ORIGINAL ARTICLE

Reducing *Clostridium difficile* in the Inpatient Setting: A Systematic Review of the Adherence to and Effectiveness of *C. difficile* Prevention Bundles

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BACKGROUND. *Clostridium difficile* infection (CDI) is the most common infectious cause of nosocomial diarrhea, and its prevention is an urgent public health priority. However, reduction of CDI is challenging because of its complex pathogenesis, large reservoirs of colonized patients, and the persistence of infectious spores. The literature lacks high-quality evidence for evaluating interventions, and many hospitals have implemented bundled interventions to reduce CDI with variable results. Thus, we conducted a systematic review to examine the components of CDI bundles, their implementation processes, and their impact on CDI rates.

METHODS. We conducted a comprehensive literature search of multiple computerized databases from their date of inception through April 30, 2016. The protocol was registered in PROSPERO, an international prospective register of systematic reviews. Bundle effectiveness, adherence, and study quality were assessed for each study meeting our criteria for inclusion.

RESULTS. In the 26 studies that met the inclusion criteria for this review, implementation and adherence factors to interventions were variably and incompletely reported, making study reproducibility and replicability challenging. Despite contextual differences and the variety of bundle components utilized, all 26 studies reported an improvement in CDI rates. However, given the lack of randomized controlled trials in the literature, assessing a causal relationship between bundled interventions and CDI rates is currently impossible.

CONCLUSION. Cluster randomized trials that include a rigorous assessment of the implementation of bundled interventions are urgently needed to causally test the effect of intervention bundles on CDI rates.

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BACKGROUND

Clostridium difficile (*C. difficile*) infection (CDI) is a major public health threat in the healthcare setting, and it is associated with considerable morbidity, mortality, and economic costs.[1–6] Reporting of CDIs has been mandatory in England's National Health Service since 2004, and *C. difficile* is considered 1 of the 3 most urgent pathogen threats by the Centers for Disease Control and Prevention in the United States.[7,8] Beginning in 2017, CDI rates will be included among the hospital-acquired complications used by the Centers for Medicare and Medicaid to penalize the lowest-performing hospitals.[9]

Control of CDI is especially challenging given multiple sources of transmission and its complex, poorly understood pathogenesis and set of risk factors.[10] *Clostridium difficile* has large reservoirs in the environment, including asymptomatic carriers that may account for more than half of disease transmission.[11,12] Its spores can persist on hard surfaces for up to 5 months, further complicating disease eradication.[13]

Bundled interventions targeting catheter-associated urinary tract infections (CAUTIs) and central-line–associated bloodstream infections (CLABSIs) have been successful in reducing the rates of these device-associated HAIs. Seeking to continue this trend, hospitals have implemented targeted *C. difficile* intervention bundles. Unlike CAUTI and CLABSI, however, the evidence for these bundles is far less robust. Few randomized clinical trials have examined interventions to reduce CDI incidence, and those that have all focused on single

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interventions, such as patient hand hygiene,[14] disposable equipment,[15] daily chlorhexidine bathing,[16] or environmental disinfection,[17,18] rather than an intervention bundle.

Bundled interventions require a high degree of compliance to be effective,[19] and adherence with complex bundle components may be challenging and variable across settings. Given the lack of direct evidence for CDI bundle adherence and intervention outcomes, we undertook a systematic review to examine common bundle components, to evaluate component adherence and study replicability, and to assess the effectiveness of bundles on reducing hospital CDI rates.

METHODS

For the purposes of this review, a bundle was defined as any set of multiple (>1) interventions focused on reducing CDI in the inpatient setting.

Search Strategies

We conducted a comprehensive search of 4 databases: the Cochrane Central Register of Controlled Trials, PubMed, Web of Science, and the Cumulative Index to Nursing and Allied Health. We sought to capture articles and abstracts published between each database's date of inception and May 28, 2015. Thus, the search start date was different for each database. Another search was run closer to publication to include articles available through April 30, 2016. The search strategy was designed and conducted by an experienced librarian with input from the study team. The following keywords were used to search for bundled interventions aimed at reducing *C. difficile* infections: (c difficile OR c. difficile OR clostridium difficile OR "c diff" OR "c. diff") AND ("infection control" OR bundle OR bundled OR bundles OR "multiple control" OR "multiple controls" OR "control package" OR "control packages" OR "integrated control" OR "integrated controls" OR multipronged OR multi-pronged). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement guidelines in conducting this systematic review.[20] The protocol was registered at PROSPERO, an international prospective register of systematic reviews (no. 2015: CRD42015023252).

All abstracts retrieved using this search strategy were screened, and potentially relevant articles were identified for a full text review. Bibliographies were manually inspected to identify relevant studies not previously identified by our database search.

Inclusion/Exclusion Criteria

We included all inpatient studies that examined the effectiveness of a CDI-specific intervention bundle and provided data on the rates of CDI before and after intervention implementation. Single intervention studies (studies without bundles) and studies that did not provide data to evaluate effectiveness were excluded, as were abstracts, review articles, and editorials. There were no language restrictions.

Data Abstraction

The primary outcome of this review was the mean difference in the rates of hospital-acquired CDI. Rates were measured at the hospital level in units defined by each article. For every study, we abstracted the following: the interventions included in each bundle; *C. difficile* case definition; infection rates before and after intervention implementation; *C. difficile* outbreak status; hospital setting; study population; study design; and intervention adherence rates.

All studies were abstracted and screened independently by 2 reviewers (A.B. and C.N.). For disagreements regarding article inclusion, resolution was reached by discussion between the 2 reviewers.

Assessing Bundle Effectiveness and Adherence

We assessed the effectiveness of the bundles by extracting the reported point estimates and calculating the difference in infection rates before and after intervention implementation. Bundled interventions were categorized into 10 primary components: antibiotic stewardship, contact precautions, dedicated equipment, staff education, patient education, environmental cleaning, hand hygiene, isolation and/or cohorting, proton-pump inhibitor stewardship, and systems and workflow changes.

