Comparative Effectiveness Review
Number 31

Effective Health Care Program

Effectiveness of Early Diagnosis, Prevention, and Treatment of *Clostridium difficile* Infection

Executive Summary

Introduction

Clostridium difficile infection (CDI) is a serious healthcare-associated infection and a growing health care problem. *C. difficile* is a Gram-positive, spore-forming, anaerobic bacterium that, when ingested, can cause CDI if it is a toxigenic strain. CDI symptoms include varying levels of diarrhea severity, as well as pseudomembranous colitis and toxic megacolon. CDI incidence is estimated at 6.5 cases per 10,000 patient days in hospital.[1] About 250,000 hospitalizations were associated with CDI in 2005.[2] Direct attributable mortality from CDI has been reported to be as high as 6.9 percent of cases.[3] Elderly people in hospitals account for the vast majority of severe morbidity and mortality.[4-6] Residents of long-term care facilities are also at higher risk.[7,8] Incidence rates may increase by fourfold or fivefold during outbreaks.[9] In addition to institutional care environments, *C. difficile* is also common in the community, being easily isolated from soil and water samples.[10] Community-associated CDI rates are generally much lower, accounting for 27 percent of all CDI cases in a recent prevalence study,[9] but are also on the rise.[11] However, the source of the *C. difficile* organisms responsible for cases of CDI in the community is not well understood.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm.**

In order for CDI to develop, a person must be infected with a strain of *C. difficile* capable of making toxin in the person's colon. Toxigenic strains are those that

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care

make toxin B (a cytotoxin), with or without toxin A (an enterotoxin). Approximately 1–2 percent of healthy individuals are colonized with *C. difficile*.[12] If these people have usual, healthy colonic flora, the risk of CDI is very low. There is a small risk of CDI if the colon flora becomes disturbed, commonly through antibiotic use, while the person is colonized with a toxigenic strain. Antibiotics that disturb colon flora enough to allow CDI to develop must get into the colon, and they are associated with alterations in relative amounts of colon bacterial constituents.[13,14] The immune status of the patient also contributes to the risk of developing CDI and the experienced severity.[15] Other risk factors include increasing age, female gender, comorbidities, gastrointestinal procedures, and use of gastric acid suppression medications.[16-25] Risk profiles for recurrent CDI are similar.[21] One study, which statistically modeled CDI within the hospital setting, suggested that reducing patient susceptibility to infection is more effective in reducing CDI cases than lowering transmission rates.[26]

New, more virulent strains have emerged since 2000. Characteristics associated with hypervirulent strains can include increased toxin production (due to a deletion in a toxin regulatory gene), an additional binary toxin, whose role in disease etiology is not well understood, hypersporulation, and high-level resistance to fluoroquinolone antibiotics.[27] These new strains affect a wider population, often people with a lack of established risk factors for CDI based on older strains, such as previous hospitalization or antibiotic use, and include children, pregnant women, and other healthy adults.[28] With hypervirulent strains, the time from symptom development to septic shock may be reduced, making quick diagnosis and proactive treatment regimens critical for positive outcomes.

The highly virulent strain associated with the epidemic of CDI described in the early 2000s may be decreasing in prevalence in limited locations.[29] Recent analysis of an archived collection of *C. difficile* isolates revealed that predominant strains shifted from year to year among a population served at a single institution,[30] suggesting that this strain shift may occur on a larger scale. However, this phenomenon potentially cuts both ways as strains drift toward lesser or higher virulence, and the possible future risks and costs of CDI remain significant.

Scope and Key Questions

The purpose of this systematic review was to provide an overarching assessment of the evidence for comparing the accuracy of diagnostic tests and the effectiveness of prevention and treatment interventions on initial and recurrent CDI-related patient outcomes in adult patients. This purpose was developed during the project's topic refinement stage. There was consensus among key informants that this systematic review's single greatest contribution to the field could be to provide a comprehensive review by an independent organization that covered the major concerns of the field. CDI is an active topic in the literature as well as a vital clinical concern. The consensus opinion included the idea that clinicians and researchers both would be well served by a reaffirmation of what is and is not supported by evidence in the literature, and at what level of evidence, to balance against this activity level.

The major impetus of this review is the presence of clinical disease, not asymptomatic carriage of the *C. difficile* organism. While we were interested in how treatment of CDI varies by organism strain, molecular epidemiology studies whose main purpose was to identify the strains of *C. difficile* present in the population are also outside the scope of this review. The review focuses on adult patients because adults, and particularly elderly adults, carry the large majority of the morbidity and mortality burden.

The following Key Questions (KQs) form the basis for this review:

KQ 1. How do different methods for detection of toxigenic *C. difficile* to assist with diagnosis of CDI compare in their sensitivity and specificity?

(a) Do the differences in performance measures vary with sample characteristics?

KQ 2. What are effective prevention strategies?

(a) What is the effectiveness of current prevention strategies?

(b) What are the harms associated with prevention strategies?

(c) How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?

KQ 3. What are the comparative effectiveness and harms of different antibiotic treatments?

(a) Does effectiveness vary by disease severity or strain?

(b) Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital- versus community-acquired setting?

(c) How do prevention and treatment of CDI affect resistance of other pathogens?

KQ 4. What are the effectiveness and harms of nonstandard adjunctive interventions?

(a) In patients with relapse/recurrent CDI?

Methods

We used the key word "difficile" to identify all articles related to *C. difficile*. Articles were limited to English language and humans. No date limits were applied. We searched MEDLINE, AMED, the Cochrane Library, and ClinicalTrials.gov. For systematic reviews, we searched MEDLINE, the Cochrane Database of Systematic Reviews, and the Web sites of the National Institute for Clinical Excellence, Guidelines.gov, and the National Health Service Health Technology Assessment Programme. We also manually searched reference lists of review articles and articles that were read for the review. Searches were conducted in February 2010 and updated in March and June 2010. An updated search was performed specifically for KQ 3 (standard treatment) in August 2011, because of a significant new study that led to FDA approval of fidaxomicin in May 2011.

For KQ 1, we included studies that used clinical stool specimens from patients suspected to have CDI. We included studies that concurrently compared at least two diagnostic tests in the same laboratory using the same stool samples and using the same reference standard to reduce heterogeneity in the estimates. Studies must have used toxigenic culture, cell cytotoxicity assay, or combinations of tests as the reference test for toxigenic CDI. Direct comparisons of diagnostic tests without a reference test were not included. We sought studies that included patient outcomes or outcomes related to changes in therapy. We present study results in positive terms, that is, true positives (sensitivity) and false positives (1 minus specificity).

For KQ 2, we included studies that examined the effects of prevention strategies aimed at breaking routes of transmission within institutional settings or reducing susceptibility to CDI through antibiotic prescribing practices. We included only studies with CDI incidence, or other measures of CDI, as an outcome. We excluded studies that used only intermediate outcomes, such as reduced spore count in environmental samples. Accepted study designs included randomized controlled trials (RCTs), prospective cohort, retrospective cohort, time series, and before/after trials. We also identified good quality studies that identified specific risk factors for development of CDI in general hospital inpatients to facilitate infectious disease control efforts to target likely effective preventive strategies.

For KQ 3, we included RCTs that compared two active antimicrobial treatments, including vancomycin, metronidazole, bacitracin, nitazoxanide, rifaximin, fidaxomicin, and rifampin, on adult patients. We also included placebo-controlled trials for vancomycin or metronidazole, the agents of most interest. We included initial cure, recurrence (variably defined by symptoms with or without a positive test for *C. difficile*), and mortality, which are outcomes of interest to clinicians and are reported in most studies. We also included time to resolution of diarrhea.

