones were added to the restricted list at the facility and required an indication for use and appropriate intervention. The average monthly rate of CDI decreased per 10,000 patient-days from 12.5 to 7.8 ( $p=.001$ ) [14].

### Recommendations

The best practice recommendations based upon the synthesis of the appraised evidence was that a bundle strategy of hand hygiene, isolation/contact precautions, environmental cleaning and antimicrobial stewardship committee to prevent the transmission and spread of *C. difficile*. Hand hygiene education should include only soap and water after contact with CDI patients, because alcohol based hand sanitizers do not kill the spores. Patient hand hygiene education should also be provided to all staff to include encouragement of patients to wash hands with soap and water prior to all meals and after using the bathroom. All patients



suspected or diagnosed with CDI should be immediately put in contact isolation with contact isolation sign on the door and soap and water only sign should be hung outside the door. CDI patients should be admitted to private rooms or in a cohort with another CDI patient to prevent the spread of CDI. All staff should strictly adhere to the contact isolation procedure of gown and gloves when entering any CDI patient room. This equipment should be removed upon leaving the patient room and hand hygiene with soap and water should follow. Environmental cleaning should be completed in the CDI patient’s room daily with an EPA-approved, spore killing hypochlorite solution. Any removable device or reusable device should be cleaned with the same solution upon leaving the patient room. The patient room after discharge should be terminally cleaned and all areas of the room cleaned with the EPA-approved, spore killing hypochlorite solution. An antimicrobial stewardship committee should be initiated to review the use of antimicrobial agents, de-escalation of antibiotics, and to reduce the use of inappropriate antibiotics. Restriction of Fluoroquinolones in all patients should be initiated and monitored. Recommendations from the committee should be made to de-escalate Fluoroquinolones when not necessary.

The educational content should be completed using a computer based module or through an in-service with small groups of healthcare staff. Specific contact isolation signs for outside patient door should be available on the inpatient unit and staff as well as housekeeping should be educated on proper contact isolation precautions with use of gowns and gloves. Proper cleaning products should be validated with the facility and education on environmental cleaning should be directed at housekeeping and healthcare staff that clean small movable devices.

**CDC Environmental Checklist for Monitoring Terminal Cleaning<sup>1</sup>**

<b>Date:</b>	
<b>Unit:</b>	
<b>Room Number:</b>	
<b>Initials of ES staff (optional):<sup>2</sup></b>	

**Evaluate the following priority sites for each patient room:**

<b>High-touch Room Surfaces<sup>3</sup></b>	<b>Cleaned</b>	<b>Not Cleaned</b>	<b>Not Present in Room</b>
Bed rails / controls			
Tray table			
IV pole (grab area)			
Call box / button			
Telephone			
Bedside table handle			
Chair			
Room sink			
Room light switch			
Room inner door knob			
Bathroom inner door knob / plate			
Bathroom light switch			
Bathroom handrails by toilet			
Bathroom sink			
Toilet seat			
Toilet flush handle			
Toilet bedpan cleaner			

**Evaluate the following additional sites if these equipment are present in the room:**

High-touch Room Surfaces <sup>3</sup>	Cleaned	Not Cleaned	Not Present in Room
IV pump control			
Multi-module monitor controls			
Multi-module monitor touch screen			
Multi-module monitor cables			
Ventilator control panel			

<sup>1</sup>Selection of detergents and disinfectants should be according to institutional policies and procedures

<sup>2</sup>Hospitals may choose to include identifiers of individual environmental services staff for feedback purposes

<sup>3</sup>Sites most frequently contaminated and touched by patients and/or healthcare worker

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