Adherence has been previously defined as the extent to which specified program components are delivered as outlined in a program manual.[21] We evaluated adherence by identifying and quantifying the number of adherence measures within a given component of the CDI prevention bundle. A study was considered to have assessed adherence if it reported a method of measuring compliance for 1 or more bundle elements, such as direct observation or tracking glove use.

TiDier Checklist

We assessed the replicability of each study included in the final analysis using the Template for Intervention Description and Replication (TiDier) checklist.[22] This tool consists of 12 dichotomous items that assess the description of an intervention and evaluate its replicability. The score reflects the number of items that a given intervention addressed, with higher scores indicating better replicability. The maximum score was 12.

Bias Assessment

To assess the quality and risk of bias for each study, we used a modified version of the Checklist for Measuring Quality instrument developed by Downs and Black.[23,24] This tool contains 27 dichotomous items regarding reporting, external

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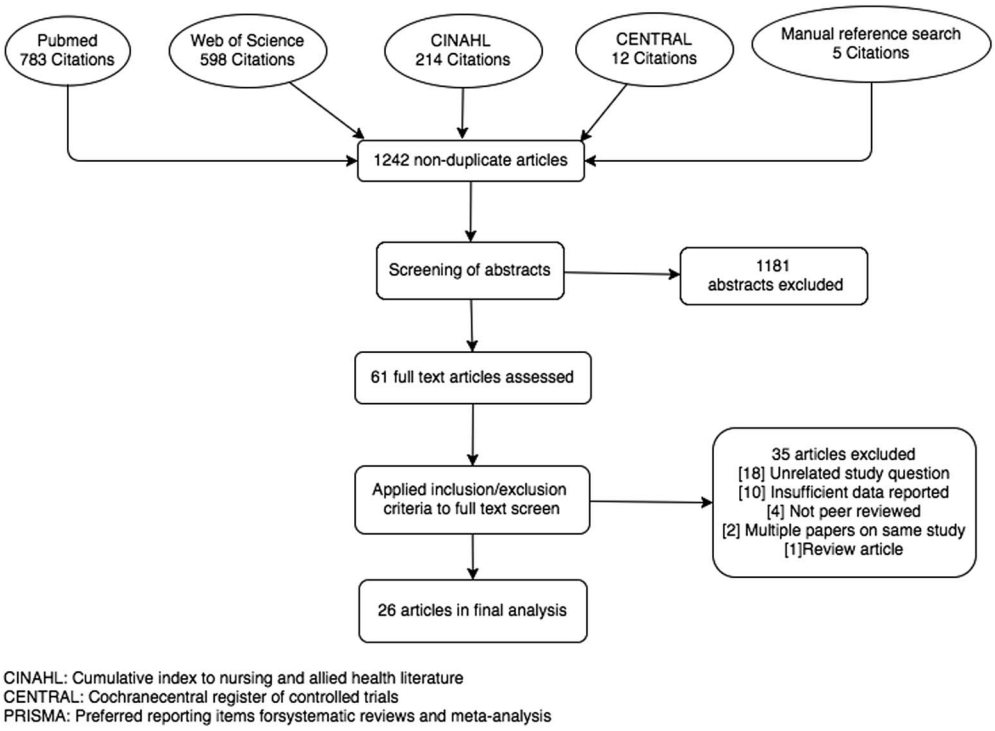

FIGURE 1. PRISMA flow diagram for CDI prevention bundle systematic review; CENTRAL: Cochrane central register of controlled trials; CINAHL: Cumulative index to nursing and allied health literature

validity, bias, confounding, and power. The maximum possible score of the modified instrument is 28, and the assessment of power was modified from a 0–5 scale to 0–1.

RESULTS

Our search strategy identified 1,242 distinct articles, of which 1,181 were excluded based on abstract information. The remaining 61 full-text articles were reviewed, and 26 met inclusion criteria. This process is summarized in the PRISMA flow diagram (Figure 1).

Characteristics of Included Studies

While details of the case definitions for CDI differ between studies, they were generally consistent. Most required clinical symptoms and a positive *C. difficile* test. A comprehensive description of the studies is listed in Table 1. The study locations varied, including 9 in Europe,[25–33] 3 in Asia,[34–36] and 14 in North America.[37–50] Most studies examined all hospital wards (17 of 26; 65%). Others analyzed specific wards or patient populations only: bone marrow transplant,[41,48] medical intensive care unit,[36,48] geriatric ward,[31] surgical inpatients,[49] all units except psychiatry and pediatrics,[37] all units except neonatal,[32] hip-fracture patients,[25] and patients over 2 years of age.[26]

Our literature search did not identify any randomized controlled trials. Among the included studies, 20 were interrupted time series[25–31,33,34,37–40,42–44,46,47,49,50] and 6 were quasi-experimental pre-/postintervention studies.[32,35,36,41,45,48] In total, 11 studies were conducted in the midst of a *C. difficile* outbreak;[27,28,32,37–39,41,43,46–48] 8 studies were quality improvement projects to reduce endemic rates;[25,26,29,35,36,45,49,50] and 7 studies were conducted in the context of upwardly trending CDI rates.[30,31,33,34,40,42,44]

Intervention Bundles Components

The types of interventions implemented as part of a CDI bundle varied widely across studies (Table 2). Among the 10 bundle components, hand-hygiene and environmental cleaning components were the most common interventions employed. Both were included in 23 of 26 studies (88.5%). These were followed by isolation and/or cohorting (20 of 26, 77%). Contact precautions, antibiotic stewardship, and staff education were each included in 19 of 26 studies (73%). System and workflow changes were reported in 14 of 16 studies (54%), dedicated equipment was reported in 7 of 26 studies (27%), patient education was reported in 5 of 26 studies (19%), and proton-pump inhibitor stewardship was reported in 3 of 26 studies (12%).

