Effective Health Care Program

Comparative Effectiveness Review
Number 31

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

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0009 (EPC2)

Prepared by:
Minnesota Evidence-based Practice Center
Minneapolis, Minnesota

Investigators:
Mary Butler, Ph.D., M.B.A.
Donna Bliss, R.N., Ph.D.
Dimitri Drekonja, M.D.
Gregory Filice, M.D.
Thomas Rector, Pharm.D., Ph.D.
Roderick MacDonald, M.S.
Timothy Wilt, M.D., M.P.H.

AHRQ Publication No. 11(12)-EHC051-EF
December 2011

This report is based on research conducted by the Minnesota Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0009—EPC2). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Suggested Citation: 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.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Agency for Healthcare Research and Quality

Shilpa Amin, M.D., MBsc, FAAFP
Task Order Officer
Agency for Healthcare Research and Quality

Robert Zuhlke
Contracting Officer
Agency for Healthcare Research and Quality

Acknowledgments

We sincerely thank all peer and public reviewers and David Samson for their comments and suggestions. The report is better because of their contributions.

We would like to thank Christa Prodzinski, Maureen Carlyle, and especially Marilyn Eells, for editing support. We would also like to thank Michelle Brasure, Jim Tacklind, and Indy Rutks, for their librarian expertise, database management, abstracting skills, and all-around general support.

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

Structured Abstract

Objectives. To conduct a systematic review and synthesize evidence for differences in the accuracy of diagnostic tests, and the effects of interventions to prevent and treat *Clostridium difficile* infection (CDI) in adult patients.

Data Sources. Searching for relevant literature was conducted in MEDLINE, the Cochrane Library, and Allied and Complementary Medicine (AMED). ClinicalTrials.gov and expert consultants provided leads to additional studies. We also manually searched reference lists from relevant literature.

Review Methods. Standard Evidence-based Practice Center methods were employed. Screening of abstracts and full text articles to identify studies meeting inclusion/exclusion criteria was performed by two independent reviewers. High-quality direct comparison studies were used to examine differences in diagnostic tests. Randomized controlled trials (RCTs) were used to examine comparative effectiveness of antibiotic treatment for CDI. Quality of data extraction was checked by separate reviewers. Quality ratings and strength of evidence grading was performed on included studies. Evidence on diagnostic tests was quantitatively synthesized focusing on differences between test sensitivities and specificities. Evidence on antibiotic treatment was quantitatively examined using pooled analysis. Qualitative narrative analysis was used to synthesize evidence from all available study types for environmental prevention and nonstandard prevention and treatment, with the exception of probiotics as primary prevention, for which a forest plot is provided.

Results. Overall, literature was sparse and strength of evidence was generally low due to small sample sizes or lack of adequate controls. For diagnostic testing, direct comparisons of commercially available enzyme immunoassays for *C. difficile* toxins A and B did not find major differences in sensitivity or specificity. Limited evidence suggests that tests for genes related to the production of *C. difficile* toxins may be more sensitive than immunoassays for toxins A and B while the comparisons of these test specificities were inconsistent. Moderate evidence in favor of antibiotic restriction policies for prevention was found. Environmental preventive interventions such as glove use and disposable thermometers have limited evidence. However, this literature is largely based on controlling outbreaks. Use of multiple component interventions further limits the ability to synthesize evidence in a meaningful way. Numerous potential new forms of treatment are being examined in placebo controlled RCTs, case series, and case reports. For standard treatment, no antimicrobial is clearly superior for the initial cure of CDI. Recurrence is less frequent with fidaxomicin than with vancomycin. Monoclonal antibodies for prevention and fecal flora reconstitution for multiple recurrences appear promising.

Conclusions. Given the frequency and severity of CDI and the fact that future reimbursement policy may withhold payment for hospital-acquired infections, this is an under-researched topic. More precise estimates of the magnitude of differences in test sensitivities and specificities are needed. More importantly, studies have not established that any of the possible differences in test accuracy would lead to substantially different patient outcomes in clinical practice. More research on effective treatment and unintended consequences of treatment, such as resistance, is needed. Gut flora may be important, but improved understanding of healthy gut ecology and the complex interactions is necessary before continuing to pursue probiotics.

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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.

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 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?
    - Do the differences in performance measures vary with sample characteristics?
- **KQ 2**. What are effective prevention strategies?
    - What is the effectiveness of current prevention strategies?
    - What are the harms associated with prevention strategies?
    - 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?
    - Does effectiveness vary by disease severity or strain?
    - Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital- versus community-acquired setting?
    - How do prevention and treatment of CDI affect resistance of other pathogens?
- **KQ 4.** What are the effectiveness and harms of nonstandard adjunctive interventions?
    - 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 Auguest 2011, because of a 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.[72-82] 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.[82] 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 Key Questions, 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	Level of Evidence	Summary/Conclusion/Comments
Key Question 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.

Table A. Summary of evidence (continued)

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Patient characteristics	Insufficient	Insufficient patient information was provided in reports of comparative data.
Key Question 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.
Key Question 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]
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 demonstrated 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.

Table A. Summary of evidence (continued)

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Key Question 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	Research Gaps	Types of Studies Needed to Answer Questions	Future Research Recommendations
Key Question 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
Key Question 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
Key Question 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

Table B. Future research recommendations (continued)

Key Question	Research Gaps	Types of Studies Needed to Answer Questions	Future Research Recommendation
Key Question 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 to help guide potential combination therapies Quality research includes power analysis, intention to treat Multicenter trials are likely needed to achieve adequate samples Probiotics trials for prevention are well represented in ongoing studies Patient characteristics for subgroup analysis
Umbrella issues			Adoption of standard definitions for diarrhea, CDI resolution

CDI = *Clostridium difficile* infection

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Introduction

Background

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.

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 (Figure 1). Toxigenic strains include those that make toxin B (cytotoxin), with or without toxin A (enterotoxin). Approximately 1 to 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.

Diagnosis

Effective prevention of transmission and treatment of CDI depends on swift and accurate diagnosis. None of the risk factors or clinical signs and symptoms alone or in combination, except possibly a documented presence of pseudo membranous colitis, is sufficient to surmise with a high degree of clinical certainty that a patient does or does not have CDI. Culturing *C. difficile* organisms in stool specimens followed by testing grown colonies for toxins (toxigenic culture) and cultured cell cytotoxicity assay of the stool specimens are historically held as the standard reference tests; however, results can take up to 48 hours, and these diagnostic methods require a level of expertise and equipment that are not widely available. A number of faster, less demanding diagnostic tests have been developed to detect the presence of toxins produced by most disease-causing *C. difficile* organisms, toxins A and/or B, or the genes involved in the production or regulation of toxins A and/or B. These tests have a variety of sensitivities, specificities, biotechnologies, costs, and time-to-results. The sensitivities and specificities of the newer tests have been studied mostly using toxigenic culture or a cultured cell cytotoxicity assay as the reference test, but the estimates vary substantially, making it difficult to determine whether there are clinically significant differences between tests.[98,99] Some of the variation is due to differences in the accuracy of the reference tests that are not 100 percent sensitive or specific. Toxigenic culture can be more sensitive than cytotoxicity assays that can be more specific. When a new test is evaluated using a more sensitive reference test, the estimate of its sensitivity may be lower. Greater than 90 percent of labs in the United States use one of the commercially available immunoassays to detect toxins in stool samples or because they are fast, inexpensive, and technically easier to perform.[108] However, the use of toxin gene detection tests has increased in recent years. A more detailed discussion of types of diagnostic tests for *C. difficile* is provided in a supplemental section at the end of this chapter.

When evaluating laboratory tests for the presence of toxigenic *C. difficile* in patients, it is important to consider how patients were selected and the consistency of the stool specimens being tested. Testing for *C. difficile* infection is recommended for a person with diarrhea (generally three or more loose or unformed stools for 1 to 2 days) and one or more risk factors for CDI.[109,110] However, these recommendations may not always be followed in practice. Several multivariable prediction models built on established risk factors have been published in an effort to optimize diagnostic testing for *C. difficile* infection.[111-113] The extent of their use in clinical practice is not known.

Identifying the most accurate diagnostics tests in clinical practice could be very important. Diagnostic tests with greater sensitivity (fewer false negatives) would reduce the number of patients who do not receive appropriate treatment and isolation. Tests with higher specificity (fewer false positives) could reduce the number of unnecessary and potentially detrimental interventions, such as withholding antibiotics for other medical conditions, or initiating treatment for CDI. Swift diagnosis leading to infection prevention precautions, faster treatment, and quicker resolution of diarrhea may reduce the amount of organisms or spores in the environment that can infect other patients.

Treatment

There are a number of algorithms available to guide treatment of CDI.[11,114-116] The only antimicrobial currently approved for the treatment of CDI by the U.S. Food and Drug Administration is oral vancomycin, and consensus appears to exist for treatment of severe initial incident CDI with vancomycin. However, there also appears to be clinical consensus to treat mild to moderate CDI with metronidazole, in part because of the concern that overuse of vancomycin may contribute to increasing pathogen resistance[117] and cost considerations. Pepin[116] suggests that both vancomycin and metronidazole are implicated in increased frequency of vancomycin-resistant enterococci (VRE). Enterococci are part of the normal gastrointestinal (GI) flora, and VRE are a major problem. Whether the increased use of vancomycin for CDI will affect the rates of VRE is unclear, especially as increased density of VRE in stool has been demonstrated in subjects receiving antimicrobials active against anaerobes (the main colonic flora), including both oral vancomycin and metronidazole.[118] Surgical treatment with colectomy can be life saving in patients with fulminant, or acute severe, colitis.[119]

Nonstandard interventions for the treatment and prevention of CDI have been sought for several reasons. Treatment with standard antibiotics, such as vancomycin and metronidazole, is ineffective in 8 to 36 percent of patients with CDI,[72,73] no antibiotic kills *C. difficile* spores, and rates of infection are increasing. Treatment for relapsed or recurrent CDI is much more problematic. CDI recurs in about 20 percent of patients;[114] a subset of recurrent patients spiral into several subsequent recurrences.[120] Clinicians have chosen from a number of antibiotics and dosing protocols and adjunctive treatments, such as the use of antimicrobials, probiotics, fecal transplant, toxin-binding agents, and immune system-enhancing agents.[121-123]

Probiotics are a very active area of discussion for CDI.[124] Probiotics are live microorganisms, including bacteria or yeast, which, when administered in adequate amounts, confer a health benefit on the host.[125] Probiotics are believed to replenish nonpathogenic microorganisms to GI flora that has become altered by antibiotic therapy. It is important that the effectiveness of probiotics and related substances are evaluated specifically for their effect on CDI and not rely on the more broadly defined antibiotic-associated disease, which includes a much broader set of potential disease etiology. Fecal flora reconstitution is another intervention currently under investigation. This approach instills donor feces into the patient with CDI to normalize the intestinal flora. The procedure has been variously termed in the literature, including fecal bacteriotherapy,[96,124,126,127] fecal transplantation,[127-129] and donated stool.[97,130]

Prevention

Prevention of CDI takes two general forms, breaking routes of transmission and improving a patient's resistance to disease should colonization occur. Preventing the spread of *C. difficile* by breaking routes of transmission within institutional settings depends on staff compliance with national guidelines and standards[131] and locally determined hygiene protocols. *C. difficile* is common in the environment of people with CDI,[101] most of whom have diarrhea, and many of whom have incontinence and often other medical problems that tend to diminish personal hygiene. *C. difficile* is found on the hands of hospital workers[46,101] and is more likely to be found on hands of people who have been working in a heavily contaminated room.[101] Thus, *C. difficile* acquired in hospital settings may be spread directly or indirectly from patient to patient.[103]

Complicated recommendations are difficult to remember and implement, and protocols for different targeted hospital acquired infections are not always congruent. For example, the

availability of alcohol hand rubs improved physician compliance and reduced methicillin-resistant *Staphylococcus aureus* (MRSA) infections,[51] yet *C. difficile* produces spores that can withstand hostile environments and are resistant to alcohol hand rubs and other routine antiseptics.[132] One concern has been that health care workers will use alcohol-based rubs or gels in circumstances where handwashing is preferred. Other institutional prevention strategies may be required as *C. difficile* transmission knowledge develops. For example, a recent study isolated *C. difficile* spores from air samples in a hospital in the United Kingdom 4 to 7 weeks after the last confirmed CDI case in the ward, and successfully cultured bacterium from the spores.[133]

Interventions to improve a patient's resistance to CDI or CDI recurrence include probiotics, a nonpathogenic strain of *C. difficile*, prebiotics, immune whey, *C. difficile* vaccine, and intravenous immunoglobulin. Probiotics, a nonpathogenic strain of *C. difficile*, and prebiotics aim to modify the patient's intestinal microbioecology to better resist CDI. Probiotics and a nonpathogenic strain of *C. difficile* deliver nonpathogenic microorganisms thought to compete with or inhibit *C. difficile*, while prebiotics aim to promote the growth of beneficial organisms. Immune whey, a *C. difficile* vaccine, and intravenous immunoglobulin confer passive immunity against *C. difficile* or its toxin.

Scope of the Review

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.

Key Questions

The following key questions form the basis for this review:

- Key Question 1. How do different methods for detection of toxigenic *C. difficile* to assist with diagnosis of CDI compare in their sensitivity and specificity?
    - Do the differences in performance measures vary with sample characteristics?
- Key Question 2. What are effective prevention strategies?
    - What is the effectiveness of current prevention strategies?
    - What are the harms associated with prevention strategies?
    - How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?

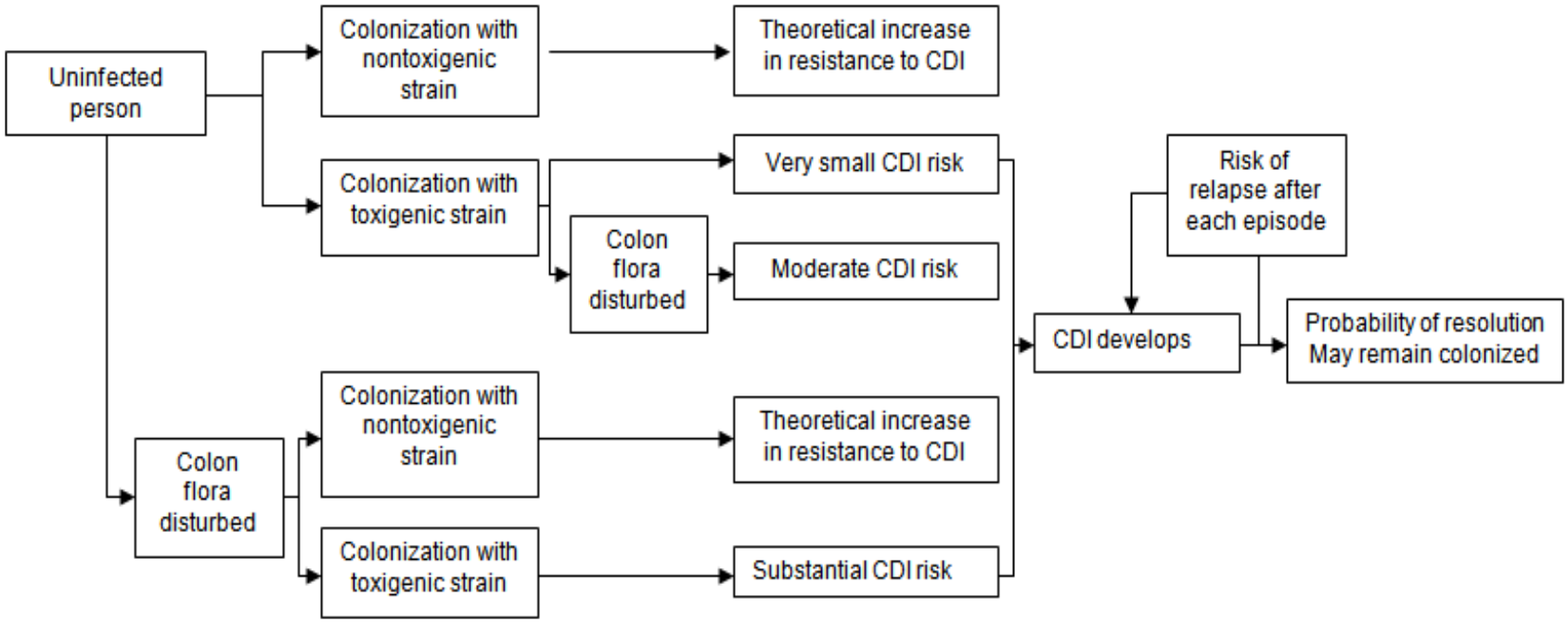
- Key Question 3. What are the comparative effectiveness and harms of different antibiotic treatments?
    - Does effectiveness vary by disease severity or strain?
    - Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital versus community-acquired setting?
    - How do prevention and treatment of CDI affect resistance of other pathogens?
- Key Question 4. What are the effectiveness and harms of nonstandard adjunctive interventions?
    - In patients with relapse/recurrent CDI?