For KQ 4, we included all studies that examined any nonstandard intervention, such as toxin binding agents, probiotics, vaccinations, or other treatments aimed at enhancing a patient's resilience. Outcomes included resolution of symptoms and recurrence.

Diagnostics (KQ1) Results

We found 13 references that provided comparative data about diagnostic tests of interest.[31-43] The number and type of paired (within study) comparisons available for each diagnostic test varied considerably, and not all possible comparisons were available.

Sixteen paired comparisons of seven commonly used immunoassays for toxins A and B provided low-strength evidence that the test sensitivities do not differ.

There was moderate-strength evidence for no differences in test specificities for two comparisons and for a difference of 2 percent in one comparison. Otherwise, there was only low-strength evidence for or against differences in test specificities. There was insufficient evidence of differences between all tests that were not directly compared.

Nine comparisons of two toxin gene detection tests that focus on toxin B to toxin immunoassays provided only low-strength evidence that the gene-based tests are substantially more sensitive. There was moderate evidence that the test specificities in one comparison did not differ. Otherwise, there was only low-strength evidence for differences in either direction between test specificities. There was insufficient evidence of differences between all tests that were not directly compared.

There was no evidence to determine whether any differences in sensitivity or specificity between diagnostic tests depend on patient or specimen characteristics or the clinical scenarios that lead to testing for toxigenic CDI.

Prevention (KQ2) Results

We found 1 Cochrane review, [44] 4 studies on antibiotic prescribing restrictions,[45-48] 11 on single preventive practices aimed at transmission interruption,[49-58] and 10 studies that bundled multiple practices into a prevention strategy.[59-68] We updated a previous systematic review and found 11 studies examining risk factors that met the inclusion criteria.[20]

Overall, the evidence available to link prevention strategies to clinically important outcomes, such as CDI incidence, is of low quality and is not extensive.

Four observational studies[45-48] and one Cochrane review[44] found that prescribing practice interventions decreasing the use of high-risk antimicrobials are associated with decreased CDI incidence. Prescribing practices were also used in multicomponent interventions credited with reducing CDI incidence; however, it is difficult to isolate the specific effects of the prescribing practices.

One controlled trial found glove use significantly reduced CDI incidence in the hospital setting.[49] Likewise, three observational studies, including two controlled, found that disposable thermometer use is likely to reduce CDI incidence.[50-52]

No study examined the effect of handwashing on CDI incidence. Four studies found use of alcohol gels as interventions for other infectious diseases, presumably in the presence of common protocols requiring handwashing in the presence of CDI or visible soiling, did not increase CDI incidence.[53-55,69]

Four single-component intervention studies provide low evidence that disinfection with a chemical compound that kills *C. difficile* spores in the hospital environment prevents CDI, at least in epidemic or hyperendemic settings.[56-58,70] Seven studies included disinfection in multicomponent interventions.[60,62,63,66,71] Disinfection agents examined included hypochlorite solution, hydrogen peroxide, aldehydes, and detergent.

Ten time series/before–after studies have examined bundled multiple interventions using before–after study designs.[59-68,71] All of the studies described the use of the measures to bring epidemic CDI, or endemic CDI which was felt to be excessive, under control. The number of interventions, and the specific nature of any particular intervention, varied widely. Studies employed between two and nine different types of interventions. Study design and intervention complexity, along with the fact that many outbreaks naturally diminish, made it difficult to conclude whether the reduced CDI prevalence was due to one or more intervention components, or entirely independent.

Risk factors for developing CDI include antibiotic use, substantial chronic illness, hospitalization in an ICU, acid suppression, and age.

No data on patient harms or harms to hospital staff due to preventive interventions were reported. Likewise, no studies assessed the sustainability of a prevention program beyond an intervention period.

Standard Treatment (KQ3) Results

Eleven randomized clinical trials were identified that evaluated different antimicrobials (or different doses of a single drug) available for treatment of CDI in the

United States.[72-84] These 11 studies enrolled 1,463 patients and reported efficacy analysis on 1,239 patients.

Overall, study quality is low. Vancomycin and metronidazole, the most frequently clinically used antimicrobials, were also the most frequently compared antimicrobials. Three RCT comparisons of vancomycin to metronidazole, with a total of 335 pooled subjects, found no significant differences in any examined outcome.[73,76,79] One RCT comparing vancomycin to metronidazole, using a prespecified subgroup analysis of 69 patients, found a small but significant increase in the proportion of subjects with severe CDI who achieved initial clinical cure with vancomycin, using a treatment-received analysis.[73] The significance of this difference did not persist when a strict intention-to-treat analysis was performed.

Moderate-strength evidence from one large, high-quality study demonstrated that vancomycin and fidaxomicin performed equally well for initial cure, but that recurrence was significantly decreased with fidaxomicin versus vancomycin.[82] No other head-to-head trial demonstrated superiority of any single antimicrobial for initial clinical cure, clinical recurrence, or mean days to resolution of diarrhea. Combination therapy with rifampin and metronidazole resulted in significantly higher mortality when compared to treatment with metronidazole only.[74] Pooled data of 104 subjects comparing vancomycin to bacitracin showed significantly higher rates of organism or toxin clearance for vancomycin.[77,80]

Harms were not reported with sufficient detail to compare the risks of any particular antimicrobial with another antimicrobial. When harms were reported, they were generally not serious (e.g. nausea, emesis) and transient.

A single study assessed initial cure and recurrence by strain, categorized as North American pulsed-field gel electrophoresis type 1 (NAP1) versus non-NAP1. Strain data was available for 324 of 629 (51.5%) participants. For initial cure, no significant difference was observed, regardless of strain. However, among patients with non-NAP1 strains, those treated with fidaxomicin recurred less frequently than those treated with vancomycin (10% vs. 28%: P<0.001), whereas among patients with the NAP1 strain, recurrence was similarly frequent regardless of treatment.[82]

Nonstandard Treatment (KQ4) Results

Five RCTs on nonstandard adjunctive treatments of CDI and 13 studies that addressed prevention of CDI formed the basis of this analysis. Four of the studies on treatment of CDI compared a nonstandard intervention with an active control, that is, a standard antibiotic treatment for CDI, oral vancomycin or metronidazole.[83-86] One study compared a nonstandard intervention with placebo.[87] All of the 13 prevention studies compared the nonstandard intervention with placebo rather than with another intervention, reflecting the current state of the science in this area. Five of the 13 prevention studies analyzed antibiotic-acquired diarrhea as a primary outcome and CDI as a secondary outcome.[83-86] Numerous published case reports, as well as nonexperimental studies, describe additional nonstandard approaches for treatment of CDI and their possible harms. As found with the other KQs, overall, study quality was low. Definitions of CDI with regard to diarrhea, that is, number and consistency of stools, were inconsistent across studies.