Within each category, the interventions were multifaceted. Hand-hygiene measures included sink installation, improving signage, and education initiatives. Hand hygiene referred to a variety of practices across studies, including increased use of pure alcohol-based hand rubs, soap and water, and chlorhexidine scrubs.

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TABLE 1. Study Characteristics

First Author, Publication Year	Study Design	Bundle Start Date(s)	Setting	Study Population[a]	CDI Definition	Context
Abbett, 2009[40]	Interrupted time series	1/06–4/06	Brigham and Women's Hospital, Boston, MA; 750-bed tertiary, academic	All inpatients	+Toxin	Rates trending upward pre-intervention
Apisarnthanarak, 2004[48]	Pre-/postintervention	6/02–8/02	Barnes-Jewish Hospital, St Louis, MO; academic	BMT and MICU	+Toxin	Outbreak
Bishop, 2013[49]	Interrupted time series	9/08	Stamford Hospital, Stamford, CT; academic	All surgical patients (n = 39,093)	+Toxin or pseudomembranous colitis	Endemic rates
Brakovich, 2013[50]	Interrupted time series	12/09	Southeast USA; long-term acute-care hospital	All inpatients	+Combined antigen markers, glutamate dehydrogenase, toxin A/B	Endemic rates
Cheng, 2015[34]	Interrupted time series	Q2,10	Hong Kong; 1 acute and 3 extended-care hospitals; 3,200 beds	All inpatients	Diarrhea, + toxin, and +stool culture	Rates trending upward preintervention
Gulihar, 2009[25]	Interrupted time series	8/06–5/07	University Hospitals of Leicester NHS Trust; UK	Adults with femur fracture (n = 3,417)	Diarrhea and + toxin	Endemic rates
Hanna, 2000[41]	Pre-/postintervention	5/95	University of Texas, MD Anderson Cancer Center, Houston	BMT patients	Diarrhea and +toxin	Outbreak
Lai, 1997[47]	Interrupted time series	10/91–2/92	University of Massachusetts Memorial Medical Center, Worcester; 370-bed, tertiary, academic	All inpatients	Diarrhea and +toxin	Outbreak
Marufu, 2015[26]	Interrupted time series	2/03–10/11	King's College Hospital NHS Foundation Trust, London, UK	Inpatients over age 2 (n704,654)	Loose stools and +toxin test or pseudomembranous and CDI histopathology	Endemic rates
Mattner, 2008[27]	Interrupted time series	5/07–4/08	Northern Germany, academic	All inpatients	Diarrhea and +toxin	Outbreak
Mermel, 2013[44]	Interrupted time series	Q4,06–Q3,12	Rhode Island Hospital, Providence; 719-bed, tertiary, academic	All inpatients	Diarrhea or toxic megacolon and +toxin or pseudomembranous colitis	Rates trending upward preintervention
Muto, 2007[38]	Interrupted time series	7/00–7/03	University of Pittsburgh Medical Center–Presbyterian, Pittsburgh, PA; 834-bed, tertiary, academic	All inpatients	+toxin or pseudomembranous colitis	Outbreak
Oleastro, 2014[28]	Interrupted time series	4/12	Centro Hospitalar do Algarve, Lagos, Portugal; 330-bed secondary hospital and 40-bed internal medicine center	All inpatients	+toxin	Outbreak
Power, 2010[29]	Interrupted time series	2/07–12/07	Salford Royal NHS Foundation Trust, England; 850-bed, academic	All inpatients	Diarrhea and +toxin	Endemic rates
Price, 2010[30]	Interrupted time series	1/08	Brighton and Sussex University Hospitals NHS trust, UK; 820-bed acute secondary and tertiary, academic	All inpatients (n = 200,245)	Diarrhea and + toxin	Rates trending upward preintervention
Salgado, 2009[46]	Interrupted time series	11/04	Medical University of South Carolina Hospital; 610-bed, tertiary	All inpatients	Diarrhea and +toxin	Outbreak
Stone, 1998[31]	Interrupted time series	7/95	Royal Free NHS Trust, London, England; academic	Non-MRSA geriatrics patients (n = 2,467)	Diarrhea and + toxin	Rates trending upward pre-intervention
Struelens, 1991[32]	Pre-/postintervention	8/88–7/89	University of Brussels Hospital Erasme, Brussels, Belgium; 840-bed, tertiary	All except neonatal	Diarrhea or pseudomembraneous colitis and +stool culture or +toxin	Outbreak
Suzuki, 2013[35]	Pre-/postintervention	10/11	Tsukuba Medical Center Hospital, Tsukuba, Japan; 409-bed, tertiary, academic	All inpatients	+toxin	Endemic rates
Valiquette, 2007[37]	Interrupted time series	9/03-10/04	Centre Hospitalier Universitaire de Sherbrooke, Quebec; 683-bed secondary/tertiary	All except psychiatry, pediatrics	+toxin, pseudomembranous/ antibiotic associated/ *C. difficile* colitis	Outbreak
Weiss, 2009[39]	Interrupted time series	6/05–11/05	Maisonneuve-Rosemont Hospital, Montreal, Quebec; 554-bed acute care, tertiary, academic	All inpatients	Diarrhea and +toxin	Outbreak
Whitaker, 2007[42]	Interrupted time series	10/03–7/04	University Community Hospital, Tampa, FL; 469-bed tertiary	All inpatients	+toxin	Rates trending upward pre-intervention
White, 2016[33]	Interrupted time series	08/06	University Hospitals of Leicester (UHL), 2,000-bed acute UK NHS Trust	All inpatients	Diarrhea and +toxin	Rates trending upward pre-intervention
Wong-McClure, 2013[43]	Interrupted time series	1/09–5/09	Costa Rica; 685 bed, tertiary	All inpatients	Diarrhea, +toxin, and +stool culture	Outbreak
You, 2014[36]	Pre-/postintervention	4/12	Wonkwang University Hospital, Iksan, South Korea; academic	MICU (n = 567)	Diarrhea and + toxin	Endemic rates
Zafar, 1998[45]	Pre-/pos intervention	4/90-93	Columbia Arlington Hospital, Arlington, VA; 350-bed acute care community teaching	All inpatients	Diarrhea and +toxin	Endemic rates

[a]The total sample size is reported for all studies that provided this information.