Review Framework

The conceptual framework that guided this review is provided in Figure 2. The figure lays out the clinical path for patients with the potential to develop CDI, from diagnostic laboratory tests, through their impact on treatment decisions, to finally implications for prevention strategies, and locates the key questions of this review within the context of the framework. Diagnostic testing has two parts, the technical efficiency of the tests and diagnostic accuracy. Technical efficiency is outside the scope of this review; rather, for Key Question 1 we focus on the comparative diagnostic accuracy of commonly used rapid tests, such as immunoassays for *C. difficile* toxin and toxin gene detection tests, which may reduce the time lapse between the onset of symptoms and laboratory confirmation of CDI and treatment decisions. Repeat testing of selected specimens does not provide good comparative information about test accuracy and therefore is not covered in the focused review of diagnostic test accuracy. When a patient is treated for CDI, whether for an initial case, a relapse, or recurrence, the clinical outcomes of interest establish the patient treatment efficacy. Of particular interest, Key Question 3 will compare effectiveness of established treatments used for CDI, particularly vancomycin and metronidazole. For Key Question 4, the clinical question of interest is what nonstandard treatments are being utilized, and their efficacy, particularly for recurrent CDI. After diagnostic accuracy, treatment, and patient outcome efficacy concerns, prevention is a societal-level efficacy measure, as the benefits of prevention of infectious disease can extend beyond the individual patient. This is the area of focus for Key Question 2. Key Question 4 also contributes to this area to the extent that nonstandard treatments assist a patient in fending off an infection.

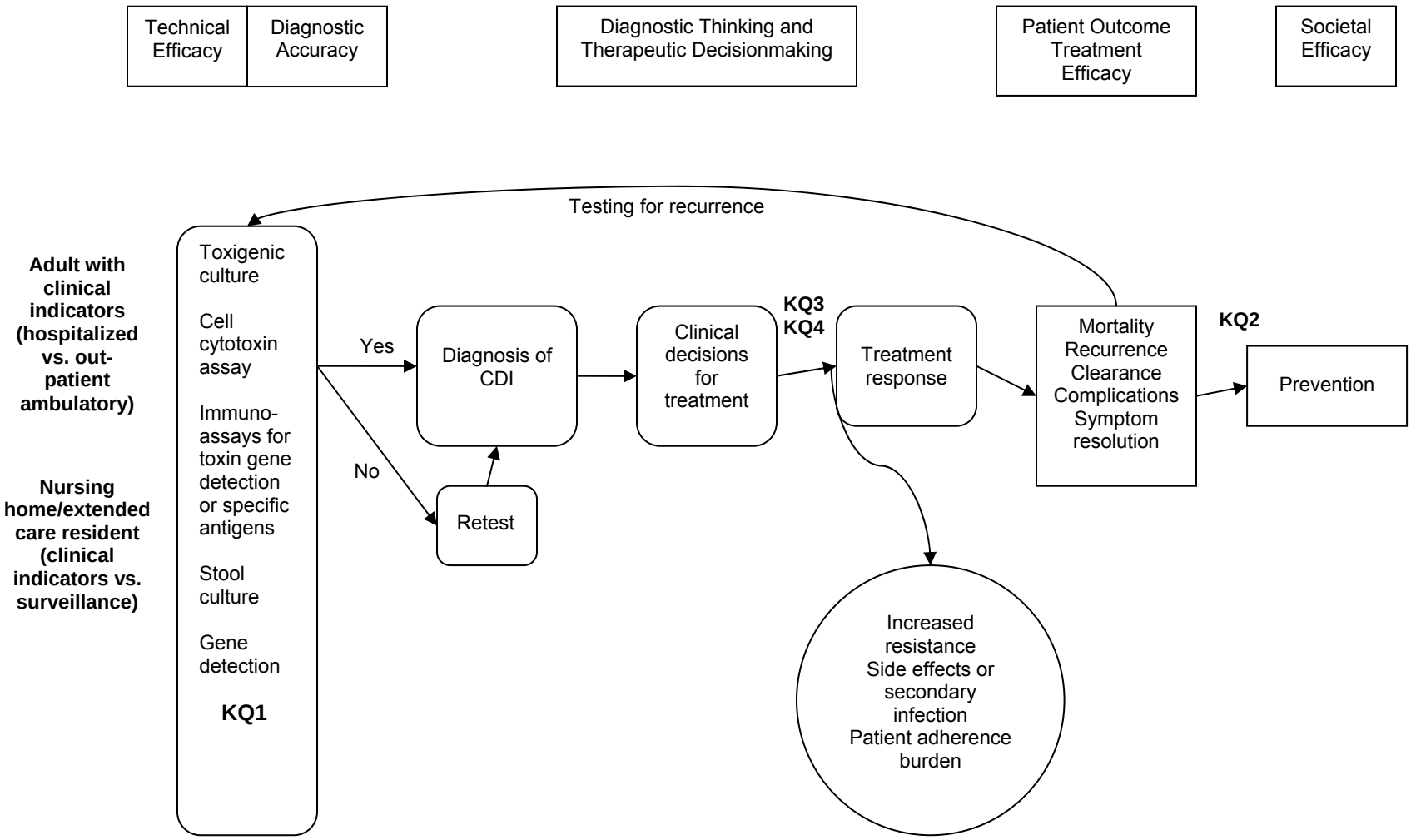
Figure 3 expands the framework for the key question related to prevention. The illustration lays the pathway of preventive strategies and practices from the target patient population of patients at risk for CDI due to potential for exposure, through intermediate outcomes and on to health outcomes. This framework was included to highlight both the linkage and the conceptual difference between the intermediate outcomes of prevention and health outcomes of clinical significance important to the patient. Intermediate outcomes are often process measures of the uptake of a prevention strategy, or counts of vegetative *C. difficile* or spores remaining in the environment. Key Question 2 is mainly concerned with evidence for the direct effect of prevention on health outcomes.

Figure 1. Pathogenesis of CDI



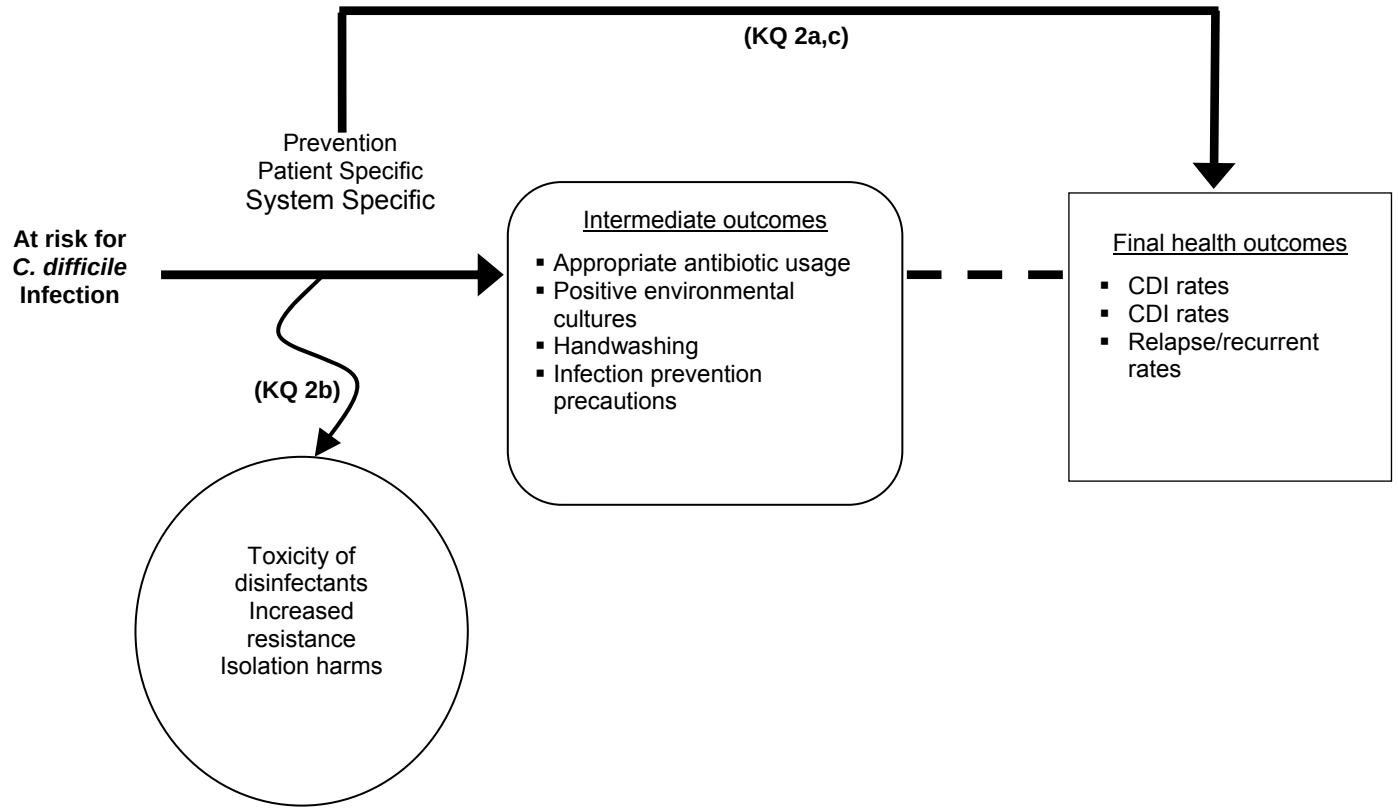
CDI = *Clostridium difficile* infection

Figure 2. Analytic framework for CDI diagnostic testing, prevention, and treatment



CDI = *Clostridium difficile* infection; KQ = Key Question

Figure 3. Supplemental prevention framework



CDI = *Clostridium difficile* infection; KQ = Key Question

Diagnostic Test Descriptions

Cytotoxicity Assay

The cultured cell cytotoxicity assay often has been used as a reference test for evaluating new diagnostic tests for toxigenic *C. difficile*. Briefly, a diluted and filtered aliquot of a stool sample is mixed with cultured test cells. The test cells are examined for toxin effects (cell rounding) that are not seen in comparator test cells where an excess amount of antitoxin is present.[134] The diagnostic rounding of cultured test cells and the clinical signs and symptoms of CDI can be caused by cellular interactions with both *C. difficile* toxins, although toxin B is much more cytotoxic and the cytotoxicity assay is often considered to be a test for toxin B.[135,136] A cytotoxicity assay requires up to 48 hours for the toxin effects to appear, especially when toxin level in the test material is low. Cytotoxicity testing is not a perfectly accurate gold standard.[137] Methodological differences in the time to process and dilution of stool samples, the age and type of cultured test cells being used for the test, the antitoxins, and the interpretation of results all can cause cytotoxicity assay results to vary.[138] Toxins can degrade or be inactivated depending on how long stool specimens are stored before being tested and the storage temperature. Nevertheless, the imperfect cytotoxicity assay is often used as the reference test in the evaluation of other diagnostic tests for *C. difficile*.

Detection of *C. difficile* Organisms

Culturing *C. difficile* by anaerobic incubation of fecal aliquots on selective cycloserine-cefoxitin, fructose agar or other media can be more sensitive than the cytotoxicity assay for detecting the presence of *C. difficile* organisms.[138,139] However, *C. difficile* culture techniques also are not standardized, are susceptible to methodological variation, and require expertise, equipment, and several days to complete. Furthermore, cultured *C. difficile* organisms need to be tested to determine whether they can produce disease-causing toxins because many individuals may be carriers of *C. difficile* organisms that do not produce toxins or clinically significant CDI. Nevertheless, expert culture of *C. difficile* from stool samples followed by a cytotoxicity assay or another method of detecting toxins is considered the most sensitive method for detection of toxigenic *C. difficile*, albeit not very practical.[110,140] However, the concentration of toxins produced in culture might not be the same as that present in patients.

Assays for glutamate dehydrogenase enzyme constitutively produced by *C. difficile* have been used as a faster and less demanding alternative to culturing *C. difficile* organisms. These tests are not entirely specific because other organisms can produce glutamate dehydrogenase or interfering substances.[104,138] Like stool cultures, a positive glutamate dehydrogenase test requires a second test to detect *C. difficile* toxins. Because stool cultures and the cytotoxicity assay are demanding, costly, and time consuming, and most stool samples sent to clinical laboratories turn out to be negative for toxigenic *C. difficile*, some laboratories have proposed using a test for glutamate dehydrogenase first, and then testing only the positive specimens for toxins.[141-143] In this two-stage approach, a negative test for glutamate dehydrogenase would preclude the need for a toxin test. However, the sensitivities of glutamate dehydrogenase assays need to be high enough to have an acceptably low number of false negatives.[109] Furthermore, the performance of a two-stage test also will depend on the sensitivity and specificity of the second test used to detect toxins.

Immunoassays for Toxins

A variety of faster (within a few hours), less costly commercial immunoassays for *C. difficile* toxins have been developed and have been commercially available since the late 1980s. Initially, most immunoassays detected only toxin A. More recently it was discovered that a small but increasing number of clinically significant *C. difficile* strains produced only toxin B.[144-147] The incidence of clinically significant toxin A-negative, B-positive organisms in the United States is not known and could vary by site and time.[148] When the performance of a diagnostic test depends on the level of toxins in test specimens and most organisms produce both toxins A and B, immunoassays that detect both toxins might be more sensitive if other critical factors such as dilution of the specimens are equal.[149] Therefore, experts have recommended using immunoassays that can detect both toxins A and B.[109,110,137,148] A highly sensitive and specific immunoassay for these toxins may be used as a second test after either stool culture or the glutamate dehydrogenase assay.