For treatment of CDI, *C. difficile* immune whey that binds *C. difficile* toxin A is similar to metronidazole in a small study of 38 patients with recurrent CDI.[85] Colestipol, an absorptive resin, is not more effective in treating CDI than placebo.[87] Probiotics administered as an adjunct to antibiotic treatment were not more effective than treatment with antibiotics alone.[83,84,86]

There is low-strength limited evidence that the probiotic[88-93] interventions in this review are not more effective than placebo for primary prevention of CDI. There is low-strength limited evidence from one subgroup analysis that a prebiotic may reduce diarrhea recurrence in patients treated for CDI more so than placebo with standard antibiotics.[94,95] Fungemia is a serious potential harm associated with administration of probiotics for CDI in critically ill patients.[96,97] In one review, 46 percent of 60 critically ill patients who developed fungemia had been administered a probiotic containing *Saccharomyces boulardii* and 5 more patients were in the vicinity of an administered probiotic. Seventeen patients subsequently died.[96]

There is limited moderate-strength evidence from one study that monoclonal antibodies are effective in preventing recurrence of CDI.[98]

There is limited low-strength evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year.[99,100]

Discussion

There is very limited high-strength evidence to support the diagnostic, preventive, and treatment practices for CDI carried out by providers in hospital, long-term care, and outpatient settings. Table A provides a summary of the evidence and results presented in this review. Inconsistency in definitions of diarrhea, severity, resolution of symptoms, recurrence, or cure contributes to the difficulty in drawing conclusions from the evidence.

In general, there is little evidence that the sensitivities of commonly used immunoassays for toxins A and B differ, and any differences in their percent of false positives (1 minus specificity) most likely are small (3 percent or less). However, the strength of the evidence is low due to the number of studies that have directly compared various immunoassays in the literature. Future research possibly could impact the findings. The available comparative data does not rule out the possibility of larger differences in test sensitivities between some of the immunoassays that have or have not been directly compared in adequate numbers. While the precision of the findings is such that we cannot rule out the possibility of differences in sensitivity on the order of 3 to 5 percent, it is unclear whether such differences would affect clinical decisionmaking.

Gene detection tests that focus on toxin B tended to have better sensitivity than immunoassays for toxins A and B. Results, however, should be viewed with caution, given rather imprecise confidence intervals on the estimated differences. Further study of the differences in false positives, if any, is needed, too. Few studies contributed to the findings, and many direct comparisons were not found. Furthermore, variation in the stability of the toxins in stool specimens as they were collected, stored, and processed may have contributed to the observed variation between studies in the estimates of the sensitivities of the immunoassays, whereas detection of amplified toxin gene fragments could be less susceptible to specimen degradation and more susceptible to contamination of specimens. Differences in the sensitivities of the reference tests could affect the estimated sensitivity for immunoassays to greater degrees than gene detection tests as well.

The immunoassays and gene detection tests require varying skills, equipment, and time to carry out, and heterogeneity is a significant factor in reviewing the literature. Previous reviews by Planche et al.[101] and Crobach et al.[102] encountered difficulty comparing the sensitivities and specificities of immunoassays in large part because there was too much variation between studies in the estimates of the sensitivity and specificity of a particular test. We attempted to control for the heterogeneity between studies by examining the differences in sensitivity and specificity in stool samples tested within the same lab using the sample patient stool specimens and reference test, and we did not find strong evidence of differences between tests within several immunoassays for toxins type A and B. The extent of any publication bias for these comparisons is unknown.

A clinically important question is whether the potential differences in the accuracy of the diagnostic tests being employed in practice would translate into differences in clinical behaviors or patient outcomes. Indeed, how well clinicians actually know the sensitivity and specificity of the test(s) for toxigenic *C. difficile* employed by their laboratories and incorporate this information into their patient care decisions is not clear. If test results are combined with pretest probabilities that patients have toxigenic *C. difficile* using Bayes' formula, then the differences in post-test probabilities might not lead to different clinical decisions even if there are substantial differences in the sensitivities and specificities of tests for toxigenic *C. difficile*.

Very little evidence connects prevention strategies and techniques directly to patient-related outcomes, such as CDI incidence. Available evidence is generally from before–after study designs or limited time series. Hospital settings with outbreaks or hyperendemic episodes further limit applicability of the findings and leave open the question of the relative contribution of regression to the mean (i.e., that CDI rates returned to baseline rates even in the absence of effective interventions). The studies also varied in the degree to which they described CDI surveillance, diagnostic accuracy, or laboratory performance. In most, surveillance was passive and depended on a positive toxin test on a stool specimen sent by clinicians caring

for a patient with diarrhea. Unknown numbers of cases might have been missed or misdiagnosed. Additionally, attention has not been given to describing a prevention strategy's potential harm (e.g., increase in other pathogens, reduction in direct patient care contact due to isolation or restrictive contact requirements, increased costs) or the long-term sustainability of a practice.

There is low-strength evidence that antibiotic prescribing practices appear to reduce CDI incidence, a finding consistent with the Cochrane review.[44] None of the studies explicitly addressed the potential harms of changes in antibiotic use policy, but there are several theoretical harms. They include the possibility that preferred drugs will be less effective than drugs that physicians are discouraged from using, or drugs that are made unavailable for treating infections other than CDI. Preferred antimicrobials might have greater costs or greater toxicities unrelated to CDI. *C. difficile* strains might evolve to develop resistance to the preferred antibiotics, which might increase the likelihood that the recommended antibiotics might induce CDI.

While several studies found increased risk with specific antibiotics or antibiotic classes, the antibiotics that confer greater risk for CDI have changed over time and vary by location because of differences in prevalent toxigenic strains and especially the susceptibility patterns of those strains.[103] Clindamycin resistance was identified soon after the role of *C. difficile* in pathogenesis was discovered.[49,104,105] More recently, quinolones have assumed greater importance because strains have become more resistant over time.[106]

Fewer studies are available to support prevention practices aimed at breaking transmission. There was limited low-strength evidence that gloves, disposable thermometers, handwashing, and intensive disinfection solutions help to reduce CDI incidence. In addition, the presence and use of alcohol gel to prevent other hospital-acquired infections, such as MRSA, did not increase the rate of CDI incidence as might be expected if alcohol gel use replaced handwashing.

Similar to the antibiotic prescribing practice research, none of the studies aimed at breaking transmission addressed potential harms for other prevention practices. Costs of disinfection, time to perform disinfection, and the possible harm to surfaces and equipment should be anticipated. Failures with vapor disinfection systems would be possible and might lead to toxic exposures of personnel or patients. Nor is there evidence to inform infection control professionals whether such practices are sustainable after an intervention period. That is, we cannot answer whether environmental cleaning staff will have developed professional habits that will continue when the intense monitoring related to an intervention period discontinues.

The potential for prevention research is often compromised by the swift uptake of newly described prevention strategies with the belief that these will improve institutional practices and health care quality and will reduce CDI morbidity and mortality. Current prevention strategies often rely on studies using intermediate outcomes such as process. Newly acquired strategies are then added to current practice, bundling them into multiple component interventions. When introduced in outbreak or hyperendemic situations, these "bundled" multipronged prevention efforts in natural settings have been associated with reduction in CDI incidence. The bundles appear to be beneficial, but from a research standpoint, it is challenging to design research that would tease out the relative contributions of single components to the overall bundle of prevention strategies to determine which ones are essential or what might be added.

The available evidence is insufficient to say whether any antimicrobial treatment is better than another, including the two most commonly used treatments, metronidazole and vancomycin. The total number of subjects from comparative studies on metronidazole and vancomycin is just 335 patients. This raises the possibility that, although a significant difference in effectiveness has not been detected, a true difference may exist. There is moderate strength of evidence that recurrence is less frequent with fidaxomicin than with vancomycin, and that these two agents are not significantly different from one another for initial cure. Otherwise, there is no evidence for a difference in effectiveness for other agents, but again the possibility remains that such a difference exists. However, at this time, any claims that one agent is superior to another for all cases of CDI are not supported by available evidence. The findings apply to general adult inpatients. Bias due to selectively reporting outcomes is possible if

cut-points are changed for CDI definitions, for example, number or consistency of stools. The clinical differences of changes in cut-points are also unknown, however, so the clinical significance could remain.