NOTE. BMT, bone marrow transplant; *C. difficile, Clostridium difficile;* CDI, *C. difficile* infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MICU, medical intensive care unit; NHS, National Health System.

TABLE 2. Intervention Details

First Author	Intervention	Component Details
Abbett[40]	Antibiotic stewardship	Discontinue nonessential antimicrobials when suspected case
	Contact precautions	Enhanced measures; gowns, gloves, alcohol gel before, soap and water after patient contact
	Dedicated equipment	Stethoscope in patient rooms
	Education, staff	CDI and prompt responses; nurses, doctors, physician assistants, environmental services, and administration
	Environmental cleaning	Hyperchlorite disinfectant at discharge
	Hand hygiene	Described in contact precautions
	Isolation and/or cohorting	Suspected cases in a single room
	Systems and workflow	Infection control for suspected cases; communication improved between lab and nurses; infection preventionists and environmental services; infection preventionists sent daily CDI list and confirm prevention practices; electronic medical record flagging; standardize CDI treatment
Apisarnthanarak[48]	Contact precautions	Not specified
	Education, staff	Regarding contact precaution
	Environmental cleaning	Patient rooms and staff areas cleaned with 10% hypochlorite; carpeted areas cleaned
	Hand hygiene	Signage
Bishop[49]	Antibiotic stewardship	Prophylactic antibiotics regulated, fluoroquinolones limited
	Contact precautions	Limit patient contact to 1 member of surgical team, lab coats provided, glove changes
	Environmental cleaning	Terminal cleaning focused on immediate patient environment
	Hand hygiene	Before and after gloving, increased education, increased monitoring, facility improvements,
	Proton-pump inhibitor stewardship	Limited to intensive care unit or specific clinical indications
	Systems and workflow	Resident rounding to limit staff exposure
Brakovich[50]	Environmental cleaning	New cleaning equipment (microfiber mops vs cotton); decontaminate more frequently; hydrogen peroxide vapor decontamination
	Antibiotic stewardship	Lower frequency and duration of antimicrobials; restrict clindamycin and cephalosporin
	Education, staff	Hands on training for environmental services
	Hand hygiene	Recommend soap and water; reminder stickers; staff and visitors
	Isolation and/or cohorting	CDI patient isolate to private room
	Contact precautions	Contact precautions for all CDI patients
	Systems and workflow	Improved diagnostic testing; cleaning checklist for environmental services staff
Cheng[34]	Antibiotic stewardship	Immediate concurrent feedback; focus on broad-spectrum intravenous antibiotics
	Contact precautions	Gloves and gowns
	Dedicated equipment	Bedpans and commodes
	Education, staff	Train cleaning staff, emphasizing high-touch areas; training ward staff quarterly
	Environmental cleaning	Clean rooms twice daily; 1,000 parts per million sodium hypochlorite; curtain change at discharge
	Hand hygiene	Soap and water
	Isolation and/or cohorting	Nursed as cohort, preferably in single rooms
Gulihar[25]	Antibiotic stewardship	5-day antibiotic stop policy; approval for high-risk antibiotics; surgery prophylaxis changed from cefuroxime to co-amoxiclav or vancomycin
	Education, patient	Focus on hand hygiene
	Education, staff	Focus on hand hygiene
	Environmental cleaning	Sodium-dichloroisocyanurate for environmental cleaning
	Hand hygiene	Alcohol gel on rounds; soap/water before and after ward and isolation bays; new sinks
	Isolation and/or cohorting	Rapid isolation of diarrheal patients in side rooms or isolation bays
Hanna[41]	Contact precautions	Enteric precautions for all diarrheal patients; disposable gowns, gloves in CDI rooms
	Dedicated equipment	Mercury thermometers
	Education, staff	On-ward sessions on CDI
	Environmental cleaning	Daily, routine, and terminal cleaning with 1:100 bleach
	Hand hygiene	Chlorhexidine gluconate before and after patient care, individual rolls of paper towels
	Isolation and/or cohorting	Not specified
Lai[47]	Contact precautions	Universal precautions
	Education, staff	Intense education on modes of transmission, prevention, and control
	Environmental cleaning	New commode cleaning; new commodes
	Hand hygiene	Emphasized for staff, new soap dispensers in patient bathrooms; towelettes before meals
	Isolation and/or cohorting	CDI patients cohorted
Marufu[26]	Antibiotic stewardship	Microbiologist-led antibiotic rounds; restrictive antibiotic policy, audits
	Dedicated equipment	Disposable bedpans and macerators
	Education, staff	Infection control training consults; ongoing notices for staff
	Environmental cleaning	Clean equipment and environment with hypochlorite; new cleaning strategy group
	Hand hygiene	WHO Clean your hands campaign
	Isolation and/or cohorting	Isolation unit introduced
	Systems and workflow	Infection control scorecard, new infection control strategy team, review meetings; CDI feedback to all wards; Saving Lives toolkit; United Kingdom infection control code; diarrhea care plan and action cards; CDI ward rounds
Mattner[27]	Education, staff	Occupational groups trained
	Environmental cleaning	Sporicidal disinfection done more frequently
	Hand hygiene	Recommend gloves, hand wash, disinfection
	Isolation and/or cohorting	Introduced
Mermel[44]	Antibiotic stewardship	Audit antibiotic use; provide feedback; use electronic drug orders; pre-authorization requirements; streamline therapy based on labs; optimize doses; intravenous to oral conversion; increase narrow spectrum antibiotic use; limit quinolones, clindamycin
	Contact precautions	Easily accessible; many size gloves, gowns, masks in isolation rooms; empty trash often