Data from the College of American Pathology proficiency testing program for *C. difficile* toxin detection indicated that 90 percent of labs used an immunoassay for toxins A and B in June 2009. The most commonly used tests were the Immunocard and Premier A & B test kits manufactured by Meridian, the TechLab Tox AB II and Toxin A/B QUIK CHEK kits, and the Remel ProSpecT and Xpect Toxin A/B tests. These data are consistent with an online survey of members of the Association for Professionals in Infection Control and Epidemiology, Inc. in 2008 that indicated that an immunoassay was used in 95 percent of patients who were diagnosed with CDI in 648 responding American laboratories, and 60 percent were diagnosed using an immunoassay for toxins A and B, while only 3 percent used an immunoassay for only toxin A.[9]

Toxin Gene Detection Tests

Three tests of stool specimens for the presence of genes involved in the production of *C. difficile* toxins have recently become commercially available. These tests use the polymerase chain reaction to amplify (replicate) targeted gene fragments to detect the presence of a gene or genes involved in the production of toxins, not the actual toxins. The target of the assays can be the genes that produce toxin B and a gene C that negatively regulates the production of toxins A and B. A mutation in gene C has been detected in an increasingly common hypervirulent strain of *C. difficile* that produces large amounts of toxins A and B.[148] One concern about using the tests based on amplification of toxin gene fragments is that very small, clinically unimportant genetic residue or specimen contamination may be detected. Clinically speaking, these would be false positives that would reduce test specificity. Therefore, some experts have recommended using this type of test only when a patient has clinical signs and symptoms suggestive of CDI.[109,138]

Methods

Topic Refinement

The topic for this report was nominated in a public process through the Agency for Healthcare Research Quality's nomination Web site. We drafted the initial key questions with input from a key informant panel composed of researchers; clinicians; professional organizations representing hospitals, infectious diseases, and clinicians; federal and state agencies; patient-safety advocates; and consumers. After approval from AHRQ, the key questions were posted to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary and conferencing with the Technical Expert Panel (Appendix A), we drafted final key questions and submitted them to AHRQ for approval.

Systematic Review

Search Strategy

Our search strategy used the key word "*difficile*" to identify all articles related to *C. difficile* because we found the keyword to be a more sensitive term than the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature. Articles were limited to English language, humans, and MeSH filters for adult populations. We searched MEDLINE, AMED, the Cochrane Library, and ClinicalTrials.gov. Details of the major search strategies are provided in Appendix B.

To identify 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 NHA Health Technology Assessment Programme. We used results from previously conducted meta-analyses and systematic reviews when appropriate. We also manually searched reference lists of review articles and articles that were read for the review. All citations were imported into Refworks for initial screening, and then EndNote X for database management.

During the manual search of included articles' reference lists, we found a number of studies not identified in our original search. We performed a forensic examination of those missed articles and determined that diagnostic test and prevention articles in particular were often not indexed by patient ages. We therefore performed a second search without the age filters. These search strategies are also included in Appendix B.

We conducted the initial searches in October 2009. The no-age filtered searches were conducted in February 2010 and updated in March and June 2010. An updated search was performed specifically for Key Question 3 (standard treatment) in August 2011, because of a significant new study that led to FDA approval of fidaxomicin in May 2011.

Inclusion/Exclusion Criteria

In brief, we developed criteria for inclusion and exclusion of studies based on the patient populations, interventions, outcome measures, and types of evidence specified in the key questions. We retrieved full-text articles of potentially relevant abstracts and conducted a second review for inclusion by reapplying the inclusion criteria. Results published only in abstract form

are generally not included in our reviews unless adequate information was available to assess the validity of the data. Full details by key question are provided below.

Key Question 1

Patients

We restricted the review to studies that used clinical stool specimens from patients suspected to have *Clostridium difficile*-associated infection (CDI). Information that described patient characteristics that could be related to CDI, hence test performance, was of particular interest.

Study Selection

We sought studies that concurrently compared at least two diagnostic tests in the same laboratory using the same stool samples and the same reference standard. This was done in order to reduce the heterogeneity in the estimates of differences in sensitivity and specificity, given the inter- and intralaboratory variation in the application of diagnostic tests for toxigenic *C. difficile*, the varying accuracy of the reference standards, and differences in patient and stool specimen characteristics. Diagnostic tests of interest were the immunoassays commonly used in the United States to test for the presence of both toxins A and B, and newer tests to detect the presence of *C. difficile* gene fragments involved in the production of toxin. We did not include articles that only compared tests that are not currently commercially available in the United States. We focused on tests for toxigenic *C. difficile* because the presence of toxins is a requisite for diagnosing clinical disease or CDI. We sought diagnostic studies that included patient outcomes or outcomes related to changes in therapy.

Measures of Diagnostic Accuracy

We sought to compare diagnostic tests in terms of differences in their sensitivity (true positives for toxigenic *C. difficile*) and specificity (true negatives for toxigenic *C. difficile*). These statistics are believed to be most relevant to clinical decisionmakers. To be consistent with other common statistical analyses, such as receiver operator characteristic curves and likelihood ratios, we present and discuss study results in positive terms, that is, true positives (sensitivity) and false positives (1 minus specificity). The review was restricted to studies that used toxigenic culture, cell cytotoxicity assay, or combinations of tests as the reference test for the presence or absence of toxigenic *C. difficile*. To be able to compare estimates of sensitivity and specificity, the report had to provide the counts of test results for those that were positive or negative according to the reference test. Direct comparisons of diagnostic tests without a reference test were not included.

Key Question 2

Patients

We included studies targeting adult patients at risk for exposure to *C. difficile* in hospital and long-term care facilities.

Interventions

We included studies that examined the effects of prevention strategies aimed at (1) breaking routes of transmission within institutional settings, the major focus of institutional infectious

disease programs, and (2) reducing susceptibility to CDI through antibiotic prescribing practices. Reducing susceptibility to CDI through other agents is covered in Key Question 4.

Comparators

No restrictions were placed on the comparators, although we anticipated that most studies would use some form of usual processes of care.

Outcomes

We included only studies with CDI incidence, or other measures of CDI as an outcome. We excluded studies that used only process measures, or intermediate outcomes, such as reduced spore count in environmental samples, and did not tie these measures to CDI incidence. We looked for harms including difficulties experienced by employees responsible for environmental cleaning, or overtreatment harms, such as increased exposure risk to CDI if a patient without CDI is located in an isolation ward. We also sought evidence for how well prevention strategies and practices can be sustained past a study period or a period of intensive effort and monitoring.

Study Designs

Accepted study designs included randomized controlled trials (RCTs), prospective cohort, retrospective cohort, time series, and before/after trials.

In addition to studies examining prevention practices, we also identified good quality studies that identified specific risk factors for development of CDI to facilitate infectious disease control efforts to target likely effective preventive strategies. Inclusion criteria were: (1) prospective study design; (2) the methods for the risk factor analysis were specified; (3) the study included a clearly defined control group; (4) the study was of risk for CDI, not *C. difficile* colonization; (5) the CDI definition included diarrhea and a positive test for *C. difficile* toxin, and (6) the population was general hospital inpatients, not specialized patients. We included studies in which the influence of confounding variables was minimized in one of three ways: (1) randomization; (2) possible confounding variables were controlled in case and control selection process; or (3) multivariable analysis was done to determine the relative contribution of each potential risk factor included in the study.

Key Question 3

Patients

We included target populations of adult patients with clinical signs consistent with CDI in hospital, outpatient, or long-term care settings. We also looked for studies assessing efficacy when stratified by disease severity or strain, or by patient characteristics such as age, gender, comorbidity, and location of disease acquisition.

We sought studies that examined differences in treatment effect by disease severity. We did not exclude any studies based on the definitions they used for disease severity. In mild disease, discontinuation of the inciting antibiotic may be sufficient to resolve the symptoms of CDI,[115,150] making it difficult to detect any difference in the efficacy of antimicrobial therapy. In severe disease, differences in treatment efficacy are easier to detect and are of more importance because of the high morbidity and mortality associated with severe CDI.[151] However, a major difficulty with stratifying therapy by disease severity is the lack of a standardized, reproducible, and validated tool for measuring severity.[110,152] Elements that have been incorporated into various

severity definitions include, but are not limited to, age, degree of leukocytosis, fever, ileus, endoscopic findings, presence of fecal leukocytes, and need for intensive care unit treatment or colectomy.[70]

We sought studies that examined the comparative effectiveness of the antimicrobial treatments by organism strain. We also sought evidence of the potential impact of CDI treatment on developing antibiotic resistance in other infectious pathogens. There has historically been reluctance to use vancomycin as a first-line drug for CDI because of the drug's important role in treating serious bacterial infections, especially drug-resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. However, with the increase in CDI incidence and severity,[3,153] and a randomized trial reporting superiority to metronidazole in treating severe CDI,[70] this reluctance has been largely overcome. This may also be due to the high levels of vancomycin, which would likely inhibit even strains with reduced susceptibilities to vancomycin, and the emerging recognition that vancomycin resistance is complex (versus a single mutation).[154]

Interventions

We sought studies that tested vancomycin, metronidazole, bacitracin, nitazoxanide, rifaximin, fidaxomicin, and rifampin, which have only been studied as an adjunct to other active drugs. As fusidic acid and teicoplanin are not currently approved for use in the United States, these treatments were excluded. Fidaxomicin was added as an intervention because FDA approval was granted in May 2011.

Comparators

We sought studies that compared two active antimicrobial treatments, although we accepted studies that included placebo as the comparator for the two antimicrobials of interest, vancomycin and metronidazole.

Outcomes

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, which may be important because of effects on patient comfort, duration of hospitalization, and for infection control purposes. While we included clearance of the organism or toxin where reported, it is an outcome of uncertain significance if it is used without taking into account the patient's clinical status. We included any reported harms to patients using any of the standard antimicrobial treatments.

Study Designs

We also included RCTs, prospective cohort or case control studies, retrospective cohort studies, and case control study designs.

Key Question 4

Patients

We included target populations of adult patients with clinical signs consistent with CDI in hospital, outpatient, or long-term care settings. Patients with relapsing or recurrent CDI are of

special concern due to the demonstrated difficulty with permanent cure of the infectious organism, and are often the stated targeted patient population for nonstandard treatments. Likewise, preventing recurrence is an important clinical goal. We sought studies that examined either preventing or treating relapsing or recurrent CDI, as the target population or a specified subgroup. When more than one nonstandard intervention was administered concurrently during the treatment of CDI before resolution of CDI was documented, both interventions were classified as treatment. We accepted both a priori and post hoc subgroup analysis.

Interventions

We included all studies that examined any nonstandard interventions. Nonstandard interventions include a broad range of treatments, such as antimicrobial agents, agents that bind the toxins produced by *C. difficile*, or treatments that reduce a patient's susceptibility, from prebiotics or probiotics that support the gut flora to vaccinations or antibodies to enhance immune functions. We did not limit studies to a particular set of nonstandard interventions but instead sought to catalogue the range of interventions. However, we did not include the toxin binding agent tolevamer as an intervention, as it is no longer under development in the United States.

Comparators

We included studies that used either another active treatment, such as metronidazole, or placebo.

Outcome

We examined patient outcomes, such as resolution of symptoms for treatment studies, and CDI incidence and presence of toxins for prevention studies. We sought evidence for harms associated with nonstandard interventions, whether for treatment or prevention, such as side effects or secondary infections.

Study Designs

We anticipated few controlled trials for newer interventions and so included all study designs. We did not limit comparators for nonstandard interventions; however, we did exclude studies on nonhuman, in vivo, and healthy volunteers.

Study Selection

Results of the literature search were imported to a bibliographic database for screening. At least two independent reviewers examined all titles and abstracts for eligibility based on the inclusion/exclusion criteria. Titles and abstracts with insufficient information to determine eligibility were pulled for full article text review. Disagreements between reviewers were resolved through consensus. Final results of the screening process were then imported to an EndNote file for database management.

Data Extraction

We extracted the following data from included trials directly into study tables: study design; setting; population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; characteristics of the interventions; numbers screened, eligible, enrolled, and

lost to followup according to the research design; method of outcome ascertainment; study quality items; and results for each outcome. All tables were subject to a quality check of all data items by independent reviewers.

Quality Assessment

Key Question 1

To assess the quality of reports for diagnostic studies, we used the criteria developed for the Quality Assessment of Diagnostic Accuracy Studies.[155,156] These criteria include: (1) tested specimens (patients, stool) and their selection were clearly described and representative of those that are tested in clinical practice; (2) the time period and handling of specimens between tests most likely did not change what is being measured; (3) all test procedures were adequately described and replicable; (4) the same credible reference test was used for all specimens, performed regardless of other test results; (5) the reference and diagnostic tests being evaluated were conducted and interpreted independently of each other, that is, blinded; (6) any clinical information that was used in the interpretation of test results was reported; (7) indeterminate results were reported and analyzed in a reasonable manner; and (8) excluded test results, specimens, or patients were reported and explained. This quality assessment does not have a method for scoring the criteria or reliably categorizing the studies. Some studies that did not meet a key criterion for inclusion in the review were excluded without further assessment of their quality.

Studies that are summarized in this review were rated as having "good" internal validity. Comparisons were made in the same laboratory using the same specimens and a credible reference standard. There were no major differences in the processing and storing of the specimens between tests that were independently conducted. Indeterminate results were discussed and handled in a reasonable manner.

Key Question 2

Quality assessment for nonrandomized studies used primarily in assessing prevention strategies was based on study design (case control versus case series), the selection of cases or cohorts and controls (how well matched), and adjustment for confounders. Studies were rated as higher quality if they met the following a priori defined criteria: (1) prospective, (2) had explicitly detailed the methods of their study, (3) patients were representative of typical CDI patients, and (4) used multivariate analysis to isolate the effect of the variable in question.

Key Questions 3 and 4

We rated the study quality of individual randomized controlled or clinically controlled trials using criteria based on Cochrane Collaboration recommended domains.[157] These domains assess the risk of bias of studies included in a systematic review. The first domain is adequate allocation concealment, based on the approach by Schulz and Grimes.[158] The second domain regards blinding methods, such as participant, investigator, or outcome assessor. The third domain regards how incomplete data are addressed: did the study analyze the data based on the intention-to-treat principle (i.e., were all subjects who were randomized included in the outcomes analyses), and were reasons for dropouts/attrition reported?

Studies were rated to be of good, fair, or poor quality. A rating of good generally indicates that the trial reported adequate allocation concealment, blinding, analysis by intent to treat, and

reasons for dropouts or attrition. Studies were generally rated poor if the method of allocation concealment was inadequate or not defined, blinding was not defined, analysis by intent to treat was not utilized, and reasons for dropouts or attrition were not reported and/or there was a high rate of attrition.

Rating the Body of Evidence

For randomized trials, the overall strength of evidence was evaluated using methods developed by AHRQ and the Effective Health Care Program.[159] The strength of the evidence was evaluated based on four required domains: (1) risk of bias (do the studies for a given outcome or comparison have good internal validity); (2) consistency (the degree of similarity in the effect sizes [i.e., same direction of effect] of the included studies); (3) directness (reflecting a single, direct link between the intervention of interest and the outcome); and (4) precision (degree of certainty surrounding an effect estimate of a given outcome). The risk of bias, based on study design and conduct, is rated low, medium, or high. Consistency is rated consistent, inconsistent, or unknown/not applicable (e.g., a single study was evaluated). Directness can either be direct or indirect, and precision is either precise or imprecise. A precise estimate is one that would yield a clinically meaningful conclusion.

The evidence is rated using high, moderate, low, and insufficient for grades. A high grade indicates that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence is believed to reflect the true effect. A moderate grade denotes further research may change our confidence in the estimate of effect and may, in fact, change the estimate. A low grade indicates that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate. Thus, there is low confidence that the evidence reflects the true effect. An insufficient grade indicates that the evidence is unavailable or does not permit a conclusion. An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias and consistent, direct, and precise domains.