We found insufficient evidence that vancomycin was superior to metronidazole for subjects classified as having severe disease. One subgroup analysis of a single trial used a prespecified analysis, and the severity classification appears to have been made before treatment allocation. However, the superiority of vancomycin over metronidazole does not persist when a strict intention-to-treat analysis is used.

We sought to document the range of treatments under investigation for treatment and prevention of CDI, particularly recurrent CDI. The evidence for effectiveness of nonstandard interventions for treating CDI shows that probiotics, prebiotics, *C. difficile* immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or compared with placebo. The evidence supporting this conclusion is limited and of low strength.

Prevention of CDI, both initial and recurrent cases, through interventions intended to improve gut flora and host immunity is also a very active topic in the literature. There is limited, low-strength evidence that the nonstandard prevention interventions are not more effective than placebo for primary prevention of CDI. There is limited evidence of low strength that administering the prebiotic oligofructose or a monoclonal antibody to *C. difficile* toxins A and B along with standard antibiotics for CDI are better than placebo and active control in preventing recurrence of CDI in patients treated for CDI. Although the studies for both treatment and prevention of CDI using a nonstandard intervention included components of experimental designs, few had adequate rigor to yield high-quality findings or power to detect a significant difference between the interventions (or placebo) compared. In some studies, a low rate of CDI precluded statistical testing.

Caution is recommended regarding new, nonstandard treatments and not extrapolating study findings beyond the data. For example, one cannot assume that if a probiotic treatment is effective for antibiotic-associated diarrhea, it will be effective for CDI. Likewise, attention should be paid to which patients were included and excluded in probiotic treatment studies. Such studies generally exclude high-risk patients. Thus, there is no evidence for the use of probiotics in high-risk patients.

Future Research

A number of important questions need to be addressed regarding diagnostic testing, prevention, and treatment of CDI. Table B summarizes the research recommendations.

Diagnostic tests. It is difficult to apply the available evidence from comparative studies to help select the best diagnostic test(s) for clinical applications. The reviewed comparative studies did not clearly define the testing scenario including the setting, disease prevalence, patient selection criteria, patient characteristics, or signs and symptoms of the suspected CDI, making it difficult to judge to whom the study results might apply. Ultimately, the clinical importance of estimated differences in sensitivity (true positives), false positives, specificity (true negatives), and false negatives depends on how these types of test results would affect clinical decisions, hence patient outcomes.

More research is needed to understand how test sensitivities and specificities are used to make decisions in clinical practice, and to define clinically meaningful differences based on their effects on clinical decisions and patient outcomes. Multicenter studies that (1) consistently use the most clinically relevant reference test, (2) use explicit clinical criteria to select patients and stool specimens to be tested, (3) randomly assign patients to different diagnostic tests, and (4) use key clinical outcomes as study endpoints are needed to fill this major gap in knowledge about diagnostic tests for toxigenic *C. difficile*.

Questions about whether the newer toxin gene amplification and detection tests are more consistent across laboratories, and more sensitive than the currently used toxin immunoassays for toxin without substantial loss of specificity, need further study. Most importantly, studies are needed to demonstrate that use of tests that detect genetic residue related to *C. difficile* toxin production rather than the toxins per se lead to better patient outcomes.

Prevention. A number of potential prevention strategies can and should be investigated as a single intervention in a controlled trial in order to understand its potential contribution to a prevention program. However, the main obstacle to research in this area is the contextual setting.

Prevention happens within an institutional environment, as a comprehensive approach for preventing multiple potential hospital-acquired infectious agents and attending to multiple potential vectors of transmission and host susceptibility. Researchers and decisionmakers may need to consider another approach to inform decisionmaking: a collaborative research process in which consensus agreements are reached for minimum datasets and followup periods, and definitions of interventions are agreed to in order to facilitate pooling data across organizations. For example, minimum datasets might be those that would yield statistically significant results in a controlled trial if the intervention arm could prevent 10 to 20 percent of CDI cases. Datasets of this nature could allow for employing more sophisticated epidemiological and decision analytic techniques to tease apart the relative contributions of different prevention strategies. The nature of the decisions faced by infection control professionals is qualitatively different from a physician's clinical decisions for an individual CDI patient. Decision analytic techniques may be particularly valuable in this venue.

Standard treatment. The greatest needs for future studies for CDI treatment are consistent definitions and reporting of outcomes, a uniform and clinically relevant definition of disease severity, and trials with adequate power to detect clinically meaningful differences in outcomes. In particular, trials need to include adequate numbers of subjects to allow stratification by patient characteristics such as age, gender, and comorbid conditions in order to address questions regarding the most effective therapy for CDI. A well-validated and clinically meaningful severity score would also assist in treatment decisions. Although most agents for CDI appear to be well tolerated, explicit reporting of adverse events by treatment allocation is another area where future research can improve our understanding of optimal management of this disease.

Although identifying the strain of *C. difficile* is of great relevance to researchers and can offer useful information to hospital epidemiologists, at present, strain identification is rarely performed in clinical settings. Thus, few clinicians treating CDI are aware of which strain of *C. difficile* is causing an individual patient's disease and can, at most, make an assumption as to the strain type based on current epidemiology reported in the literature. This limitation makes any difference by strain in treatment efficacy of uncertain relevance.

Nonstandard treatment. Additional research on nonstandard interventions as adjunctive or alternatives to standard antibiotics for preventing and treating CDI is needed and encouraged. Studies to prevent recurrence of *C. difficile* are a priority of prevention. As no single approach has been shown to be superior, promoting studies of different types of interventions is reasonable at this time.

Fecal flora reconstitution is one novel therapy for which continued research is supported. Of all the nonstandard interventions, probiotics have been investigated in the most studies, and the results are not encouraging. Unlike fecal flora reconstitution, probiotics provide only a single strain or a few strains of bacteria, and thus may be insufficient to correct alterations in the complex and extensive microbiome to the extent needed to be therapeutic. The genomic mapping of indigenous microflora may offer new information to guide future formulation of a probiotic that can effectively target alterations in the microbiome in CDI and other diseases of the colon. A third strategy related to modifying microbial ecology in CDI for which additional research is supported is administration of a nontoxigenic strain of *C. difficile*.

Developing agents to treat severe cases of refractory CDI is another area in need of research. Identifying new antibiotics may be one approach. Two of the larger case series of immunoglobulin use are in severely ill patients, and results are inconsistent.[107,108] Whether immunoglobulin might confer greater benefit if initiated earlier in the course of CDI prior to extensive systemic involvement is an area for further study.

Studies are needed to determine whether some patients might be more likely to respond to nonstandard

interventions. Sampling in current studies of nonstandard interventions varies considerably, ranging from individuals who are just starting antibiotics for infections other than *C. difficile*, to those who have had multiple failures of antibiotic treatment for CDI itself, to those who have had *C. difficile* in the past. Whether any one type of nonstandard intervention is effective in all of these types of cases is a question. More information is needed about patients who are at high risk for recurrence of CDI.

The effect of sequencing therapies (antibiotic as well as nonstandard) on the resolution of CDI merits further research. Studies show a variety of procedures for administering probiotics to prevent CDI, for example, such as during standard antibiotic therapy or for a period after standard treatment is completed. Determining the optimal timing to introduce nonstandard interventions to possibly maximize their effect is recommended.