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TABLE 2. *Continued*

First Author	Intervention	Component Details
	Dedicated equipment	Blood pressure cuff, thermometer, stethoscope in isolation rooms
	Education, staff	Annual infection control education, including antibiotic policy
	Environmental cleaning	Hire more housekeepers; hypochlorite-based cleaning of isolation rooms; dedicated team monitor for cleaning supplies; enhanced daily room cleaning
	Hand hygiene	Soap and water use encouraged
	Systems and workflow	New tool to identify high-risk patients; nurses order CDI test and initiate isolation; improve CDI test sensitivity; increase testing frequency; develop management guidelines
Muto[38]	Antibiotic stewardship	Clindamycin, ceftriaxone, levofloxacin, broad-spectrum antimicrobials require approval
	Contact precautions	Sustained for duration of hospitalization
	Education, staff	Printed material; lecture at staff meetings on epidemiology, risk factors, clinical findings, control measures, and rates
	Environmental cleaning	Daily cleaning with bleach (1:100) of high-touch surfaces, later increased to 1:10
	Hand hygiene	Soap and water (not alcohol) for CDI patients
	Isolation and/or cohorting	Cohorting facilitated by EMR
	Systems and workflow	Nurses can order lab test; EMR flag high-risk patients and email alert physicians; establish CDI management team for rapid evaluation, real-time lab notifications
Oleastro[28]	Antibiotic stewardship	Limit quinolones and 3rd-generation cephalosporins by time and indication
	Contact precautions	Gloves and aprons
	Education, staff	Educate on treatment, prevention, diagnosis
	Education, patients	Distribute written material
	Environmental cleaning	Clean ward and equipment every 8 hours with 5,000 parts per million hypochlorite, with peroxide hydrogen vaporization after discharge
	Hand hygiene	Soap and water
	Isolation and/or cohorting	Admit to individual room; cohort cases
	Proton-pump inhibitor stewardship	Limited to those clinically indicated
	Systems and workflow	Report outbreak to authorities, nurses, ward leaders; establish Regional Infection Control Group network; protocol for early diagnosis and treatment; type toxin positive samples
Power[29]	Antibiotic stewardship	Antimicrobial management team developed new guidelines to restrict certain antibiotics
	Education, staff	Focused and systematic education for all staff; target knowledge gaps identified by questionnaire
	Education, patients	Symptom reporting; poster campaign
	Environmental cleaning	Clean seals used for equipment; disposable washbowls, bed linens stored centrally; identify key surfaces
	Hand hygiene	Practices studied and improved; common errors identified; strict enforcement; hand-washing rounds for patient initiated
	Isolation and/or cohorting	Isolated at start of suspected symptoms
Price[30]	Antibiotic stewardship	Cephalosporin and quinolone restrictions
	Contact precautions	Scrubs, gloves, and aprons changed between patient contacts
	Isolation and/or cohorting	Phase 1: All diarrheal patients isolated in side rooms; phase 2: CDI patients in CDI cohort ward within 24 hours of CDI diagnosis, kept until discharge; dedicated nursing staff
Salgado[46]	Contact precautions	Keep until CDI ruled out as cause of diarrhea; CDI patients kept in contact precaution for duration of hospitalization; gown, gloves; private rooms
	Environmental cleaning	Use bleach in areas occupied by CDI patients
	Hand hygiene	Require soap and water, not alcohol gel
Stone[31]	Antibiotic stewardship	Limit antibiotics to seven day course, restrict the use of cephalosporins
	Hand hygiene	Emphasized between patients, 4% chlorhexidine scrub if prolonged contact, 0.5% chlorhexidine rub otherwise; dispensers at each bay and side room
	Systems and workflow	Providers alerted to new cases; quarterly rates discussed at teaching sessions; nurses informed
Struelens[32]	Antibiotic stewardship	Alternatives to clindamycin
	Contact precautions	Gloves and gowns for fecal contact
	Environmental cleaning	Daily furniture and floor cleaning (0.04% formaldehyde, 0.03% glutaraldehyde), dedicated utensils, single use towels
	Hand hygiene	Soap and water between patient contacts
	Isolation and/or cohorting	Single rooms for those with diarrhea; cohorting of infected patients
	Systems and workflow	Early diagnostic testing
Suzuki[35]	Antibiotic stewardship	Carbapenem use restricted
	Contact precautions	In place beginning with diarrhea
	Systems and workflow	Previous microbiology results of all admissions chart reviewed by infection preventionists; MDRO information provided to ward staff; infection control rounds within 2 days of new MDRO or hospital admission of patient with previous MDRO infection or colonization
Valiquette[37]	Antibiotic stewardship	Decrease use of second and third generation cephalosporin, ciprofloxin, clindamycin, and macrolides; decreased course of treatment
	Dedicated equipment	Rectal thermometers
	Education, staff	Lectures on isolation, disinfection, cleaning, antibiotic guidelines
	Environmental cleaning	Hypochlorite sodium for terminal disinfection; comprehensive ward sodium hypochlorite disinfection for wards with <3 cases
	Isolation and/or cohorting	Isolate suspected cases until discharge
Weiss[39]	Antibiotic stewardship	Change antibiotic use according to Quebec guidelines
	Contact precautions	Contact isolation for test-positive patients; routine gloving in CDI wards
	Education, patient	CDI hand hygiene handout
	Education, staff	60-minute lecture on CDI transmission, epidemiology, hand hygiene, and isolation; regular education on wards with >2 cases
	Environmental cleaning	1:50 bleach/water solution used for cleaning (down from 1:10)
	Hand hygiene	Soap and water encouraged over alcohol gel before/after visit patient room; 85 new sinks
	Isolation and/or cohorting	Dedicated CDI ward