We modified this approach for diagnostic tests in the following manner. As previously stated, all of the studies that provided comparative evidence for differences between diagnostic tests were selected based on having ‘good’ protection against bias (internal validity). Furthermore, all of the comparative studies were rated as providing only indirect evidence because none presented evidence that the differences in sensitivity and/or specificity of the diagnostic tests would lead to any differences in patient outcomes. Indeed, studies that provide evidence that the observed differences would or would not be clinically meaningful were not found, nor were estimates of how much of a difference would be required to make a different clinical decision about the diagnosis. Thus, any differences in the overall grades of the strength of evidence for comparisons of the diagnostic tests are based on the consistency (direction and size) of the estimated differences in sensitivity and specificity and the precision (width of the estimated confidence intervals).

Applicability

Applicability of the treatment results, both standard and nonstandard adjuvant treatment, of this review are affected by the representativeness of the patient samples in the included studies, which are general adult inpatient populations. Applicability of diagnostic test results is limited by the samples used in the analyses; to the extent that they were typical clinical samples derived from patients with suspected CDI, they represent the typical patient population that was tested.

However, the ability to explicitly state the applicability of such samples is dependent on the completeness of the study reporting on the characteristics of the patients/specimens that were selected for the study. Furthermore, the substantial heterogeneity between studies in estimates of sensitivity and specificity of many of the diagnostic tests being reviewed, and perhaps their differences, raises concerns about generalization of the results. The evidence tables in Appendix C identify reported details on the patient inclusion and exclusion criteria.

Data Synthesis

For key questions with trial data, we applied quantitative techniques to estimate a summary effect size for reported outcomes for which heterogeneity of interventions and outcomes measures was minimal. Qualitative narratives were provided for key questions for which heterogeneity of interventions or measured patient outcomes was too great, or for which available studies were observational. Results of the quantitative and qualitative analyses are compared to relevant published systematic reviews for consistency of findings. (See Appendix C tables for details of systematic reviews.)

Data were analyzed in Review Manager 5.2.[160] Random effects models were used to generate pooled estimates of relative risks and weighted mean differences with 95 percent confidence intervals. Statistical heterogeneity was summarized using the I^2 statistic (50 percent indicates moderate heterogeneity and 75 percent or greater indicates high heterogeneity).[161]

Key Question 1

We focused on the differences between test sensitivities and specificities rather than on the specific test sensitivities and specificities themselves. Thus, methods of meta-analysis typically used for clinical trials with binary endpoints were employed rather than methods typically used for sensitivities and specificities, such as diagnostic odds ratios. To be able to estimate the correlation between two tests that were applied to the same patients/stool specimens, hence calculate proper confidence intervals on the differences of the sensitivities and specificities of two tests, the results of each test for each individual are needed.[162] Many reports did not provide this information. Therefore, the estimated confidence intervals on the differences in sensitivities and specificities ignored the unknown correlation between test results. Ignoring the correlation most likely increased the estimated variances of the differences and the width of the confidence intervals depending on the direction and magnitude of the correlation between the estimates for the two tests.

Each study had two primary endpoints, difference in sensitivities and difference in specificities. Furthermore, some studies made multiple comparisons. Some adjustment for multiple endpoints and comparisons was made by calculating 99 percent confidence intervals on the differences.

Publication Bias

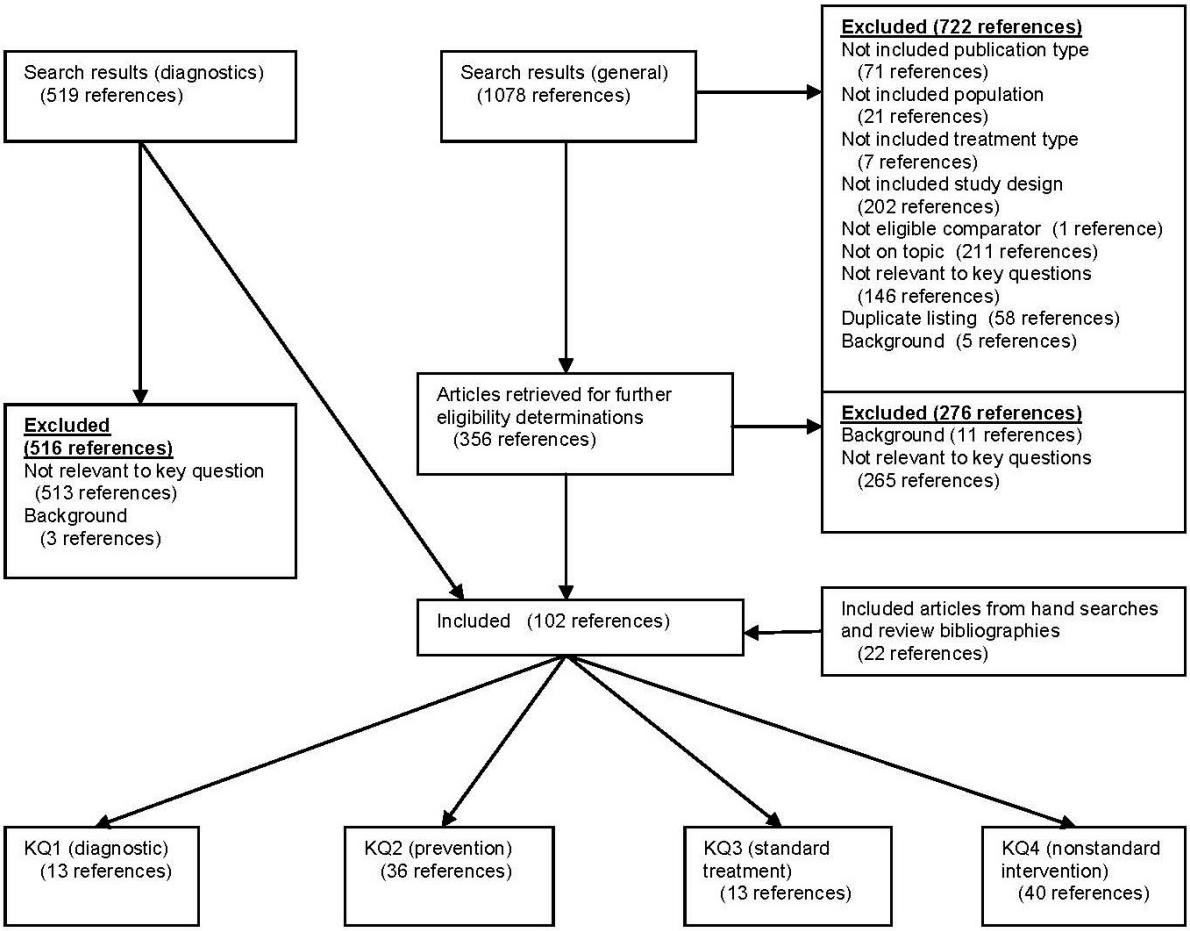
Grey literature was searched for relevant trials and other material to inform the likelihood of publication bias. Regulatory sources included Federal Drug Administration, Health Canada, and Authorized Medicines for the European Union. Clinical trial registries accessed were ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, and World Health Organization's Clinical Trials. Grants and federally funded research sources included NIH RePORTER, a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions, and HSRProj, a database providing access

to ongoing grants and contracts in health services research. Other sources searched were Hayes, Inc. Health Technology Assessment, New York Academy of Medicine's Grey Literature Index, Conference Papers Index, and Scopus.

Results

The general search identified 1,078 citations from MEDLINE. Of these, 356 studies were pulled for full text screening. Of these 356 references, we included 69 randomized controlled trials (RCTs), systematic reviews, observational studies, and an additional 22 articles obtained from hand searching and review article bibliographies. We excluded 998 articles. A supplemental search for diagnostics identified 519 citations from MEDLINE, of which 516 references were excluded. Figure 4 provides a literature flow diagram. A bibliography of the excluded articles, and their reasons for exclusion, is provided in Appendix D.

Figure 4. Reference flow diagram



KQ = Key Question

Key Question 1. How do Different Methods for Detection of Toxigenic *C. difficile* Compare in Their Sensitivity and Specificity?

Search Results

We included 13 references that provided comparative data about diagnostic tests of interest. The studies were published from 2001 to 2010. Five studies were from the United States, two were from the United Kingdom and Spain, and one each were from Belgium, Ireland, Israel, and the Netherlands. Table 1 provides a summary of the available comparisons. Overall, these reports included data on seven named immunoassays for toxins A and B, one two-stage method where an immunoassay for glutamate dehydrogenase was combined with an immunoassay for toxins A and B, and two tests to detect gene fragments involved in the production of toxin B. Only three comparative studies included one of the recently FDA-approved toxin gene detection tests. Thus, the number and type of paired (within study) comparisons available for each diagnostic test varied considerably, and not all possible comparisons were available. Evidence summary tables, including study quality items, are available in Appendix C of this report (see Appendix Table C1).

Key Points

- Sixteen paired comparisons of seven immunoassays for toxins A and B provided low-grade evidence that the test sensitivities do not differ. There was moderate-grade evidence for no differences in test specificities for three comparisons and for a difference of 2 percent in one comparison. Otherwise, there was only low-grade 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 different gene detection tests to toxin immunoassays provided only low-grade evidence to support the notion that the gene-based tests are substantially more sensitive than immunoassays. There was moderate evidence that the test specificities in one comparison did not differ. Otherwise, there was only low-grade 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 insufficient evidence to determine whether any differences in sensitivity or specificity between diagnostic tests depend on patient or specimen characteristics or the strain of toxigenic *Clostridium difficile.*

Quality of the Comparative Studies

All studies used stool specimens from mostly inpatients that were submitted by clinicians to test for *Clostridium difficile* infection (CDI). However, the clinical scenarios that prompted the clinicians to test for CDI, such as the nature of the patient's diarrhea, or exposure to antibiotics, were not described in many reports. Seven of the 13 studies that provided data mentioned that the stool samples were liquid, unformed, or diarrhea, whereas the other reports did not clearly describe the consistency of the stool specimens. Six of the studies included more than one specimen from some patients, and three studies only reported the total number of stool specimens and not the number of patients. Two studies selected stool samples based on previous diagnostic test results to enhance the percentage of positive tests in their sample, and two included a facility with a recent outbreak of CDI or high prevalence. Thus, the reviewed reports

were somewhat deficient in reporting pertinent information about patient selection criteria and the spectrum of patients/specimens included the comparisons (Appendix Table C2).

Differences within studies in the timing and handling of specimens for the different tests being compared were not a major issue in the reviewed studies. Verification using the reference standard was applied consistently to all stool specimens. However, the same reference standard was not used in all studies. Five of the 13 studies used a cell cytotoxicity test as the reference, five used a cell cytotoxicity test in conjunction with toxigenic culture, one used a toxin immunoassay in conjunction with toxigenic culture, one used multiple immunoassays for toxins A and B in conjunction with toxigenic culture, and one used an in-house gene detection test. None of the reference methods that were used are a true gold standard in that they are not 100 percent sensitive or specific for toxigenic *C. difficile* and their accuracies are not all the same. Within each study, the diagnostic tests were carried out independently of each other although the reports usually did not state that each test was interpreted without knowledge of other results. Only two reports explicitly stated that all diagnostic tests being compared, including the reference test, were conducted in a blinded manner. Sometimes the independence of the tests could be inferred from their sequence and the time needed to get results.

The handling of indeterminate test results presents problems when comparing the sensitivity and specificity of diagnostic tests. Some investigators repeated indeterminate tests and used the result of the second test as recommended, although some repeated tests were also indeterminate. Some assumed indeterminate results were negative and thereby could have inflated the number of false negatives. Some comparisons excluded indeterminate results; thus, the varying number of indeterminate tests did not count for or against a test. However, differences in the number of indeterminate results produced by different tests resulted in some differences in the stool specimens being used to compare the tests. Other types of subject or specimen withdrawal were not an issue in the studies that were reviewed.

Detailed Analysis

Comparisons of Immunoassays for Toxins A and B

As summarized in Table 2, none of the seven immunoassays for toxins A and B was compared to all others. When more than one study compared the same two immunoassays, the heterogeneity in the differences in sensitivity was significant in only one out of nine cases. None of the nine pooled comparisons based on two to four studies indicated that any of the immunoassays were more sensitive than another. The pooled estimates of the differences (99 percent confidence interval [CI]) in test sensitivities were 0±6 percent, 1±7 percent, 3±6 percent, 3±7 percent, -1±10 percent, 3±8 percent, 6±12 percent, 1±9 percent, and 3±24 percent. The confidence intervals for single-study estimates of differences in sensitivity were wide. Thus, the available data often could not rule out substantial differences in sensitivities.

There was some significant heterogeneity in the corresponding estimates of differences in false positives (1 minus specificity) for two of the nine multiple study comparisons of immunoassays for toxins A and B. Ignoring the heterogeneity, the differences (99 percent CI) in false positives were 0±2 percent, 0±1 percent, 2±1 percent, 0±1 percent, -3±3 percent, -1±10 percent, -6±14 percent, 3±2 percent, and 2±2 percent. Thus, the available data often ruled out differences in false positives of only a few percent. One study that compared several immunoassays found some differences in the false positives of approximately 6 percent.

Gene Detection Tests Versus Immunoassays for Toxins A and B

As summarized in Table 3, two studies compared the same tests to detect genes related to toxin B production to the same immunoassay for toxins A and B.[32,37] There was significant heterogeneity between the estimated differences in sensitivities for both comparisons; however, in each case both studies suggested the gene-based test was more sensitive than the immunoassay. The pooled estimate of the difference in sensitivities was 17 percent in favor of the gene based test with a 99 percent confidence interval of from 3 to 37 percent in one comparison, and 25 with a 99 percent confidence interval of from -36 to 86 percent in the other comparison. There was no heterogeneity in the corresponding estimated differences in false positive percentages of these tests. The pooled estimate of the differences in the false positives were 0 percent with a 99 percent confidence interval of from 1 percent to 1 percent for one comparison, and 2 with a 99 percent confidence interval of from -1 percent to 5 percent for the other comparison. The percentage of false positives tended to be greater with the gene detection test in the later comparison.

Three studies provided one pairwise comparisons of a gene detection test to an immunoassay for toxins A and B.[32] The sensitivity of the gene detection test was consistently better, although the point difference ranged widely from 3 percent to 56 percent, and the confidence intervals didn't always exclude a difference of zero. The false positives for the gene-based test were approximately 3 percent greater compared to one of the immunoassays for toxins A and B.

The sensitivities of the two gene detection tests in the three studies ranged from 89 percent to 100 percent. In contrast, the sensitivities of the immunoassays for toxins A and B were much more variable, ranging from 44 percent to 86 percent. The methodological differences between studies, including use of different reference tests, might have affected the toxin immunoassays more than the gene detection tests. The estimated sensitivities of the immunoassays were remarkably low (only 44 or 58 percent) in two studies that used the generally most sensitive reference test (toxigenic culture).