Methodological improvements. It is essential that future studies of a nonstandard intervention for treatment or prevention of CDI be supported by a power analysis, adequate sample size, and an intent-to-treat analysis, in addition to other standard quality components of experimental design. Study designs must separate interventions for prevention versus treatment of recurrent CDI if this approach is desired. Multicenter studies may be necessary to achieve adequate sample sizes. Laboratory confirmation of a pathogenic C. difficile organism (e.g., by toxin testing) and clinical symptoms of disease (e.g., diarrhea) are essential not only for study eligibility but for determination of recurrence in long-term followup. Adoption of a standard definition of diarrhea as part of the definition of CDI is strongly recommended. Similarly, a standard definition of CDI resolution should be adopted. RCTs that compare more than one type of nonstandard intervention are suggested for efficiency.

Table A. Summary of evidence

Key Questions (KQs)	Level of Evidence	Summary/Conclusion/Comments
KQ 1 Diagnostics		
Immunoassays for toxins A and B	Low to moderate	• Ten studies directly compared at least 2 immunoassays for toxins A and B, providing 16 pairwise comparisons of 7 different immunoassays. Comparative data were not found for many currently used tests. • There were no statistical differences between the sensitivities of immunoassays that were compared; however, the estimates of the differences in sensitivity were not very precise and could not rule out substantial differences. • Substantial differences in false positives, that is, specificity, were not found among the tests that were compared.
Gene detection tests versus immunoassays for toxins A and B	Low to moderate	• Four studies compared at least one toxin gene detection test to at least one immunoassay for toxins A and B, providing a total of nine direct comparisons. Comparative data were not always available for the three currently available gene detection tests. • The gene detection tests could be substantially more sensitive than many immunoassays for toxins A and B, with no or relatively modest loss of specificity.
Patient characteristics	Insufficient	• Insufficient patient information was provided in reports of comparative data.

Table A. Summary of evidence (continued)		
Key Questions (KQs)	**Level of Evidence**	**Summary/Conclusion/Comments**
KQ 2 Prevention		
Antibiotic use	Low	• Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence. • Harms were not reported.
Gloves	Low	• One controlled trial found use of gloves in hospital settings reduced CDI incidence.
Disposable thermometer	Low	• Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence.
Handwashing/alcohol gel	Low	• No study examined whether handwashing reduced CDI incidence. • Two studies, one controlled trial and one before–after study, of use of alcohol gel to reduce MRSA transmission did not find significant differences in CDI incidence.
Disinfection	Low	• Thirteen before–after studies of outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills C. difficile spores reduced CDI incidence.
Sustainability	Insufficient	• No evidence was available.
Risk factors	Low	• Ten observational studies found evidence that antibiotic use, whether specific or general, increased risk of CDI. • Severe underlying disease, acid suppression, and age are indicated as risk factors. A number of other potential factors may be indicated in single studies.
Multiple component strategies	Insufficient	• Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data are insufficient to draw conclusions. • Harms were not reported.
KQ 3 Antibiotic Treatment		
Vancomycin versus metronidazole	Moderate for clinical cure, low for all other outcomes	• There were 3 head-to-head trials with a total of 335 subjects. Trials used various definitions of CDI patient and cure, especially with regard to stool count and consistency. • No significant differences in outcomes, including initial cure, clinical recurrence, and mean days to resolved diarrhea, were found. • Our results build upon, and are consistent with, the Cochrane Reviews search completed by Bricker et al.[109]

Table A. Summary of evidence (continued)		
Key Questions (KQs)	**Level of Evidence**	**Summary/Conclusion/Comments**
KQ 3 Antibiotic Treatment (continued)		
Severe disease, vancomycin versus metronidazole	Insufficient	• One RCT examined a prespecified subgroup of 69 subjects with severe CDI; improved clinical cure was based on per-protocol analysis, but not with strict intention to treat analysis.
Fidaxomycin versus vancomycin	Moderate	One large, high-quality RCT deomonstrated decreased recurrence among those receiving fidaxomicin.
All other comparisons of standard treatments	Moderate for vancomycin versus fidaxomicin, low for all other comparisons	• There were eight trials examining: vancomycin versus bacitracin (two trials), vancomycin versus fidaxomicin, vancomycin versus nitazoxanide, vancomycin high versus low dose, vancomycin versus placebo, metronidazole versus nitazoxanide, and metronidazole versus metronidazole plus rifampin (one each). No differences.
Strain of organism	Low	• One RCT (fidaxomicin vs. vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain.
Patient characteristics	Insufficient	• No comparative data were available.
Resistance of other pathogens	Insufficient	• No data were available.
KQ 4 Nonstandard Treatment		
Treating CDI, active control	Low	• Probiotics, prebiotics, *C. difficile* immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo.
Treating CDI, placebo	Low	• Administration of a probiotic with live bacteria to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any known benefit.
Treating recurrent CDI	Low	• There is limited evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year.
Preventing CDI	Low	• There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI.
Preventing recurrent CDI	Low to moderate	• There is limited evidence from one subgroup analysis that a prebiotic may reduce diarrhea recurrence in patients treated for CDI more so than placebo with standard antibiotics. • There is limited moderate-strength evidence from one study that monoclonal antibodies are effective in preventing recurrence of CDI.

CDI = *Clostridium difficile* infection; RCT = randomized controlled trial

Table B. Future research recommendations			
Key Questions (KQs)	**Research Gaps**	**Types of Studies Needed to Answer Questions**	**Future Research Recommendations**
KQ 1. How do different methods for detection of toxigenic *C. difficile* compare in their sensitivity, specificity, and predictive values?	• Few comparisons are available • Heterogeneity is an obstacle • Unknown what differences in sensitivity and specificity would alter clinician decisionmaking • Unknown influence of patient and stool characteristics on test sensitivity and specificity	• Comparison of diagnostic tests using same samples, same labs • Multicenter studies with well-documented patient samples	• Document stool sample characteristics, patient selection criteria, patient characteristics, and signs and symptoms of suspected CDI
KQ 2. What are effective prevention strategies?	• Little evidence available with clinically important outcomes	• High-quality comparative studies evaluating effectiveness and harms of single and/or multicomponent prevention strategies, including cleaning, isolation, antibiotic restriction • Discrete simulation models	• Pool data from multiple participating hospital sites • Establish minimum datasets for observational data points that can inform models
KQ 3. What are the comparative effectiveness and harms of different antibiotic treatments?	• Limited evidence available on whether vancomycin is more effective for severe CDI	• High-quality comparative studies with adequate power to detect significance in a priori subgroups	• A uniform and clinically relevant definition of severity • Subgroup analysis may include age, gender, comorbid conditions • Explicit reporting of adverse events
KQ 4. What are the effectiveness and harms of nonstandard adjunctive interventions?	• Probiotics as a treatment adjuvant is not supported. Potential harms to seriously ill patients may outweigh potential benefits for further prevention research • Probiotics as prevention warrants further study • Further research of monoclonal antibodies for prevention is warranted • Further research of fecal transplant is warranted	• High-quality comparative studies with adequate power	• Placebo comparators would contribute indirect evidence that would help guide potential combination therapies • Quality research includes power analysis, intention to treat • Multicenter trials are likely needed to achieve adequate samples • Trials of probiotics for prevention are well represented in ongoing studies • Patient characteristics for subgroup analysis
Umbrella issues			• Adoption of standard definitions for diarrhea, CDI resolution