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TABLE 2. *Continued*

First Author	Intervention	Component Details
	Systems and workflow	Low turnover; dedicated CDI ward housekeeping team trained; rapid enzyme immunoassay diagnostic test on first liquid stool; hire 4 infection preventionists
Whitaker[42]	Antibiotic stewardship	Formulary restriction for high-risk antibiotics
	Contact precautions	Gowns, gloves, soap and water hand hygiene only until ruled CDI negative
	Education, patient	Flyer on CDI and prevention
	Education, staff	Information on antibiotic use, clinical signs, prescriptive patterns, and awareness
	Environmental cleaning	10% hypochlorite disinfection in patient rooms, nursing units, horizontal surfaces, and medical equipment
	Hand hygiene	Soap and water
	Isolation and/or cohorting	Not specified
	Systems and workflow	Automated report of MDR organism history at admission; standardized nursing units for isolation; lab results shared immediately
White[33]	Antibiotic stewardship	5-day duration policy for the treatment of most common infections; limitation on the use of common classes of broad spectrum agents; "prescription codes" to sanction the use of restricted antibiotics
	Education, staff	Mandatory training program for clinical staff: an online or face-to-face module on infection prevention matters and a module on antimicrobial prescribing for all medical staff and nurse prescribers
	Environmental cleaning	Additional housekeeping staff; individual wards were vacated and deep cleaned before being treated with aerosolized hydrogen peroxide
	Hand hygiene	Colorful signs throughout the hospital; computer screensavers; audio messages, "naked from the elbow down" policy; prohibition of white coats and wrist and hand jewelry.
	Isolation and/or cohorting	A 22-bed combined isolation and cohort ward, with 6 single rooms, and the remainder arranged in 4 bedded bays; patient cohorting
	Proton-pump inhibitor stewardship	Limited the use of proton-pump inhibitors within the hospital and mandated regular review of prescriptions
	Systems and workflow	"Paper care pathway," new Infection Control Operational Group, individual Directorate Infection Control Groups, and a dedicated infection prevention nurse post in CDI
Wong-McClure[43]	Antibiotic stewardship	Broad-spectrum antibiotics restricted
	Contact precautions	Enforced for suspected cases, single-use personal protective equipment
	Environmental cleaning	Clean affected wards with 1:10 hypochlorite solution; clean equipment with 1:10 quaternary ammonium.
	Hand hygiene	Enforcement campaign for staff and patients
	Isolation and/or cohorting	Strict isolation for confirmed cases
You[36]	Contact precautions	Gloves and gowns
	Education, staff	Lecture for all medical staff on baseline data
	Environmental cleaning	Twice daily disinfection with 1,000 ppm sodium hypochlorite
	Hand hygiene	0.3% Triclosan soap and water before and after contact with CDI patients
	Isolation and/or cohorting	CDI patients in isolation zone, 2.2 m between beds and sink, isolation until 48 h symptom free
Zafar[45]	Contact precautions	Gloves and gowns required in CDI rooms
	Dedicated equipment	Equipment dedicated to individual patients and gas sterilized
	Education, staff	Monthly lecture program, videos, handouts, posters
	Environmental cleaning	Phenol-containing disinfectant for surfaces contaminated with body fluids; cart wash sterilizer installed on wheelchairs, stretchers
	Hand hygiene	0.03% Triclosan soap and water required; education
	Isolation and/or cohorting	Cohort patients and nurses; restrict patient movement
	Systems and workflow	Centralize processing department, infection preventionist on rounds, regular meetings between infection preventionists and nurses, CDI rates disseminated monthly

NOTE. CDI, *Clostridium difficile* infection; MDRO, multidrug-resistant organism.

Environmental cleaning interventions included a diverse range of practices and agents. Some focused on increasing cleaning frequency, including enhanced daily decontamination, cleaning at discharge, and environmental cleaning for patients meeting symptomatic and diagnostic criteria. Others expanded the types of surfaces to be cleaned. The most common agent used for cleaning was sodium hypochlorite.

For isolation and cohorting interventions, CDI patients were often assigned single or side rooms and were nursed as a cohort after a positive lab test. Some studies isolated symptomatic patients before case confirmation. Isolation was typically required until 48 hours after resolution of symptoms or continued until discharge. Enhanced contact precautions included expanding precautions to suspected cases and continuing these practices throughout the duration of hospitalization.

Antibiotic stewardship programs involved formulary restrictions, monitoring physician prescribing, and tracking hospital antibiotic consumption and purchasing. Antibiotic-specific education initiatives promoted shortened treatment courses, limited nonessential medications, and promoted the timely de-escalation of empiric therapy.

Staff education initiatives included information on CDI treatment, prevention, diagnosis, transmission, etiology, and epidemiology, as well as contact precaution and isolation policies, hand hygiene, and antibiotic use. These interventions were disseminated through both ongoing and solitary programs. Patient education was conducted primarily via handouts, flyers, and signs that stressed the importance of hand hygiene in preventing *C. difficile* transmission.