Table 1. Summary of diagnostic comparisons in included studies

Diagnostic Test	Premier Toxin A&B, Meridian	Tox A/B II, TechLab	Tox A/B QUIK CHEK, TechLab	ImmunoCard A&B, Meridian	Xpect Toxin A/B, Remel	ProSpecT Toxin A/B, Remel	*C. diff* Tox A/B, VIDAS
A and B Toxin Immunoassays							
Premier Toxin A&B, Meridian	n/a	4 studies	1 study	3 studies	2 studies	2 studies	2 studies
Tox A/B II, TechLab	none	n/a	2 studies	2 studies	none	none	none
Tox A/B QUIK CHEK, TechLab	none	none	n/a	4 studies	3 studies	1 study	1 study
ImmunoCard A&B, Meridian	none	none	none	n/a	none		1 study
Xpect Toxin A/B, Remel	none	none	none	none	n/a	1 study	1 study
ProSpecT Toxin A/B, Remel	none	none	none	none	none	n/a	1 study
C. diff Tox A/B, VIDAS	none	none	none	none	none	none	n/a
Gene Detection Tests							
GeneOhm, Becton Dickinson	1 study	2 studies	1 study	1 study	1 study	1 study	2 studies
GeneXpert, Cepheid	1 study	none	none	none	none	none	1 study

Table 2. Comparisons of immunoassays for toxins A and B

Study	Sensitivity (% True Positive)			% False Positives (1 Minus Specificity)		
	Toxin Immunoassay X	Toxin Immunoassay Y	% Difference	Toxin Immunoassay X	Toxin Immunoassay Y	% Difference
Eastwood, 2009[32]	*Premier Toxin A&B, Meridian*	*Tox A/B II, TechLab*	1 (-12 to 14)*	*Premier Toxin A&B, Meridian*	*Tox A/B II, TechLab*	-1 (-4 to 1)
Musher, 2007[33]	101/125 (80.8%)	100/125 (80.0%)	0 (-9 to 9)	12/475 (2.5%)	19/475 (4.0%)	-6 (-19 to 6)
Turgeon, 2003[38]	52/54 (96.3%)	52/54 (96.3%)	-4 (-20 to 12)	5/77 (6.5%)	10/77 (13.0%)	0 (-1 to 1)
O'Connor, 2001[36]	74/101 (73.3%)	78/101 (77.2%)	2 (-17 to 20)	8/898 (0.9%)	5/902 (0.6%)	0 (-3 to 3)
Pooled Estimate	50/61 (82.0%)	49/61 (80.3%)	0 (-7 to 6)	1/139 (0.7%)	1/139 (0.7%)	0 (-3 to 2)
heterogeneity†			p=0.92;I^2=0%			p=0.06;I^2=60%
Eastwood, 2009[32]	*Tox A/B QUIK CHEK, TechLab*	*ImmunoCard A&B, Meridian*	0 (-15 to 14)	*Tox A/B QUIK CHEK, TechLab*	*ImmunoCard A&B, Meridian*	0 (-1 to 1)
Alcala, 2008[31]	93/125 (74.4%)	86/115 (74.8%)	-12 (-29 to 6)	3/473 (0.6%)	2/444 (0.4%)	0 (-5 to 4)
Miendje Deyi, 2008[39]	56/102 (54.9%)	68/102 (66.7%)	4 (-14 to 23)	12/265 (4.5%)	13/265 (4.9%)	0 (-3 to 3)
Samra, 2008[34]	22/23 (95.7%)	21/23 (91.3%)	0 (-8 to 8)	0/77 (0%)	0/77 (0%)	0 (-6 to 6)
Pooled Estimate	89/94 (94.7%)	89/94 (94.7%)	-1 (-9 to 6)	3/106 (2.8%)	3/106 (2.8%)	0 (-1 to 1)
heterogeneity			p=0.26;I^2=25%			p=0.98;I^2=0%
Eastwood, 2009[32]	*Premier Toxin A&B, Meridian*	*ImmunoCard A&B, Meridian*	6 (-8 to 20)	*Premier Toxin A&B, Meridian*	*ImmunoCard A&B, Meridian*	2 (0 to 4)
Sloan, 2008[35]	101/125 (80.8%)	86/115 (74.8%)	0 (-27 to 27)	12/475 (2.5%)	2/444 (0.4%)	1 (-3 to 4)
Musher, 2007[33]	21/44 (47.7%)	21/44 (47.7%)	3 (-4 to 9)	3/156 (1.9%)	2/156 (1.3%)	2 (-1 to 4)
Pooled Estimate	75/76 (98.7%)	73/76 (96.1%)	3 (-3 to 9)	10/370 (2.7%)	4/370 (1.1%)	2 (0 to 3)
heterogeneity			p=0.77;I^2=0%			p=0.67;I^2=0%
Eastwood, 2009[32]	*Tox A/B QUIK CHEK, TechLab*	*Xpect Toxin A/B, Remel*	1 (-14 to 15)	*Tox A/B QUIK CHEK, TechLab*	*Xpect Toxin A/B, Remel*	0 (-1 to 1)
Alcala, 2008[31]	93/125 (74.4%)	86/117 (73.5%)	6 (-12 to 24)	3/473 (0.6%)	3/475 (0.6%)	0 (-4 to 5)
Miendje Deyi, 2008[39]	56/102 (54.9%)	50/102 (49.0%)	4 (-14 to 23)	12/265 (4.5%)	11/265 (4.2%)	0 (-3 to 3)
Pooled Estimate	22/23 (95.7%)	21/23 (91.3%)	3 (-6 to 13)	0/77 (0%)	0/77 (0%)	0 (-1 to 1)
heterogeneity			p=0.84;I^2=0%			p=0.96;I^2=0%
Eastwood, 2009[32]	*Tox A/B QUIK CHEK, TechLab*	*Tox A/B II, TechLab*	-6 (-19 to 8)	*Tox A/B QUIK CHEK, TechLab*	*Tox A/B II, TechLab*	-3 (-6 to -1)
Samra, 2008[34]	93/125 (74.4%)	100/125 (80.0%)	1 (-8 to 10)	3/473 (0.6%)	19/475 (4.0%)	-3 (-10 to 4)
Pooled Estimate	89/94 (94.7%)	88/94 (93.6%)	-1 (-11 to 8)	3/106 (2.8%)	6/106 (5.7%)	-3 (-6 to -1)
heterogeneity			p=0.22;I^2=35%			p=0.85;I^2=0%
Eastwood, 2009[32]	*Premier Toxin A&B, Meridian*	*ProSpecT Toxin A/B, Remel*	-1 (-14 to 12)	*Premier Toxin A&B, Meridian*	*ProSpecT Toxin A/B, Remel*	-4 (-8 to -1)
Musher, 2007[33]	101/125 (80.8%)	102/125 (81.6%)	6 (-7 to 8)	12/475 (2.5%)	32/475 (6.7%)	4 (-5 to 13)
Pooled Estimate	52/54 (96.3%)	49/54 (90.7%)	3 (-6 to 11)	5/77 (6.5%)	2/77 (2.6%)	-1 (-11 to 10)
heterogeneity			p=0.31;I^2=4%			p=0.02;I^2=80%
Eastwood, 2009[32]	*Premier Toxin A&B, Meridian*	*Xpect Toxin A/B, Remel*	7 (-7 to 21)	*Premier Toxin A&B, Meridian*	*Xpect Toxin A/B, Remel*	2 (0 to 4)
Sloan, 2008[35]	101/125 (80.8%)	86/117 (73.5%)	0 (-27 to 27)	12/475 (2.5%)	3/475 (0.6%)	-14 (-22 to -6)
Pooled Estimate	21/44 (47.7%)	21/44 (47.7%)	6 (-7 to 18)	3/156 (1.9%)	25/156 (16.0%)	- 6 (-32 to 20)
heterogeneity			p=0.54;I^2=0%			p=0.0001;I^2=97%

Table 2. Comparisons of immunoassays for toxins A and B (continued)

Study	Sensitivity (% True Positive)			% False Positives (1 Minus Specificity)		
	Toxin Immunoassay X	Toxin Immunoassay Y	% Difference	Toxin Immunoassay X	Toxin Immunoassay Y	% Difference
Eastwood, 2009[32] Samra, 2008[34] Pooled Estimate heterogeneity	*Tox A/B II, TechLab* 100/125 (80.0%) 88/94 (93.6%)	*ImmunoCard A&B, Meridian* 86/115 (74.8%) 89/94 (94.7%)	5 (-9 to 19) -1 (-10 to 8) 1 (-8 to 10) p=0.25;I^2=24%	*Tox A/B II, TechLab* 19/475 (4.0%) 6/106 (5.7%)	*ImmunoCard A&B, Meridian* 2/444 (0.4%) 3/106 (2.8%)	4 (1 to 6) 3 (-4 to 10) 3 (1 to 6) p=0.80;I^2=0%
Eastwood, 2009[32] van den Berg, 2007[162] Pooled Estimate heterogeneity	*Premier Toxin A&B, Meridian* 101/125 (80.8%) 30/31 (96.8%)	*VIDAS C. diff Tox A/B, bioMerieux* 100/116 (86.2%) 26/31 (83.8%)	-5 (-18 to 7) 13 (-6 to 32) 3 (-21 to 27) p=0.03;I^2=78%	*Premier Toxin A&B, Meridian* 12/475 (2.5%) 29/509 (5.7%)	*VIDAS C. diff Tox A/B, bioMerieux* 2/464 (0.4%) 15/509 (2.9%)	2 (0 to 4) 3(-1 to 6) 2 (1 to 4) p=0.62;I^2=0%
Eastwood, 2009[32]	*Premier Toxin A&B, Meridian* 101/125 (80.8%)	*Tox A/B QUIK CHEK, TechLab* 93/125 (74.4%)	6 (-7 to 20)	*Premier Toxin A&B, Meridian* 12/475 (2.5%)	*Tox A/B QUIK CHEK, TechLab* 3/473 (0.6%)	2 (0 to 4)
Eastwood, 2009[32]	*Tox A/B QUIK CHEK, TechLab* 93/125 (74.4%)	*ProSpecT Toxin A/B, Remel* 102/125 (81.6%)	-7 (-21 to 6)	*Tox A/B QUIK CHEK, TechLab* 3/473 (0.6%)	*ProSpecT Toxin A/B, Remel* 32/475 (6.7%)	-6 (-9 to -3)
Eastwood, 2009[32]	*Tox A/B QUIK CHEK, TechLab* 93/125 (74.4%)	*VIDAS C. diff Tox A/B, bioMerieux* 100/116 (86.2%)	-12 (-25 to 1)	*Tox A/B QUIK CHEK, TechLab* 3/473 (0.6%)	*VIDAS C. diff Tox A/B, bioMerieux* 2/464 (0.4%)	0 (-1 to 1)
Eastwood, 2009[32]	*Xpect Toxin A/B, Remel* 86/117 (73.5%)	*ProSpecT Toxin A/B, Remel* 102/125 (81.6%)	-8 (-22 to 6)	*Xpect Toxin A/B, Remel* 3/475 (0.6%)	*ProSpecT Toxin A/B, Remel* 32/475 (6.7%)	-6 (-9 to -3)
Eastwood, 2009[32]	*Xpect Toxin A/B, Remel* 86/117 (73.5%)	*VIDAS C. diff Tox A/B, bioMerieux* 100/116 (86.2%)	-13 (-26 to 1)	*Xpect Toxin A/B, Remel* 3/475 (0.6%)	*VIDAS C. diff Tox A/B, bioMerieux* 2/464 (0.4%)	0 (-1 to 1)
Eastwood, 2009[32]	*ProSpecT Toxin A/B, Remel* 102/125 (81.6%)	*VIDAS C. diff Tox A/B, bioMerieux* 100/116 (86.2%)	-5 (-17 to 8)	*ProSpecT Toxin A/B, Remel* 32/475 (6.7%)	*VIDAS C. diff Tox A/B, bioMerieux* 2/464 (0.4%)	6 (3 to 9)
Alcala, 2010[164]	*ImmunoCard A&B, Meridian* *42/62 (67.7%)*	*VIDAS C. diff Tox A/B, bioMerieux* 43/62 (69.4%)	-2 (-23 to 20)	*ImmunoCard A&B, Meridian* 21/425 (4.9%)	*VIDAS C. diff Tox A/B, bioMerieux* 8/425 (1.9%)	3 (0 to 6)

***** Values in parentheses are 99% confidence intervals for the difference between tests conservatively assuming statistical independence between the paired tests.

† The p-value is a chi-square test for nonrandom variation in the differences between studies, and I^2 is the proportion of the total variance in the estimated differences that reflects true variation (i.e. heterogeneity between studies).

Table 3. Toxin gene detection tests compared to immunoassays

Study	Sensitivity (% True Positives)			% False Positives (1 Minus Specificity)		
	Toxin Gene Test	Toxin Immunoassay	% Difference	Toxin Gene Test	Toxin Immunoassay	% Difference
Kvach, 2010[37] Eastwood, 2009[32] Pooled Estimate heterogeneity†	*GeneOhm, Becton Dickinson* 96/105 (91%) 92/103 (89%)	*Tox A/B II, TechLab* 70/105 (67%) 100/125 (80%)	25 (11 to 39)* 9 (-3 to 21) 17 (-3 to 37) p=0.03; I^2=79%	*GeneOhm, Becton Dickinson* 0/295 (0%) 16/449 (3.6%)	*Tox A/B II, TechLab* 1/295 (0.3%) 19/475 (4.0%)	0 (-4 to 3) 0 (-2 to 1) 0 (-1 to 1) p=0.90; I^2=0%
Swindells, 2010[165] Eastwood, 2009[32] Pooled Estimate heterogeneity†	*GeneOhm, Becton Dickinson* 17/18 (94.4%) 92/103 (89%)	*VIDAS Clostridium difficile A and B, bioMerieux* 8/18 (44.4%) 100/116 (86%)	50 (17 to 83) 3 (-8 to 14) 25 (-36 to 86) p<0.001; I^2=92%	*GeneOhm, Becton Dickinson* 1/132 (0.8%) 16/449 (3.6%)	*VIDAS Clostridium difficile A and B, bioMerieux* 0/132 (0%) 2/464 (0.4%)	1 (-2 to 3) 3 (1 to 6) 2 (-1 to 5) p=0.07; I^2=70%
Eastwood, 2009[32]	*GeneOhm, Becton Dickinson* 92/103 (89%)	*Premier Toxin A&B, Meridian* 101/125 (81%)	9 (-3 to 21)	*GeneOhm, Becton Dickinson* 16/449 (3.6%)	*Premier Toxin A&B, Meridian* 12/475 (2.5%)	1 (-2 to 4)
Eastwood, 2009[32]	*GeneOhm, Becton Dickinson* 92/103 (89%)	*ImmunoCard A&B, Meridian* 86/115 (75%)	15 (1 to 28)	*GeneOhm, Becton Dickinson* 16/449 (3.6%)	*ImmunoCard Toxin A&B, Meridian* 2/444 (0.4%)	3 (1 to 6)
Eastwood, 2009[32]	*GeneOhm, Becton Dickinson* 92/103 (89%)	*Tox A/B QUIK CHEK, TechLab* 93/125 (74%)	15 (2 to 28)	*GeneOhm, Becton Dickinson* 16/449 (3.6%)	*Tox A/B QUIK CHEK, TechLab* 3/473 (0.6%)	3 (0 to 5)
Eastwood, 2009[32]	*GeneOhm, Becton Dickinson* 92/103 (89%)	*ProSpecT Toxin A/B, Remel* 102/125 (82%)	8 (-4 to 20)	*GeneOhm, Becton Dickinson* 16/449 (3.6%)	*ProSpecT Toxin A/B, Remel* 32/475 (6.7%)	-3 (-7 to 1)
Eastwood, 2009[32]	*GeneOhm, Becton Dickinson* 92/103 (89%)	*Xpect Toxin A/B, Remel* 86/117 (74%)	16 (3 to 29)	*GeneOhm, Becton Dickinson* 16/449 (3.6%)	*Xpect Toxin A/B, Remel* 3/475 (0.6%)	3 (0 to 5)
Swindells 2010[165]	*GeneXpert, Cepheid* 18/18 (100%)	*VIDAS Clostridium difficile A and B, bioMerieux* 8/18 (44.4%)	56 (25 to 86)	*GeneXpert, Cepheid* 1/132 (0.8%)	*VIDAS Clostridium difficile A and B, bioMerieux* 0/132 (0%)	1 (-1 to 3)
Novak-Weekly, 2010[40]	*GeneXpert, Cepheid* 68/72 (94%)	*Premier Toxin A&B, Meridian* 42/72 (58%)	36 (20 to 53)	*GeneXpert, Cepheid* 13/356 (3.7%)	*Premier Toxin A&B, Meridian* 19/360 (5.3%)	-2 (-6 to 2)

* Values in parentheses are 99% confidence intervals for the difference between tests conservatively assuming statistical independence between the paired tests.