References

1. Gravel D, Miller M, Simor A, et al. Health care-associated Clostridium difficile infection in adults admitted to acute care hospitals in Canada: a Canadian Nosocomial Infection Surveillance Program Study. Clinical Infect Dis 2009 Mar 1; 48(5):568–76.
2. McDonald LC. Confronting Clostridium difficile in inpatient health care facilities. Clin Infect Dis 2007 Nov 15; 45(10):1274–6.
3. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med 2005 Dec 8; 353(23):2442–9.
4. Brandt LJ, Kosche KA, Greenwald DA, et al. Clostridium difficile-associated diarrhea in the elderly. Am J Gastroenterol 1999 Nov; 94(11):3263–6.
5. Hebuterne X. Gut changes attributed to ageing: effects on intestinal microflora. Curr Opin Clin Nutr Metab Care 2003 Jan; 6(1):49–54.
6. Kim J, Smathers SA, Prasad P, et al. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. Pediatrics 2008 Dec; 122(6):1266–70.
7. Simor AE, Bradley SF, Strausbaugh LJ, et al. Clostridium difficile in long-term-care facilities for the elderly. Infect Control Hosp Epidemiol 2002 Nov; 23(11):696–703.
8. Laffan AM, Bellantoni MF, Greenough WB, 3rd, et al. Burden of Clostridium difficile-associated diarrhea in a long-term care facility. J Am Geriatr Soc 2006 Jul; 54(7):1068–73.
9. Jarvis WR, Schlosser J, Jarvis AA, et al. National point prevalence of Clostridium difficile in US health care facility inpatients, 2008. Am J Infect Control 2009 May; 37(4):263–70.
10. Kim KH. Isolation of Clostridium difficile from the environment and contacts of patients with antibiotic-associated colitis. J Infect Dis 1981 Jan; 143(1):42–50.
11. McFarland LV. Renewed interest in a difficult disease: Clostridium difficile infections--epidemiology and current treatment strategies. Curr Opin Gastroenterol 2009 Jan; 25(1):24–35.
12. Viscidi R, Willey S, Bartlett JG. Isolation rates and toxigenic potential of Clostridium difficile isolates from various patient populations. Gastroenterol 1981 Jul; 81(1):5–9.
13. Chang JY, Antonopoulos DA, Kalra A, et al. Decreased diversity of the fecal Microbiome in recurrent Clostridium difficile-associated diarrhea. J Infect Dis 2008 Feb 1; 197(3):435–8.
14. Young VB, Schmidt TM. Antibiotic-associated diarrhea accompanied by large-scale alterations in the composition of the fecal microbiota. J Clin Microbiol 2004 Mar; 42(3):1203–6.
15. Aslam S, Musher DM. An update on diagnosis, treatment, and prevention of Clostridium difficile-associated disease. Gastroenterol Clin North Am 2006 Jun; 35(2):315–35.
16. Dial S, Alrasadi K, Manoukian C, et al. Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. CMAJ 2004 Jul 6; 171(1):33–8.
17. Dial S, Delaney JAC, Barkun AN, et al. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA 2005 Dec 21; 294(23):2989–95.
18. Aseeri M, Schroeder T, Kramer J, et al. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalized patients. Am J Gastroenterol 2008 Sep; 103(9):2308–13.
19. Linsky A, Gupta K, Lawler EV, et al. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 2010 May 10; 170(9):772–8.
20. Bignardi GE. Risk factors for Clostridium difficile infection. J Hosp Infect 1998 Sep; 40(1):1–15.
21. Garey KW, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. J Hosp Infect 2008 Dec; 70(4):298–304.
22. Cunningham R, Dial S. Is over-use of proton pump inhibitors fuelling the current epidemic of Clostridium difficile-associated diarrhoea? J Hosp Infect 2008 Sep; 70(1):1–6.
23. Thibault A, Miller MA, Gaese C. Risk factors for the development of Clostridium difficile-associated diarrhea during a hospital outbreak. Infect Control Hosp Epidemiol 1991 Jun; 12(6):345–8.
24. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol 2007 Sep; 102(9):2047–56; quiz 57.

25. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. Arch Intern Med 2010 May 10; 170(9):784–90.

26. Starr JM, Campbell A, Renshaw E, et al. Spatio-temporal stochastic modelling of Clostridium difficile. J Hosp Infect 2009 Jan; 71(1):49–56.

27. Gerding DN, Muto CA, Owens RC, Jr. Measures to control and prevent Clostridium difficile infection. Clin Infect Dis 2008 Jan 15; 46 Suppl 1:S43–9.

28. Centers for Disease Control and Prevention. Severe Clostridium difficile-associated disease in populations previously at low risk: four states, 2005. MMWR Morb Mortal Wkly Rep 2005 Dec 2; 54(47):1201–5.

29. Hensgens MP, Goorhuis A, Notermans DW, et al. Decrease of hypervirulent Clostridium difficile PCR ribotype 027 in the Netherlands. Euro Surveill 2009; 14(45).

30. Belmares J, Johnson S, Parada JP, et al. Molecular epidemiology of Clostridium difficile over the course of 10 years in a tertiary care hospital. Clin Infect Dis 2009 Oct 15; 49(8):1141–7.

31. Alcala L, Sanchez-Cambronero L, Catalan MP, et al. Comparison of three commercial methods for rapid detection of Clostridium difficile toxins A and B from fecal specimens. J Clin Microbiol 2008 Nov; 46(11):3833–5.

32. Eastwood K, Else P, Charlett A, et al. Comparison of nine commercially available Clostridium difficile toxin detection assays, a real-time PCR assay for C. difficile tcdB, and a glutamate dehydrogenase detection assay to cytotoxin testing and cytotoxigenic culture methods. J Clin Microbiol 2009 Oct; 47(10):3211–7.

33. Musher DM, Manhas A, Jain P, et al. Detection of Clostridium difficile toxin: comparison of enzyme immunoassay results with results obtained by cytotoxicity assay. J Clin Microbiol 2007 Aug; 45(8):2737–9.

34. Samra Z, Luzon A, Bishara J. Evaluation of two rapid immunochromatography tests for the detection of Clostridium difficile toxins. Dig Dis Sci 2008 Jul; 53(7):1876–9.

35. Sloan LM, Duresko BJ, Gustafson DR, et al. Comparison of real-time PCR for detection of the tcdC gene with four toxin immunoassays and culture in diagnosis of Clostridium difficile infection. J Clin Microbiol 2008 Jun; 46(6):1996–2001.

36. O'Connor D, Hynes P, Cormican M, et al. Evaluation of methods for detection of toxins in specimens of feces submitted for diagnosis of Clostridium difficile-associated diarrhea. J Clin Microbiol 2001 Aug; 39(8):2846–9.

37. Kvach EJ, Ferguson D, Riska PF, et al. Comparison of BD GeneOhm Cdiff real-time PCR assay with a two-step algorithm and a toxin A/B enzyme-linked immunosorbent assay for diagnosis of toxigenic Clostridium difficile infection. J Clin Microbiol 2010 Jan; 48(1):109–14.

38. Turgeon DK, Novicki TJ, Quick J, et al. Six rapid tests for direct detection of Clostridium difficile and its toxins in fecal samples compared with the fibroblast cytotoxicity assay. J Clin Microbiol 2003 Feb; 41(2):667–70.

39. Miendje Deyi VY, Vandenberg O, Mascart G, et al. Diagnostic value of five commercial tests for the rapid diagnosis of Clostridium difficile-associated disease. Clin Lab 2008; 54(1–2):9–13.

40. Novak-Weekley SM, Marlowe EM, Miller JM, et al. Clostridium difficile testing in the clinical laboratory by use of multiple testing algorithms. J Clin Microbiol 2010 Mar; 48(3):889–93.