Systems and workflow interventions aimed to change hospital practices to optimize prompt CDI diagnosis, and upon diagnosis,

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TABLE 3. CDI Bundle Effectiveness

First Author	Preintervention CDI Rate (Cases/1,000 PD)	Postintervention CDI Rate (Cases/1,000 PD)	CDI Rate Reduction, %
8-Intervention Bundle[a]			
Abbett[40]	1.1 (95% CI, 1.00–1.21)	0.66 (95% CI, 0.60–0.72)	40% RR, 0.60 (95% CI, 0.52–0.68) $P < .001$
Oleastro[28]	0.823[b]	0.119	85.5%
7-Intervention Bundle			
Brakovich[50]	5.652	3.151	44.2%, $P < .001$
Cheng[34]	Increase 17.0% per quarter	Decrease 6.1% per quarter	
Marufu[26]	5.2 /1,000 admissions	1.1 /1,000 admissions	78.7%
Mermel[44]	12.2/1,000 discharges[b]	3.6/1,000 discharges	70.5%
Muto[38]	10.4/1,000 discharges[b]	3.0/1,000 discharges	71% OR, 0.286 (95% CI, 0.185, 0.435) $P < .001$
Weiss[39]	37.28 /1,000 admissions[b]	14.48 /1,000 admissions	61% OR, 0.379 (95% CI, 0.331–0.435) $P < .001$
Whitaker[42]	1.33	0.45	66%
White[33]	170 cases/month	2–11 cases/month	80%
Zafar[45]	155/year	65/year	60%, $P < .05$
6-Intervention Bundle			
Bishop[49]	4.13/month (SD, 2.64)	1.93/month (SD, 1.56)	53%, $P = .03$
Hanna[41]	60% attack rate[b]	17% attack rate	72%, $P < .05$
Struelens[32]	0.178[b]	0.034	77.3%
5-Intervention Bundle			
Gulihar[25]	7.1% patients develop CDI	1.5% patients develop CDI	79%, $P < .001$
Lai[47]	22.5/1,000 discharges[b]	13.2/1,000 discharges	41.3%
Power[29]	2.60 (95% CI, 2.11–3.17) intervention; 1.15 (95% CI, 1.03–1.29) control	0.69 (95% CI, 0.50–0.91) intervention; 0.51 (95% CI, 0.44–0.60) control	73.46% intervention; 55.65% control
Valiquette[37]	2.03[b]	0.82	60%, $P = .007$
Wong-McClure[43]	2.96[b]	2.12	28.4%, $P = .001$
You[36]	4.70	1.53	67%; OR, 0.36 (95% CI, 0.13–0.85), $P = .012$
4-Intervention Bundle			
Apisarnthanarak[48]	5.8 MICU; 8.0 BMT[b]	2.1 MICU; 4.2 BMT	MICU, 63.8%, $P = .05$; BMT 47.5%, $P = .04$
Mattner[27]	1.08[b]	Data in bar graph	8 wards significantly reduced CDI
3-Intervention Bundle			
Price[30]	1.30	0.69	46.9%, $P = .03$
Salgado[46]	5.52[b]	1.24	77.5%
Stone[31]	33.5 /1,000 admissions	19.4 /1,000 admissions	42%, $P < .05$
Suzuki[35]	0.471[b]	0.108	77%, $P < .001$

NOTE. BMT, bone marrow transplant; CDI, *Clostridium difficile* infection; CI, confidence interval; MICU, medical intensive care unit; OR, odds ratio; PD, patient days; SD, standard deviation; RR, relative risk.

[a]Education is considered 1 intervention, even when it includes staff and/or patient components.

[b]Preintervention data were collected during CDI outbreak.

to rapidly involve infection prevention teams and to start appropriate CDI patient care. Most interventions improved communication between diagnostic labs and healthcare providers using electronic medical record flagging or email notifications. Two studies addressed patients identified as asymptomatic *C. difficile* carriers.[34,41] Use of dedicated equipment included stethoscopes, thermometers, blood pressure cuffs, and bed pans. Finally, proton-pump inhibitor interventions restricted these medications according to specific clinical indications.

Adherence to Bundle Components

The measures used to assess adherence varied across studies. Evaluation of contact precautions included direct observations of staff, availability and quantity of personal protective equipment, and glove use. Antibiotic stewardship programs were quantified by the reduction of antibiotic use and typically reported reduction at the single antibiotic level. Hand-hygiene adherence was measured by direct observation and alcohol-based gel rub use. Surface swabbing and usage of cleaning materials was tracked to assess environmental decontamination.

Almost all articles reported measuring adherence for at least 1 component in the bundle (25 of 26, 96.2%) and 46.2% measured adherence for each component (12 of 26, Supplementary S1). However, most studies only stated that they had evaluated adherence to a bundle component without reporting compliance results. For example, adherence to antibiotic stewardship was assessed in 17 of 19 studies (89.5%). However, only 3 studies reported the actual results of their adherence data (Supplementary S1).[31,32,39] Furthermore, because all three studies used different adherence measures, average antibiotic stewardship compliance could not be determined.

TiDier Scores

The level of detail with which interventions were described varied widely both between and within studies. The average

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TiDier score across all interventions was 6.0, ranging from 1.0[27] to 10.4.[45] Two studies provided comprehensive descriptions for a single bundle component, obtaining the maximum score of 12 for these interventions.[37,44] Only 9 studies scored ≥10 on any single intervention (Supplementary S1).[29,33,34,37–39,44,45,49] The average TiDier score for a given bundle component was 5.7, ranging from 8.2 for systems and workflow interventions to 3.0 for proton-pump inhibitor stewardship. Most interventions had an average TiDier score between 5 and 7. Each intervention component evaluated an average of 2.1 adherence measures, ranging from 3.3 for systems and workflow interventions to 1.3 for dedicated equipment.