† The p-value is a chi-square test for nonrandom variation in the differences between studies, and I^2 is the proportion of the total variance in the estimated differences that reflects true variation (i.e. heterogeneity between studies).

Key Question 2. What are Effective Prevention Strategies?

Search Results

We found 1 Cochrane review,[41] 4 studies on antibiotic prescribing restrictions,[42-45] 12 on single preventive practices aimed at transmission interruption,[46-55,67] and 10 that bundled multiple practices into a prevention strategy.[56-65] Only two trials were controlled trials;[46,49] one was an interrupted time series study,[42,66] and the remaining studies were before/after designs.[43-45,47,48,50-55,66,67] The included studies are provided in Table 4.

Eight studies examining risk factors met the inclusion criteria and updated the period following a systematic review[20] (Appendix Table C3). Five studies were conducted in the United States,[111,166-169] two in Israel,[112,170] and one in the United Kingdom.[171] The average CDI patient sample was 86 patients, with a range of 28 to 154. Studies varied in the degree to which the investigators verified that positive tests reflected disease.

Key Points

- Overall, the evidence available to link prevention strategies to clinically important outcomes, such as CDI incidence, is of low strength and is not extensive.
- Four observations studies and one Cochrane review found 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.
- Three observational studies, including two controlled, found disposable thermometer use is likely to reduce CDI incidence.
- No study examined the effect of handwashing, rather than alcohol gels, on CDI incidence. Four observational studies found use of alcohol gels as interventions for other infectious diseases, presumably in the presence of protocols requiring handwashing in the presence of CDI or visible soiling, did not increase CDI incidence.
- Three 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. Seven studies included disinfection in multicomponent interventions. 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. Data are insufficient to draw conclusions.
- Risk factors for developing CDI include antibiotic use, substantial chronic illness, hospitalization in an ICU, age, and acid suppression therapy.
- No data on patient harms or harms to hospital staff due to preventive interventions were reported.
- No studies assessed the sustainability of a prevention program beyond an intervention period.

Quality of the Studies

Overall, the quality of the evaluated studies was considered low (Table 4). In the Cochrane review[41] focusing on improving antibiotic prescribing practices, the evidence from one article[172] was judged to be of "good" quality, and evidence from the others was considered "weak." The evidence for the 10 single preventive practices aimed at transmission interruption was low because they predominately used before/after design and were done in response to epidemic or hyperendemic conditions. In particular, there is insufficient evidence that handwashing is associated with reduced CDI incidence, as no study assessed this intervention. Of the four studies assessing alcohol based rubs or gels, only one had concurrent controls. Thirteen studies examining environmental disinfections were all before/after studies, generally done in response to epidemics.

For the 10 articles that described multiple component preventive interventions, none had concurrent controls or was blinded, and there was considerable variability in the types of interventions, so pooling could not be done. In addition, it was indeterminable to attribute decreases in CDI incidence to any single intervention in all of these studies.

Detailed Analysis

Due to the low-quality studies, we provide a qualitative narrative of the evidence for prevention practice interventions.

Antibiotic Use

The five studies summarized in the Cochrane review,[41] and the additional four individual studies here,[42-45] found that changes in antimicrobial education, policies, or formularies, which result in decreasing use of high-risk antimicrobials, are associated with decreased CDI incidence. It was not possible to clearly isolate the impact of the antibiotic-related interventions in the studies examining multiple interventions.[58-60,62,63] In the individual studies, which were usually done in response to outbreaks, interventions in addition to those aimed at antibiotic use may have been done but not reported. The interventions and antibiotics targeted for reduction differed among the various studies.

The Cochrane review[41] determined the impact of interventions to improve antibiotic prescribing practices for hospital inpatients on CDI incidence. The authors found that four interventions were associated with significant reductions in CDI incidence[62,172-174] and that one was associated with a nonsignificant trend toward a reduction.[61]

A prospective controlled interrupted time series[42] of an antibiotic improvement intervention on three acute medical wards for elderly people with 21-month predefined pre- and postintervention periods, evaluated a "narrow-spectrum" antibiotic policy (reinforced by an established program of audit and feedback of antibiotic usage and CDI rates). The program targeted broad-spectrum antibiotics (cephalosporins and amoxicillin/clavulanate) for reduction and narrow-spectrum antibiotics (benzyl penicillin, amoxicillin. and trimethoprim) for increase. CDI rates decreased significantly with incidence rate ratios of 0.35 (95 percent CI 0.17 – 0.73). Incidence of Methicillin-resistant *Staphylococcus aureus* (MRSA), the control, did not change significantly.

The effect of a new antibiotic policy favoring piperacillin-tazobactam over cefotaxime on the long-term incidence of CDI and antibiotic utilization in a large elderly medicine unit was studied in a before/after observational study.[43] Restrictions were associated with reduced cefotaxime use

and reduced CDI incidence. Subsequently, the piperacillin-tazobactam became unavailable at the end of 2001. Cefotaxime use and CDI incidence rates increased during 2002.

In a geriatrics department of a university hospital, antimicrobial recommendations for treatment of several common infectious diseases were changed from broad-spectrum cephalosporins to other drugs thought to be less likely to induce CDI.[44] Investigators changed department policy to reflect these recommendations, educated providers, monitored antibiotic use, and gave periodic feedback to providers. Cephalosporin use dropped, and the relative risk of CDI decreased to 0.31 (95 percent CI 0.93 to 0.10) compared with usage before the policy change.

In a geriatrics department of another university hospital, broad-spectrum cephalosporin use was restricted due to an increase in CDI incidence.[45] In the following year, cephalosporin use decreased 92 percent, and CDI incidence decreased 50 percent from the previous year incidence. CDI incidence did not change in other hospital departments.

Measures to Reduce Transmission

Gloves

One controlled trial examined the use of gloves to prevent *C. difficile* transmission, with CDI incidence monitored by active surveillance.[46] An intensive education campaign on two wards urged personnel to use gloves when handling body substances, and gloves were made easily available to personnel working with patients. Two other wards with no education campaign served as control wards, and gloves on these wards were stocked in supply rooms. Incidence of CDI decreased significantly from 7.7 cases/1,000 patient discharges during the 6 months before intervention to 1.5/1,000 during the six months of intervention on the intervention wards. No significant change in CDI incidence was observed on the control wards. Asymptomatic *C. difficile* carriage also decreased significantly on the intervention wards but not on the control wards. The cost of 61,500 gloves (4,505 gloves/100 patients) used was $2,768 for the glove-using wards, compared with $1,895 (42,100 gloves; 3,532 gloves/100 patients) on the control wards.

Disposable Thermometers

Three studies, one randomized crossover design,[49] and two before/after studies without concurrent controls[47,48] have shown that use of disposable thermometers prevent CDI. In one hospital with an increased CDI incidence, 21 percent of electronic rectal thermometer handles were contaminated with *C. difficile*.[47] Efforts to reinforce infection control practices were already in place, but CDI incidence remained elevated. A before/after trial was conducted in that hospital and a chronic care facility to determine if use of disposable thermometers instead of multiple-use electronic rectal thermometers would reduce the CDI incidence. Surveillance for CDI was active, but toxin was detected with a latex agglutination test. During the 6-month postintervention period, the CDI incidence decreased from 2.71/1,000 patient days to 1.76/1,000 patient days in the acute hospital and from 0.41/1,000 patient days to 0.11/1,000 patient days in the skilled nursing facility. The harms associated with use of disposable thermometers were costs for purchase of disposable thermometers and the need to dispose of these thermometers. In these institutions, annual outlays increased from $7,731 to $14,055. These costs were offset by the need to purchase fewer electronic thermometers and to sterilize them periodically and by decreased costs of treating CDI cases.

In a later report, the same group reported that the rate of *C. difficile* infections increased from 1991 to 1993, although it was unclear how many patients had symptoms of disease with *C. difficile*.[48] One ward used disposable tympanic membrane thermometers instead of disposal oral or rectal thermometers. Different interventions were implemented in two other wards. Regression analysis determined that the *C. difficile* infection rate decreased 40 percent (relative risk [RR], 0.59, 95 percent CI, 0.47-0.67).

A randomized, controlled crossover study compared the use of disposable thermometers with electronic thermometers to prevent nosocomial CDI.[49] Twenty hospital wards were randomly assigned to disposable thermometers or electronic thermometers for 6 months, and then the assignments were reversed for 5 months. CDI rates were reduced 44 percent (P=0.026, 95 percent CI, 0.21 to 0.93) with disposable thermometers compared to electronic thermometers. Rates of nosocomial diarrhea or nosocomial infections did not differ significantly between the two groups. A cost analysis estimated that the hospital using disposable thermometers would need to spend an additional $5,926 to prevent a single CDI case. It was estimated that a CDI case resulted in $2,000 to $6,000 in excess costs.

Handwashing

No study addressed whether handwashing was associated with reduced CDI incidence. Many institutions encourage the use of alcohol-based rubs or gels for hand hygiene unless hands are grossly soiled or unless a health care worker has had potential contact with *C. difficile* either from patient contact or environmental contamination. Neither alcohol nor soap will kill *C. difficile* spores, but when health care workers wash hands properly with soap, most spores are removed because of friction and the detergent action of soap. Complicated recommendations are difficult to remember and implement, and one concern has been that health care workers will use alcohol-based rubs or gels in circumstances where handwashing is preferred.

Four studies have addressed this concern. One 2-year, prospective, controlled, crossover trial compared alcohol-based hand gel provided in addition to hand soap containing the antimicrobial 0.3 percent chloroxylenol with antimicrobial soap alone in two intensive care units.[50] In units using adjuvant alcohol-based gel, there was a significant, sustained improvement in the rate of hand hygiene adherence but no detectable change in the incidence of healthcare-associated CDI (diagnosis determined by clinicians).[50] Employees still had access to soap and water when their hands were soiled or when they were caring for a patient with *C. difficile,* and if workers used soap and water in these circumstances, it would have decreased the likelihood that differences in CDI rates would be detected.

The second study used a before/after design.[51] Hospital employees were encouraged to wash hands with the antimicrobial 0.3 percent triclosan in the first 3-year period, and an alcohol-based hand rub with 62.5 percent ethyl was placed in dispensers in inpatient and outpatient clinic rooms in the next 3 years. There was a 21 percent decrease in new, nosocomially acquired MRSA isolates and a 41 percent decrease in vancomycin-resistant enterococci (VRE) isolates, but the incidence of new CDI cases remained similar (diagnosis determined by clinicians/toxin A assay).[51]

A retrospective time-series analysis, the secondary objective, was done to determine the relationship between use of alcohol-based hand rub and antibiotic consumption on the incidence of CDI.[52] CDI incidence was determined retrospectively from records of patients put in isolation for CDI. Multivariable time series analyses showed no association between alcohol-based hand

rub and CDI incidence. Macrolide and third-generation cephalosporin use was associated with increased CDI incidence after lag times of 1 to 3 months.

A retrospective, interventional time-series analysis was used to determine the effects of two interventions on CDI incidence.[66] The interventions were promotional campaigns to encourage use of alcohol-based hand rub for hand hygiene. Time series analysis was done with autoregressive integrated moving average models. There was no association between alcohol-based hand rub and CDI incidence.

Disinfection

Four studies examined if disinfection reduces the incidence of CDI as a single component intervention,[53-55,67] and seven studies included disinfection in multicomponent interventions.[56,57,59,60,63,65,68] Disinfection agents examined included hypochlorite solution, hydrogen peroxide, aldehydes, and detergent.

Three studies examined **hypochlorite solution** as a single intervention. One before/after intervention investigated whether cleaning patient rooms that tested positive for *C. difficile* toxin with unbuffered with 1:10 hypochlorite solution reduced the incidence of CDI in three patients' units.[53] Before the intervention, patient rooms were cleaned with quaternary ammonium. In one housing bone marrow transplant patients and having the greatest rate before the intervention, the CDI incidence rate decreased significantly, from 8.6 to 3.3 cases per 1,000 patient-days (hazard ratio 0.37, 95 percent CI, 0.19 to 0.74) after hypochlorite was used to clean rooms. In the other two with lesser rates before the intervention, there was no significant change. In response to a subsequent outbreak of VRE infections, the hospital used quaternary ammonium solution for all patient room disinfection. The incidence of VRE infection decreased, but the CDI incidence rate increased. Hypochlorite disinfection was reinstituted and the CDI incidence rate subsequently decreased. A followup report documented subsequent increases in incidence and further interventions to control CDI.

An epidemiological investigation of an outbreak of CDI occurring in a single ward of a Michigan hospital documented nosocomial acquisition from the environment.[54] After use of unbuffered hypochlorite to disinfect wards, contamination decreased and the outbreak ended. Subsequently, it was shown that phosphate-buffered hypochlorite was even more effective for disinfection.

Hypochlorite was used in various ways in conjunction with other interventions to prevent CDI in seven studies (multiple intervention table part B).[56,57,59,60,63,65,68] The effect of the hypochlorite disinfection cannot be isolated from the other intervention components.

A high rate of CDI was noted in three hospitals joined in a single health care system. Hospitals changed the disinfectant used for the discharge cleaning of rooms of patients with CDI from a quaternary ammonium compound to dilute bleach.[67] There was a 48 percent reduction in the prevalence of *C difficile* after the bleaching intervention (P=0.0001, 95 percent CI, 36 to 58).

Two before/after studies were conducted to evaluate whether disinfection with **hydrogen peroxide** as part of multiple component interventions reduces CDI incidence.[57,63] In the first study, an abrupt increase in nosocomial CDI (defined as diarrhea with a positive toxin test) incidence led to multiple interventions in attempts to control the outbreak. Surveillance was based on laboratory and patient medical records.[57] A liquid vapor hydrogen peroxide decontamination system was used to decontaminate five high incidence wards of *C. difficile* organisms.[57] There followed a slight decrease in nosocomial CDI incidence. Liquid vapor hydrogen peroxide was then used to decontaminate patient rooms vacated by patients with CDI

throughout the hospital on an ongoing basis. Nosocomial CDI incidence continued to decrease and remained at levels roughly equivalent to rates prior to the outbreak. Quality of the diagnosis and surveillance system was good. No harms to hospital personnel, patients, or equipment were observed. The authors noted that the area to be decontaminated must be appropriately sealed, hydrogen peroxide levels outside the area being decontaminated must be closely monitored, and hydrogen peroxide concentrations within the decontaminated area must be reduced to less than 1 part per million before allowing patients or health care workers to re-enter. A subsequent study by the same investigators reported that hydrogen peroxide vapor disinfection was feasible in their hospital.[175] The peroxide vapor disinfection took 2 hours and 20 minutes to complete compared with 32 minutes for routine cleaning. The median cumulative times for all phases of cleaning and disinfection were 234 minutes (range 174–838) for peroxide vapor compared with 55 minutes (range 28–256) for conventional hypochlorite.