41. van den Berg RJ, Vaessen N, Endtz HP, et al. Evaluation of real-time PCR and conventional diagnostic methods for the detection of Clostridium difficile-associated diarrhoea in a prospective multicentre study. J Med Microbiol 2007 Jan;56(Pt 1):36–42.

42. Alcala L, Marin M, Madrid M, et al. Comparison of ImmunoCard Toxins A&B and the new semiautomated Vidas Clostridium difficile Toxin A&B tests for diagnosis of C. difficile infection. J Clin Microbiol 2010 Mar;48(3):1014–5.

43. Swindells J, Brenwald N, Reading N, et al. Evaluation of diagnostic tests for Clostridium difficile infection. J Clin Microbiol 2010 Feb;48(2):606–8.

44. Davey P, Brown E, Fenelon L, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2005;(4):CD003543.

45. Fowler S, Webber A, Cooper BS, et al. Successful use of feedback to improve antibiotic prescribing and reduce Clostridium difficile infection: a controlled interrupted time series. J Antimicrob Chemother 2007 May; 59(5):990–5.

46. Wilcox MH, Freeman J, Fawley W, et al. Long-term surveillance of cefotaxime and piperacillin-tazobactam prescribing and incidence of Clostridium difficile diarrhoea. J Antimicrob Chemother 2004 Jul; 54(1):168–72.

47. O'Connor KA, Kingston M, O'Donovan M, et al. Antibiotic prescribing policy and Clostridium difficile diarrhoea. QJM 2004 Jul; 97(7):423–9.

48. Ludlam H, Brown N, Sule O, et al. An antibiotic policy associated with reduced risk of Clostridium difficile-associated diarrhoea. Age Ageing 1999 Oct; 28(6):578–80.

49. Johnson S, Gerding DN, Olson MM, et al. Prospective, controlled study of vinyl glove use to interrupt Clostridium difficile nosocomial transmission. Am J Med 1990 Feb; 88(2):137–40.

50. Brooks SE, Veal RO, Kramer M, et al. Reduction in the incidence of Clostridium difficile-associated diarrhea in an acute care hospital and a skilled nursing facility following replacement of electronic thermometers with single-use disposables. Infect Control Hosp Epidemiol 1992 Feb; 13(2):98–103.

51. Brooks S, Khan A, Stoica D, et al. Reduction in vancomycin-resistant Enterococcus and Clostridium difficile infections following change to tympanic thermometers. Infect Control Hosp Epidemiol 1998 May; 19(5):333–6.

52. Jernigan JA. A randomized crossover study of disposable thermometers for prevention of Clostridium difficile and other nosocomial infections. Infect Control Hosp Epidemiol 1998; 19(7):494–9.

53. Rupp ME, Fitzgerald T, Puumala S, et al. Prospective, controlled, cross-over trial of alcohol-based hand gel in critical care units. Infect Control Hosp Epidemiol 2008 Jan; 29(1):8–15.

54. Gordin FM, Schultz ME, Huber RA, et al. Reduction in nosocomial transmission of drug-resistant bacteria after introduction of an alcohol-based handrub. Infect Control Hosp Epidemiol 2005 Jul; 26(7):650–3.

55. Kaier K. Two time-series analyses of the impact of antibiotic consumption and alcohol-based hand disinfection on the incidences of nosocomial methicillin-resistant Staphylococcus aureus infection and Clostridium difficile infection. Infect Control Hosp Epidemiol 2009; 30(4):346–53.

56. Mayfield JL, Leet T, Miller J, et al. Environmental control to reduce transmission of Clostridium difficile. Clin Infect Dis 2000 Oct; 31(4):995–1000.

57. Kaatz GW, Gitlin SD, Schaberg DR, et al. Acquisition of Clostridium difficile from the hospital environment. Am J Epidemiol 1988 Jun; 127(6):1289–94.

58. Struelens MJ, Maas A, Nonhoff C, et al. Control of nosocomial transmission of Clostridium difficile based on sporadic case surveillance. Am J Med 1991 Sep 16; 91(3B):138S–44S.

59. Abbett SK, Yokoe DS, Lipsitz SR, et al. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated Clostridium difficile infection. Infect Control Hosp Epidemiol 2009 Nov; 30(11):1062–9.

60. Boyce JM, Havill NL, Otter JA, et al. Impact of hydrogen peroxide vapor room decontamination on Clostridium difficile environmental contamination and transmission in a healthcare setting. Infect Control Hosp Epidemiol 2008 Aug; 29(8):723–9.

61. Brown E, Talbot GH, Axelrod P, et al. Risk factors for Clostridium difficile toxin-associated diarrhea. Infect Control Hosp Epidemiol 1990 Jun; 11(6):283–90.

62. Cartmill TD, Panigrahi H, Worsley MA, et al. Management and control of a large outbreak of diarrhoea due to Clostridium difficile. J Hosp Infect 1994 May; 27(1):1–15.

63. Drudy D, Harnedy N, Fanning S, et al. Emergence and control of fluoroquinolone-resistant, toxin A-negative, toxin B-positive Clostridium difficile. Infect Control Hosp Epidemiol 2007 Aug; 28(8):932–40.

64. McNulty C, Logan M, Donald IP, et al. Successful control of Clostridium difficile infection in an elderly care unit through use of a restrictive antibiotic policy. J Antimicrob Chemother 1997 Nov; 40(5):707–11.

65. Pear SM, Williamson TH, Bettin KM, et al. Decrease in nosocomial Clostridium difficile-associated diarrhea by restricting clindamycin use. Ann Intern Med 1994 Feb 15; 120(4):272–7.

66. Valiquette L, Cossette B, Garant MP, et al. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of Clostridium difficile-associated disease caused by the hypervirulent NAP1/027 strain. Clin Infect Dis 2007 Sep 1; 45 Suppl 2:S112–21.

67. Zafar AB, Gaydos LA, Furlong WB, et al. Effectiveness of infection control program in controlling nosocomial Clostridium difficile. Am J Infect Control 1998 Dec; 26(6):588–93.

68. Whitaker J, Brown BS, Vidal S, et al. Designing a protocol that eliminates Clostridium difficile: a collaborative venture. Am J Infect Control 2007 Jun; 35(5):310–4.

69. Vernaz N, Sax H, Pittet D, et al. Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA and Clostridium difficile. J Antimicrob Chemother 2008 Sep; 62(3):601–7.

70. Hacek DM, Ogle AM, Fisher A, et al. Significant impact of terminal room cleaning with bleach on reducing nosocomial Clostridium difficile. Am J Infect Control 2010 Jun; 38(5):350–3.

71. McMullen KM, Zack J, Coopersmith CM, et al. Use of hypochlorite solution to decrease rates of Clostridium difficile-associated diarrhea. Infect Control Hosp Epidemiol 2007 Feb; 28(2):205–7.

72. Musher DM, Logan N, Bressler AM, et al. Nitazoxanide versus vancomycin in Clostridium difficile infection: a randomized, double-blind study. Clin Infect Dis 2009 Feb 15; 48(4):e41–6.

73. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007 Aug 1; 45(3):302–7.

74. Lagrotteria D, Holmes S, Smieja M, et al. Prospective, randomized inpatient study of oral metronidazole versus oral metronidazole and rifampin for treatment of primary episode of Clostridium difficile-associated diarrhea. Clin Infect Dis 2006 Sep 1; 43(5):547–52.

75. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of Clostridium difficile colitis. Clin Infect Dis 2006 Aug 15; 43(4):421–7.