Improvement in *C. difficile* Rates

All 26 studies showed a decrease in the rate of CDIs after bundle implementation (Table 3). The improvement was significant at the 0.05 level for the 15 studies reporting *P* values (60%, 15 of 25).[25,30,31,35–41,43,45,48–50] The odd ratio for developing CDI under the intervention bundle compared to the control period was reported in 3 studies and ranged from 0.29 to 0.38.[36,38,39] The relative risk was 0.60 in the single study reporting this measure.[40]

Study Quality

The average study quality score, as assessed by the modified Downs and Black checklist,[25] was 15.2 of 28 (Supplementary S2). Total scores ranged from 13 to 18. All studies performed well on questions regarding external validity and poorly on confounding.

DISCUSSION

The overarching goal of bundled interventions is to implement combinations of evidence-based strategies that complement each other and work synergistically. In the case of CDI, the paucity of evidence-based interventions for prevention has led to considerable variation among bundle elements. The lack of adherence data and consistently low TiDier scores among many of these studies indicate that details on intervention implementation have been poorly reported. Thus, it is challenging to corroborate and compare results among studies.

According to the Society for Healthcare Epidemiology of America and Infectious Diseases Society of America's 2014 CDI prevention strategies compendium,[51] none of the 10 interventions compiled in this review were supported by level 1 evidence for CDI prevention. Antibiotic stewardship and contact precautions using gloves were designated as having a moderate quality evidence of effectiveness (level 2), referring to either a small number of supporting studies, moderate study limitations, or variation in results among studies. Contact precautions using gowns, hand hygiene, isolation and cohorting, environmental cleaning, patient and staff CDI education, dedicated equipment, and several systems and workflow interventions were rated as having low-grade evidence (level 3), a category used when studies have major flaws, considerable variation, or are based on expert consensus. The recommendation for proton-pump inhibitor stewardship was considered unresolved. This lack of strong evidence for any single intervention is likely related to the heterogeneity in the selection of bundle components.

Bundle implementation was associated with a decline in CDI rates in all 26 studies published in the literature, making this a potentially promising approach for reducing CDI. However, methodological limitations preclude the assessment of a causal relationship between bundled interventions and CDI rates.

Our systematic review extends and updates the findings of a prior review. In 2014, Yakob et al[52] conducted a review of 21 articles on CDI interventions and their effectiveness, from which they identified 6 eligible studies. In our review, we incorporated 5 articles from this prior review[38–40,46,49] as well as 21 additional articles. We did not include 1 article from Yakob's study, because pre- and postintervention rates were not clearly reported.[53] Given the rapidly changing epidemiology of *C. difficile* and use of CDI bundles, our up-to-date analysis is highly relevant to the current state of CDI control.

Many hospitals have not achieved declines in CDI rates despite intensive efforts to implement prevention strategies.[54,55] While neither of these studies implemented a CDI bundle, they are otherwise similar to many of the studies that met our inclusion criteria. Our review sheds light on 3 potential reasons for a lack of decline in CDI rates. First, compliance to interventions may be below the threshold necessary to be effective. A 2011 study by Furuya et al[19] found that the effect of a CLABSI bundle was not observed until compliance with at least 1 bundle element reached 95%. If adherence to bundle elements was low in the reviewed studies, the potential impact of *C. difficile* bundles may have been underestimated.

Second, the lack of infection control strategies focusing on asymptomatic carriers may have contributed to the lack of decline in CDI rates. Only 8% of CDI bundles included surveillance of asymptomatic carriers. However, focusing exclusively on patients with clinical CDI neglects the much larger reservoir of colonized asymptomatic hospital patients.[56] Asymptomatic patients are an important reservoir of infectious *C. difficile* spores, and the impact of interventions focusing on colonized patients should be rigorously evaluated in future studies.

Finally, hand hygiene is especially complex in the context of CDI. Alcohol-based hand rub is an essential component of most horizontal hand-hygiene interventions and its benefits have been widely reported.[57–59] Horizontal, or broad-based, approaches aim to reduce all infections, instead of targeting specific pathogens. The use of alcohol gels is typically counted

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in adherence data, but pure alcohol-based hand rubs are not active against *C. difficile* spores.[60] Chlorhexidine mixed gels have some efficacy;[61] thus, distinguishing between chlorhexidine mixed gels, pure alcohol-based rubs, and soap and water is essential in the context of CDI bundles. Hand-hygiene compliance data that include the use of pure alcohol-based rubs may provide hospitals with an inaccurate assessment of CDI prevention efforts.

This review has several limitations. First, given the heterogeneity of bundles, it is unclear whether CDI reduction can be attributed to a similar mechanism across all studies. We attempted to mitigate this aspect by loosely defining a bundle as any infection control rollout with >1 intervention, hypothesizing that successful bundle implementation is itself a significant factor regardless of the specific components implemented. Second, most studies we reviewed in this study lacked rigorous statistical testing assessing the significance of the decline in CDI rates postintervention. This deficiency was especially common among studies implementing interventions mid-outbreak, which often lacked definitive comparison rates. Outbreak rates, without contemporaneous controls, can appear statistically significant even when the observed effect is due to regression to the mean. When preintervention CDI rates were unclear, we have presented the highest level of CDI incidence during the outbreak prior to bundle implementation. In addition, publication bias may have favored the publication of studies in which bundles showed a beneficial effect. If studies reporting no reduction in CDI rates after bundle introduction were less likely to be published, then our findings may have overestimated the positive impact of bundle introduction. Finally, it was impossible to quantify the overall effectiveness of bundle implementation and intervention adherence, given the range of outcome and adherence measures employed. The variety of outcome measures used and the paucity error measurements reported made it impossible to undertake a meta-analysis. The development and use of standard intervention-specific adherence measures would facilitate comparisons across future studies.

Ultimately, this review draws from a wide range of hospital types, locations, and infection control contexts. Given that CDI rates improved across all studies despite contextual differences and the variety of bundle components, a tailored bundle approach may be effective. However, this approach should be tested using cluster randomized clinical trials in multiple sites and settings with attention to implementation and process factors to facilitate replication and generalizability.

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2017.7

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