In the second study, 7 percent accelerated hydrogen peroxide was used for terminal disinfection of rooms of patients with CDI and comprehensive ward disinfection with sodium hypochlorite was done when three or more nosocomial CDI cases (defined as cases with positive toxin or with endoscopic or histological evidence of pseudomembranous colitis) remained elevated.[63] Within 4 months of the time infection prevention measures were implemented, the investigators also took several steps to reduce antibiotic use. Nosocomial CDI incidence fell abruptly within 1 month of the changes in antibiotic use.

In one study using **aldehydes** as part of a multiple-component intervention, a cluster of CDI in a surgical ward led to a hospitalwide surveillance and control program.[55] Control interventions included terminal room disinfection with 0.04 percent formaldehyde and 0.03 percent glutaraldehyde in wards with a cluster of two or more nosocomial CDI cases per month. During a 12-month period, the quarterly incidence of nosocomial CDI remained unchanged. *C. difficile* spores were recovered from 36.7 percent of the surfaces of case patient rooms versus 6.7 percent in control rooms. Subsequently, more intensive control measures were evaluated, which included daily meticulous room disinfection for each sporadic nosocomial CDI case. Surface disinfection reduced the contamination level fourfold ($p = 0.04$). In the following 12 months, the nosocomial CDI incidence fell to 0.3/1,000 admission (protective efficacy 73 percent, 95 percent CI, 46–87 percent). Multiple interventions, including disinfection, were used to control the outbreak. The study provides low evidence that disinfection, in this case with aldehydes, might have had a role in terminating the outbreak.

These ten 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. Decreased CDI incidence might have been from natural variation (regression to the mean) in some or all studies. As stated previously, disinfection was one of multiple interventions used to prevent CDI in seven studies; it is difficult to impossible to know which intervention or combination of interventions might have led to reduced CDI incidence.

Multiple Component Studies

Ten studies described the use of multiple preventive measures to control epidemic CDI, or endemic CDI that was felt to be excessive. Tables 5 and 6 list the categories of interventions in each of these articles. The number of interventions and the specific nature of any particular interventions varied widely. Studies employed between two and nine different types of interventions, including steps to optimize antimicrobial (six studies),[58-63] enhanced surveillance (two studies),[59,60] intensified staff education about infection prevention (three studies),[60,62,63] new

isolation procedures (four studies),[59,61,63,64] and "enteric precautions" (two studies).[58,61] Two studies emphasized handwashing[61,64] and one alcohol-based gel for hand disinfection.[60] Health care workers were required to wear gloves in three studies,[61,62,64] and use of gowns for patient contact was required in two studies.[61,64] Visitors were asked to comply with infection prevention procedures in one study.[64] New dedicated patient care equipment was purchased in two studies,[60,63] and in one of these, cleaning of dedicated patient equipment was intensified. Disposable rectal thermometers were used in one study.[63] Intensified environmental cleaning was implemented in six studies.[59-64] CDI patient movement was restricted in two studies.[59,64]

Investigators often placed greater weight on one intervention over others because the timing of decreased CDI incidence appeared to follow implementation of a particular intervention. However, the time it takes for many interventions to become adopted in health care settings and the variance expected in disease incidence led us to conclude that it was not possible to attribute decreases in CDI incidence to a single intervention in any of these studies. Natural fluctuations are such that all outbreaks diminish after variable periods of time so that assigning causality to individual or a collection of prevention measures is impossible. The evidence from these studies that any single intervention or combination of interventions prevents CDI was low.

Harms

Harms, beyond cost, were not addressed in any study.

Risk Factors

Identified CDI risk factors can provide clues to researchers and health care providers for where to target prevention strategies. We identified one systematic review reviewed CDI risk factor literature through 1997[20] and 12 risk factor studies published after the review. Bignardi's systematic review identified risk factors with "substantive" evidence: age, severity of underlying diseases, nonsurgical GI procedures, nasogastric tube, acid suppression medications, ICU, length of stay, duration of antibiotic course, and multiple antibiotics.[20] Five studies identified specific antibiotics or antibiotic classes with increased CDI risk[111,168,169,176,177] (Table 7), and two studies found that antibiotic use in general was associated with increased risk for CDI.[111,171] Consistent with Bignardi's findings, the more recent literature also identified severe underlying disease as a risk factor in four studies[112,166,167,171] and acid suppression in one.[112]

Sustainability

No studies addressed the sustainability of a prevention program.

Table 4. Prevention interventions

Author/Year Country	Study Design	Population	Intervention	Outcome	Findings	Quality Issues
Antibiotic Use						
Fowler, 2007[42] UK	Prospective interrupted time series	Acute medical wards, elderly	Switch from broad to narrow spectrum antibiotics	CDI incidence	Incidence rate decreased (0.35, 95% CI 0.17 to 0.73)	No concurrent controls
Davey, 2005[41] UK	Cochrane Review five included studies	Hospital inpatients	Improve antibiotic prescribing practices	CDI incidence	Four interventions were associated with significant reductions in CDI	Only one study was judged to be of "good" quality
O'Connor, 2004[44]	Before–after	Geriatric unit N = 17 cases in 683 patients	Change in antibiotic policy; education, monitoring, feedback	CDI incidence	CDI rate decreased significantly. Use of restricted antibiotic decreased. RR 0.31 (95% CI 0.93 to 0.10)	Retrospective
Wilcox, 2004[43]	Before–after time series	Elderly Medicine Unit inpatients	Change in antibiotic policy	CDI incidence	Use of restricted antibiotic decrease	No concurrent control
Ludlam, 1999[45] UK	Prospective before–after time series	Hospital N = 4,284	Change in antibiotic policy	CDI incidence	CDI rate decreased 50%. Use of restricted antibiotic decreased 92%	Patients on wards were antibiotic policy was unchanged acted as controls
Transmission Interruption – Gloves						
Johnson, 1990[178] USA	Controlled trial		Education program to use gloves	CDI incidence	CDI incidence decreased from 7.7 cases/1,000 patient discharges to 1.5/1,000 discharges	Not randomized or blinded
Transmission Interruption – Disposable Thermometers						
Brooks, 1992[47] and 1998[48] USA	Time series (before– after)	Hospital and long-term care	Single use thermometers	CDI incidence	Decrease in incidence: acute care – from 2.71/1,000 patient days to 1.76/1000 Long term-care – from 0.41/1,000 patient days to 0.11/1,000 patient days	No concurrent controls

Table 4. Prevention interventions (continued)

Author/Year Country	Study Design	Population	Intervention	Outcome	Findings	Quality Issues
Jernigan, 1998[49] USA	Crossover RCT	Hospital patients admitted to 20 nursing units	Disposable thermometers versus electronic thermometers	Rate of nosocomial CDI	CDI rates were reduced 44% (95% CI, 21 to 93) with disposable thermometers compared with electronic thermometers. Rates of nosocomial diarrhea or nosocomial infections did not differ significantly between the two groups.	Two wards elected not to use disposable thermometers
Transmission Interruption – Hand washing						
Kaier, 2009[52] Germany	Before–after time series analysis	Tertiary care teaching hospital	Alcohol-based gel	CDI incidence	No association between alcohol-based hand rub and CDI incidence	Retrospective, no concurrent control
Vernaz, 2008[66] Switzerland	Before–after time series analysis	Primary and tertiary care teaching hospital	Promotional campaigns to encourage use of alcohol-based hand rub	CDI incidence	No association between alcohol-based hand rub and CDI incidence	Retrospective, no concurrent control
Rupp, 2008[50] USA	Controlled cross-over trial	Adult medical-surgical ICUs	Alcohol-based gel	CDI incidence	Use of gel adherence rates increased from 37% to 68%. No change in CDI rates	Not blinded
Gordin, 2005[51] USA	Before–after	Hospital	Alcohol-based gel	CDI incidence	No change in CDI rates	
Transmission Interruption – Disinfection						
Hacek 2010[67]	Before–after	Hospital patients	Hypochlorite solution for patient room cleaning	CDI incidence	48% reduction in CDI rates. (P<.0001, 95% CI 36–58%)	No concurrent controls
Mayfield, 2000[53] USA	Before–after	3 hospital units; one unit with high incidence, 2 with lower	Hypochlorite solution for patient room cleaning	CDI incidence	High incidence unit- CDI decreased from 8.6/1,000 patient days to 3.3/1,000 patient days. No change in other units	No concurrent controls

Table 4. Prevention interventions (continued)

Author/Year Country	Study Design	Population	Intervention	Outcome	Findings	Quality Issues
Kaatz, 1988[54] USA	Outbreak	Hospital patients	Hypochlorite solution for patient room cleaning	CDI incidence	Contamination decreased and the outbreak ended. Phosphate-buffered hypochlorite was effective for disinfection.	Before–after design in the setting of an epidemic
Struelens, 1991[55]	Before–after	Hospital patients	Intensive cleaning measures, aldehydes	CDI incidence	Protective efficacy 73% (95% CI 46–87%)	No concurrent controls
Multiple Interventions						
Abbett, 2009[56] USA	Prospective before–after study	Hospital patients	Infection control practices, laboratory notification procedures, and steps coordinate infection control and environmental services aimed to decrease the transmission of *C. difficile* between patients (i.e., a prevention checklist)	CDI incidence	Use of a checklist of hospital interventions to decrease the incidence of healthcare-associated CDI	No concurrent control
Boyce, 2008[57] USA	Before–after time series	Hospital	Liquid vapor hydrogen peroxide decontamination system	CDI incidence	Nosocomial CDI incidence decreased and remained at lower levels	No concurrent control
Drudy, 2007[60] Ireland	Prospective time series (before–after)	Hospital patients	Antimicrobial use, enhanced surveillance, education, hand hygiene, equipment, intensified environmental cleaning	CDI incidence	CDI incidence decreased from a peak of 21 cases/1,000 patient admissions to 5/1,000 patient admissions	No concurrent controls

Table 4. Prevention interventions (continued)

Author/Year Country	Study Design	Population	Intervention	Outcome	Findings	Quality Issues
Valiquette, 2007[63] Canada	Retrospective time series (before–after)	Hospital patients	Antimicrobial use, education, isolation, equipment, intensified environmental cleaning	CDI incidence	Nonrestrictive measures to optimize antibiotic usage (leading to decreases in usage) led to a decrease in CDI incidence by 60%	Retrospective, no concurrent control
Whitaker, 2007[65] USA	Prospective time series (before–after)	Hospital patients	Antimicrobial use, education, isolation, automated report functions, and standardized nursing unit isolation processes	CDI incidence	66% reduction in the number of healthcare-associated CDI cases was achieved during the study	No concurrent controls
Zafar, 1998[64] USA	Prospective time series (before–after)	Hospital patients	Isolation, patient/staff movement, hand hygiene, patient room practices, intensified environmental cleaning	CDI incidence	Incidence of CDI decreased by 60% from 1990 to 1996 following use of comprehensive infection control measures.	No concurrent controls
McNulty, 1997[61] UK	Retrospective time series (before–after)	Hospital patients, elderly care unit	Antimicrobial use, isolation, patient/staff movement, hand hygiene, patient room practices, intensified environmental cleaning	CDI incidence	Thirty-seven cases of CDI occurred in the period before and 16 in the period after policy change (combined approach of infection control and strict antibiotic policies).	Retrospective, no concurrent control
Cartmill, 1994[59] UK	Prospective time series (before–after)	Hospital patients	Antimicrobial use, enhanced surveillance, isolation, patient/staff movement, intensified environmental cleaning	CDI incidence	Subsequent to the intervention measures, there was a substantial and sustained decreased in the incidence of CDI	No concurrent controls

Table 4. Prevention interventions (continued)

Author/Year Country	Study Design	Population	Intervention	Outcome	Findings	Quality Issues
Pear, 1994[62] USA	Prospective time series (before–after)	Hospital patients (Veterans Affairs)	Antimicrobial use, education, isolation, patient room practices, intensified environmental cleaning	CDI incidence	Nosocomial epidemic of CDI was controlled by analysis of antibiotic use patterns and by subsequent restriction of clindamycin	No concurrent controls
Brown, 1990[58] USA	Retrospective time series (before–after)	Hospital patients	Antimicrobial policy, isolation	CDI incidence	CDI attack rate dropped progressively	Retrospective, no concurrent control

CDI = *Clostridium difficile* infection; CI = confidence interval; ICU = intensive care unit; RR = relative risk

Table 5. (A) Studies of multiple interventions used together to reduce CDI incidence

Study	Type of Study	Epidemic or Excessive Incidence?	CDI incidence Decreased After intervention?	Interventions									
								Isolation (n=8)		Patient/Staff Movement (n=3)		Hand Hygiene (n=7)	
				Improved Antimicrobial Use	Enhanced Surveillance, Analysis, and Reporting of CDI Data	Laboratory-Based Infection Prevention Alert System	Infection Prevention Education	Enteric Precautions	Isolation	CDI Patient Movement Restricted	Restriction of Nursing Cross-Cover	Enhanced Hand Washing	Alcohol-Based Rub or Gel
Abbett, 2009[56]	Prospect time series (before–after)	Yes	Yes		X	X	X		X			X	
Boyce, 2008[57]	Prospect time series (before–after)	Yes	Yes	X	X			X	X			X	
Brown, 1990[58]	Retrospect time series (before–after	Yes	Yes	X				X					
Cartmill. 1994[59]	Prospect time series (before–after)	Yes	Yes	X	X				X	X			
Drudy, 2007[60]	Prospect time series (before–after)	Yes	Yes	X	X		X						X
McMullen, 2007[68]	Prospect time series (before–after)	Yes	Yes									X	
McNulty, 1997[61]	Retrospect time series (before–after	Yes	Yes	X				X	X		X	X	
Pear, 1994[62]	Prospect time series (before–after)	Yes	Yes	X			X						

Table 5. (A) Studies of multiple interventions used together to reduce CDI incidence (continued)

Study	Type of Study	Epidemic or Excessive Incidence?	CDI incidence Decreased After intervention?	Interventions									
								Isolation (n=8)		Patient/Staff Movement (n=3)		Hand Hygiene (n=7)	
				Improved Antimicrobial Use	Enhanced Surveillance, Analysis, and Reporting of CDI Data	Laboratory-Based Infection Prevention Alert System	Infection Prevention Education	Enteric Precautions	Isolation	CDI Patient Movement Restricted	Restriction of Nursing Cross-Cover	Enhanced Hand Washing	Alcohol-Based Rub or Gel
Valiquette, 2007[63]	Retrospect time series (before–after	Yes	Yes	X			X		X				
Whitaker, 2007[65]	Prospect time series (before–after)	Yes	Yes	X	X		X		X			X	
Zafar, 1998[64]	Prospect time series (before–after)	No	Yes						X	X		X	
Total number of studies evaluating specific intervention				8	5	1	5	3	7	2	1	6	1

CDI = Clostridium difficile infection

Table 6. (B) Studies of multiple interventions used together to reduce CDI incidence