76. Wenisch C, Parschalk B, Hasenhundl M, et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. Clin Infect Dis 1996 May; 22(5):813–8.

77. Dudley MN, McLaughlin JC, Carrington G, et al. Oral bacitracin vs vancomycin therapy for Clostridium difficile-induced diarrhea. A randomized double-blind trial. Arch Intern Med 1986 Jun; 146(6):1101–4.

78. Fekety R, Silva J, Kauffman C, et al. Treatment of antibiotic-associated Clostridium difficile colitis with oral vancomycin: comparison of two dosage regimens. Am J Med 1989 Jan; 86(1):15–9.

79. Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhoea and colitis. Lancet 1983 Nov 5; 2(8358):1043–6.

80. Young GP, Ward PB, Bayley N, et al. Antibiotic-associated colitis due to Clostridium difficile: double-blind comparison of vancomycin with bacitracin. Gastroenterol 1985 Nov; 89(5):1038–45.

81. Keighley MR, Burdon DW, Arabi Y, et al. Randomised controlled trial of vancomycin for pseudomembranous colitis and postoperative diarrhoea. BMJ 1978 Dec 16; 2(6153):1667–9.

82. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Eng J Med 2011 Feb 3;364(5):422-31.

83. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. Clin Infect Dis 2000 Oct; 31(4):1012–7.

84. Wullt M, Hagslatt ML, Odenholt I. Lactobacillus plantarum 299v for the treatment of recurrent Clostridium difficile-associated diarrhoea: a double-blind, placebo-controlled trial. Scand J Iinfect Dis 2003; 35(6-7):365–7.

85. Mattila E, Anttila VJ, Broas M, et al. A randomized, double-blind study comparing Clostridium difficile immune whey and metronidazole for recurrent Clostridium difficile-associated diarrhoea: efficacy and safety data of a prematurely interrupted trial. Scand J Infect Dis 2008; 40(9):702–8.

86. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. JAMA 1994 Jun 22-29; 271(24):1913–8.

87. Mogg GA, George RH, Youngs D, et al. Randomized controlled trial of colestipol in antibiotic-associated colitis. Br J Surg 1982 Mar; 69(3):137–9.

88. Surawicz CM, Elmer GW, Speelman P, et al. Prevention of antibiotic-associated diarrhea by Saccharomyces boulardii: a prospective study. Gastroenterol 1989 Apr; 96(4):981–8.

89. Lewis SJ, Potts LF, Barry RE. The lack of therapeutic effect of Saccharomyces boulardii in the prevention of antibiotic-related diarrhoea in elderly patients. J Infect 1998 Mar; 36(2):171–4.

90. Thomas MR, Litin SC, Osmon DR, et al. Lack of effect of Lactobacillus GG on antibiotic-associated diarrhea: a randomized, placebo-controlled trial. Mayo Clin Proc 2001 Sep; 76(9):883–9.

91. Plummer S, Weaver MA, Harris JC, et al. Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of C. difficile diarrhoea. Int Microbiol 2004 Mar; 7(1):59–62.

92. Can M, Besirbellioglu BA, Avci IY, et al. Prophylactic Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea: a prospective study. Med Sci Monit 2006 Apr; 12(4):P19–22.

93. Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. BMJ 2007 Jul 14; 335(7610):80.

94. Lewis S, Burmeister S, Cohen S, et al. Failure of dietary oligofructose to prevent antibiotic-associated diarrhoea. Aliment Pharmacol Ther 2005 Feb 15; 21(4):469–77.

95. Lewis S, Burmeister S, Brazier J. Effect of the prebiotic oligofructose on relapse of Clostridium difficile-associated diarrhea: a randomized, controlled study. Clin Gastroenterol Hepatol 2005 May; 3(5):442–8.

96. Munoz P, Bouza E, Cuenca-Estrella M, et al. Saccharomyces cerevisiae fungemia: an emerging infectious disease.[see comment]. Clin Infect Dis 2005 Jun 1; 40(11):1625–34.

97. Eriksson S, Aronsson B. Medical implications of nosocomial infection with Clostridium difficile. Scand J Infect Dis 1989; 21(6):733–4.

98. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. N Engl J Med 2010 Jan 21; 362(3):197–205.

99. Tvede M, Rask-Madsen J. Bacteriotherapy for chronic relapsing Clostridium difficile diarrhoea in six patients. Lancet 1989 May 27; 1(8648):1156–60.

100. Persky SE, Brandt LJ. Treatment of recurrent Clostridium difficile-associated diarrhea by administration of donated stool directly through a colonoscope. Am J Gastroenterol 2000 Nov; 95(11):3283–5.

101. Planche T, Aghaizu A, Holliman R, et al. Diagnosis of Clostridium difficile infection by toxin detection kits: a systematic review. Lancet Infect Dis 2008 Dec; 8(12):777–84.

102. Crobach MJ, Dekkers OM, Wilcox MH, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): data review and recommendations for diagnosing Clostridium difficile-infection (CDI). Clin Microbiol Infect 2009 Dec; 15(12):1053–66.

103. Samore MH, DeGirolami PC, Tlucko A, et al. Clostridium difficile colonization and diarrhea at a tertiary care hospital. Clin Infect Dis 1994 Feb; 18(2):181–7.

104. Samore MH, Venkataraman L, DeGirolami PC, et al. Clinical and molecular epidemiology of sporadic and clustered cases of nosocomial Clostridium difficile diarrhea. Am J Med 1996 Jan; 100(1):32–40.

105. Shim JK, Johnson S, Samore MH, et al. Primary symptomless colonisation by Clostridium difficile and decreased risk of subsequent diarrhoea. Lancet 1998 Feb 28; 351(9103):633–6.

106. McFarland LV, Mulligan ME, Kwok RY, et al. Nosocomial acquisition of Clostridium difficile infection. N Engl J Med 1989 Jan 26; 320(4):204–10.

107. Gerding DN, Johnson S, Peterson LR, et al. Clostridium difficile-associated diarrhea and colitis. Infect Control Hosp Epidemiol 1995 Aug; 16(8):459–77.

108. Juang P, Skledar SJ, Zgheib NK, et al. Clinical outcomes of intravenous immune globulin in severe clostridium difficile-associated diarrhea. Am J Infect Control 2007 Mar; 35(2):131–7.

109. Abougergi MS, Broor A, Cui W, et al. Intravenous immunoglobulin for the treatment of severe Clostridium difficile colitis: an observational study and review of the literature. J Hosp Med 2010 Jan; 5(1):E1–9.

110. Bricker E, Garg R, Nelson R, et al. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults.[update in Cochrane Database Syst Rev. 2007;(3):CD004610; PMID: 17636768]. Cochrane Database Syst Rev 2005; (1):004610.

Full Report

This executive summary is part of the following document: Butler M, Bliss D, Drekonja D, Filice G, Rector T, MacDonald R, Wilt T. Effectiveness of Early Diagnosis, Prevention, and Treatment of *Clostridium difficile* Infection. Comparative Effectiveness Review No. 31. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.) AHRQ Publication No. 11(12)-EHC051-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

For More Copies

For more copies of Effectiveness of Early Diagnosis, Prevention, and Treatment of *Clostridium difficile* Infection: Comparative Effectiveness Review Executive Summary No. 31 (AHRQ Pub. No. 11(12)-EHC051-1), please call the AHRQ Clearinghouse at 1-800-358-9295 or email ahrqpubs@ahrq.gov.

AHRQ Pub. No. 11(12)-EHC051-1
December 2011