Study	Type of Study	Interventions										
		Practices Within Patient Rooms (n=5)			Equipment (n=4)		Intensified Environmental Cleaning (n=10)					
		Gloves for Patient Contact	Gowns or Aprons for Patient Contact	Visitors Comply With Infection Prevention Practices	Dedicated Equipment, Equipment Cleaning	Disposable Rectal Thermometers	Room Cleaning With Hypochlorite	Ward Cleaning With Hypochlorite	Room Cleaning With Hydrogen Peroxide	Ward Cleaning With Hydrogen Peroxide	Room Cleaning With Detergent	Unspecified
Abbett, 2009[56]	Prospect time series (before–after)		X	X	X		X					
Boyce, 2008[57]	Prospect time series (before–after)						X		X	X		
Brown, 1990[58]	Retrospect time series (before–after											
Cartmill, 1994[59]	Prospect time series (before–after)						X					
Drudy, 2007[60]	Prospect time series (before–after)				X		X					
McMullen, 2007[68]	Prospect time series (before–after)						X	X				
McNulty, 1997[61]	Retrospect time series (before–after	X	X								X	
Pear, 1994[62]	Prospect time series (before–after)	X										X
Valiquette, 2007[63]	Retrospect time Series (before–after				X	X	X		X	X		

Table 6. (B) Studies of multiple interventions used together to reduce CDI incidence (continued)

Study	Type of Study	Interventions										
		Practices Within Patient Rooms (n=5)			Equipment (n=4)		Intensified Environmental Cleaning (n=10)					
		Gloves for Patient Contact	Gowns or Aprons for Patient Contact	Visitors Comply With Infection Prevention Practices	Dedicated Equipment, Equipment Cleaning	Disposable Rectal Thermometers	Room Cleaning With Hypochlorite	Ward Cleaning With Hypochlorite	Room Cleaning With Hydrogen Peroxide	Ward Cleaning with Hydrogen Peroxide	Room Cleaning With Detergent	Unspecified
Whitaker, 2007[65]	Prospect time series (before–after)			X	X		X	X				
Zafar, 1998[64]	Prospect time series (before–after)	X	X	X								X
Total number of studies evaluating specific intervention		3	3	3	4	1	7	2	2	2	1	2

Table 7. Summary of risk factors for CDI

Study	Specific Antibiotic Use	General Antibiotic Use	Health Status or Disease Severity	Acid Suppression	Hospitalization in an ICU	Age	Miscellaneous
Peled, 2007[112]	NE	NE	Functional capacity score OR = 9.1	PPI OR = 6.1 Histamine blocker OR = 3.1	NE	NE	Hypoalbuinemia OR = 3.8 Leukocytosis OR = 2.7
Samore, 2006[169]	Clindamycin OR = 4.2	NE	NE	NE	NE	NE	
Yearsley, 2006[171]	NE	OR = 13.1	NE	OR = 1.90	NE	NS	Female gender OR = 1.79
Vesta, 2005[166]	NE	NS	Horn's Index P = 0.0022	NE	NE	NS	
Kyne, 2002[167]	NS	NS	Severe underlying dz OR = 17.6	NS	NE	NS	
Mody, 2001[168]	3rd generation cephalosporins OR = 3.6	NE	NE	NE	NE	NE	
Schwaber, 2000[170]	Cephalosporin P = 0.03; 3rd generation cephalosporins P = 0.02	Greater number used P = 0.02	NE	NE	NE	NS	
Katz, 1997[111]	Cephalosporin P = 0.001	Antibiotic use past 30 days P =0.009; Antibiotic use prior to transfer/ admission P =0.009	NE	NE	NE	NE	
Bignardi, 1998[20] Searched to March 1996		Duration of antibiotic course; multiple antibiotics	Severity of underlying diseases	Anti-ulcer medications	Yes	Yes	Non-surgical gastrointestinal procedures, nasogastric tube, hospital length of stay

dz = disease; ICU = intensive care unit; NE = not examined by multivariate analysis; NS = not significant factor; OR = odds ratio; PPI = proton pump inhibitor

Key Question 3. What are the Comparative Effectiveness and Harms of Different Antibiotic Treatments?

Search 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. These 11 studies, published from 1978 to 2009, ranged in size from 39 to 629 subjects. Table 8 provides a breakdown of the trial comparators. Vancomycin is the most frequently studied antimicrobial, examined in 8 of the 10 studies. The most frequent comparison was vancomycin versus metronidazole (three studies, one of which also included fusidic acid and teicoplanin treatment arms, which are not included in this analysis), followed by two studies of vancomycin versus bacitracin. The remaining comparisons (vancomycin vs. nitazoxanide, vancomycin vs. fidaxomicin, vancomycin high dose vs. low dose, vancomycin vs. placebo, metronidazole vs. nitazoxanide, and metronidazole vs. metronidazole plus rifampin) all occurred in single studies. Treatment duration was 10 days in 9 of 11 studies, with the other two having durations of 7 and 5 days. The typical study followup period was 21 to 31 days. The largest patient sample was 629; most studies were in the range of approximately 40 to 60 patients. (See Appendix Table C4.) Two studies that did not meet inclusion criteria merit brief mention: one[179] appears to report on the same subjects included in another publication,[78] while another[180] has been presented in abstract form only.

Table 8. Summary of trial comparators for 10 trials of antibiotic treatment of CDI

	Vancomycin	Metronidazole
Vancomycin	1 (N = 56) (dosing)	
Metronidazole	3 (N = 172 N = 62 N = 101)	
Nitazoxanide	1 (N = 50)	1 (N = 142)
Bacitracin	2 (N = 62 N = 42)	
Metronidazole + Rifampin		1 (N = 39)
Fidaxomicin	1 (N= 629)	
Placebo	1 (N = 44)	

Key Points

- Overall, study quality is low.
- Vancomycin and metronidazole, the most frequently clinically used antimicrobials, were 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.
- 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. This difference was not significant using a strict intention-to-treat analysis.

- One study demonstrated that recurrence was significantly decreased with fidaxomicin versus vancomycin; initial cure was not significantly different between fidaxomicin and vancomycin.
- The decrease in recurrence seen with fidaxomicin use appeared to be limited to those patients with non-NAP1 strains.
- 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 (nausea, emesis, etc.) and transient.

Minor Key Points

- 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.
- Pooled data of 104 subjects comparing vancomycin to bacitracin showed significantly higher rates of organism or toxin clearance for vancomycin.
- No data were available to assess the importance of general patient characteristics or the strain of organism on the effectiveness of an antimicrobial.

Quality of the Studies

Overall study quality is low. Only two studies specified that the investigators (who also assessed outcomes) were blinded with respect to treatment.[70,82] Quality summary tables are available in Appendix C of this report (see Appendix Tables C5 and C6). Strength of evidence is summarized in Appendix Tables C7 and C8.

Detailed Analysis

As vancomycin and metronidazole are the most frequently employed antimicrobials, and therefore of greatest interest to clinicians, results are broken into two sets: (1) vancomycin versus metronidazole and (2) all other comparisons of standard treatment trials.

Initial Cure

The percentage of subjects initially cured with vancomycin ranged from 84 percent to 94 percent among individual studies, with a mean value of 88 percent (Table 9). For subjects treated with metronidazole, the individual cure rates ranged from 73 percent to 94 percent, with a mean value of 81 percent. The relative risk for initial cure comparing vancomycin to metronidazole was 1.08 (95 percent CI 0.99 to 1.19).

Table 9. Initial clinical cure (# subjects / # randomized) for vancomycin versus metronidazole

Study	Vancomycin	Metronidazole	RR [95% CI]
Zar, 2007[70]	69/82 (84)	66/90 (73)	1.15 [0.98 to 1.34]
severe disease	*30/38 (79)*	*29/44 (66)*	*1.20 [0.92 to 1.57]*
Wenisch, 1996[73]	29/31 (94)	29/31 (94)	1.00 [0.88 to 1.14]
Teasley, 1983[76]	51/56 (91)	39/45 (87)	1.05 [0.91 to 1.21]
Totals	149/169 (88)	134/166 (81)	1.08 [0.99 to 1.19]

CI = confidence interval; RR = relative risk

With the exception of vancomycin versus placebo, no other treatment comparison resulted in significant differences in initial clinical cure (Table 10).

Table 10. Initial clinical cure (# subjects / # randomized) for all other standard treatment trials

Study	Treatment 1	Treatment 2 / Control	Relative Risk [95% CI]
1. Vancomycin versus Nitazoxanide			
Musher, 2009[69]	20/27 (74)	17/23 (74)	1.00 [0.72 to 1.39]
severe disease	*7/10 (70)*	*8/10 (80)*	*0.88 [0.53 to 1.46]*
2. Vancomycin versus bacitracin			
Dudley, 1986[74]*	15/23 (65)	12/16 (75)	0.87 [0.58 to 1.31]
Young, 1985[77]	18/21 (86)	16/21 (76)	1.13 [0.84 to 1.51]
Totals	33/44 (75)	28/37 (76)	1.01 [0.79 to 1.28]
4. Vancomycin versus fidaxomicin			
Louie, 2011[79]	265/313 (85)	253/289 (88)	0.97 [0.91 to 1.04]
3. Vancomycin high-dose versus vancomycin low dose			
Fekety, 1989[75]	22/28 (79)	24/28 (86)	0.92 [0.72 to 1.17]
4. Vancomycin versus placebo			
Keighley, 1978[78]*	9/12 (75)	1/9 (11)	6.75 [1.03 to 44.08]
5. Metronidazole versus Nitazoxanide			
Musher, 2006[72]	28/44 (64)	68/98 (69) *36/49 (73) 7-day* *32/49 (65) 10-day*	0.92 [0.71 to 1.19]
6. Metronidazole versus metronidazole plus rifampin			
Lagrotteria, 2006[71]	13/20 (65)	12/19 (63)	1.03 [0.64 to 1.65]

CI = confidence interval

Note: Treatment 1 is the first intervention listed in the first column, followed by treatment 2.

Clinical Recurrence

The percentage of subjects meeting the investigator-determined definition of recurrent disease (after meeting criteria for initial cure) ranged from 7 percent to 17 percent with vancomycin, with a mean value of 11 percent. For metronidazole the range was 5 percent to 21 percent, with a mean value of 12 percent. (Table 11) The relative risk for recurrence after vancomycin treatment compared to metronidazole was 0.92 (95 percent CI, 0.47 to 1.77)

Table 11. Clinical recurrence: # subjects / # initially cured (percent) for vancomycin versus metronidazole

Study	Vancomycin	Metronidazole	Relative Risk [95% CI]
Zar, 2007[70]	5/69 (7)	9/66 (14)	2.29 [0.49 to 10.76]
severe disease	*3/30 (10)*	*6/29 (21)*	*0.48 [0.13 to 1.75]*
Wenisch, 1996[73]	5/29 (17)	5/29 (17)	1.00 [0.32 to 3.09]
Teasley, 1983[76]	6/51 (12)	2/39 (5)	0.53 [0.19 to 1.50]
Totals	16/149 (11)	16/134 (12)	0.92 [0.47 to 1.77]

CI = confidence interval

Only the comparison between fidaxomicin and vancomycin showed a statistically significant difference (15 percent vs. 25 percent, P = 0.005); in all other trials there was no significant difference in percentage of patients with recurrence. Between trial comparisons for the percentage of patients with recurrence are of uncertain relevance because of the variable definitions of recurrence and duration of followup. (Table 12).

Table 12. Clinical recurrence: # subjects / # initially cured (percent) for all other standard treatment trials

Study	Treatment 1	Treatment 2 / Control	Relative Risk [95% CI]
1. Vancomycin versus Nitazoxanide			
Musher, 2009[69]	2/20 (10)	1/17 (6)	1.70 [0.17 to 17.16]
severe disease	*1/10 (10)*	*1/10 (10)*	*1.00 [0.07 to 13.87]*
2. Vancomycin versus bacitracin			
Dudley, 1986[74]*	3/15 (20)	5/12 (42)	0.48 [0.14 to 1.62]
Young, 1985[77]	6/18 (33)	5/12 (42)	0.80 [0.31 to 2.04]
Totals	9/33 (27)	10/24 (42)	0.65 [0.31 to 1.35]
3. Vancomycin high dose versus vancomycin low dose			
Fekety, 1989[75]	4/22 (18)	5/24 (21)	0.87 [0.27 to 2.84]
4. Vancomycin versus fidaxomicin			
Louie, 2011[79]	67/265 (25)	39/253 (15)	1.64 [1.15 to 2.34]
5. Vancomycin versus placebo			
Keighley, 1978[78]*	NR	NR	
6. Metronidazole versus Nitazoxanide			
Musher, 2006[72]	8/28 (29)	14/68 (21) *9/36 7-day* *5/32 (3) 10-day*	1.39 [0.66 to 2.93]
7. Metronidazole versus metronidazole plus rifampin			
Lagrotteria, 2006[71]	5/13 (38)	5/12 (42)	0.92 [0.35 to 2.41]

CI = confidence interval; NR = not reported

* Subjects without demonstrable C. difficile cytotoxin and/or positive culture for C. difficile were removed and not included in the efficacy analyses.

Note: Treatment 1 is the first intervention listed in the first column, followed by treatment 2.

Mean Days to Resolution of Diarrhea

Two of the three vancomycin versus metronidazole studies reported the mean time to resolution of diarrhea.[73,76] No differences were seen between treatment arms (Table 13).

Table 13. Mean days to resolution of diarrhea/clinical improvement for vancomycin versus metronidazole

Study	Vancomycin	Metronidazole	WMD [95% CI]
Zar, 2007[70]	Not reported	Not reported	
Wenisch, 1996[73]	3.1 ± 1.1	3.2 ± 1.1	0.10 [-0.65 to 0.45]
Teasley, 1983[76]	2.8 ± 1.8	2.4 ± 1.9	-0.40 [-0.35 to 1.15]
Totals			0.07 [-0.37 to 0.52]

CI = confidence interval; WMD = weighted mean differences

No other treatment comparison resulted in significant differences in mean days to resolution of diarrhea (Table 14).

Table 14. Mean days to resolution of diarrhea/clinical improvement for all other standard treatment trials

Study	Treatment 1	Treatment 2 / Control	WMD [95% CI]
1. Vancomycin Versus Nitazoxanide			
Musher, 2009[69]	Not reported	Not reported	
2. Vancomycin Versus Bacitracin			
Dudley, 1986[74]	Not reported	Not reported	
Young, 1985[77]	4.3 ± 1.8	4.8 ± 1.8	-0.50 [-1.59 to 0.59]
Totals			-
3. Vancomycin High Dose Versus Vancomycin low Dose			
Fekety, 1989[75]	4.3 ± 1.8	3.8 ± 1.4	0.50 [-0.44 to 1.44]
4. Vancomycin Versus Fidaxomicin			
Louie, 2011[79]	Median 3.3	Median 2.4	p = NS
5. Vancomycin Versus Placebo			
Keighley, 1978[78]	Not reported	Not reported	
6. Metronidazole Versus Nitazoxanide			
Musher, 2006[72]	Not reported	Not reported	
7. Metronidazole Versus Metronidazole Plus Rifampin			
Lagrotteria, 2006[71]	6.6	7.0	p = 0.73

CI = confidence interval; NS = not statistically significant; WMD = weighted mean differences
Note: Treatment 1 is the first intervention listed in the first column, followed by treatment 2.

All-Cause Mortality

Mortality was rare overall, in part due to the short study-followup periods. There were five deaths in each arm among the 335 subjects enrolled in studies comparing vancomycin with metronidazole (Table 15). Wenisch[73] evaluated four drugs, including two not evaluated in this review, but did not provide mortality data by subject. Depending on in which study arm the mortalities occurred in the Wenisch study,[73] there were between 10 and 13 total deaths in studies comparing vancomycin to metronidazole. Even if all three deaths in this study occurred in one arm, the difference in mortality could not reach statistical significance.

Table 15. All-cause mortality (# subjects / # randomized) for vancomycin versus metronidazole

Study	Vancomycin	Metronidazole	Nitazoxanide	Bacitracin	Placebo
Zar, 2007[70]	3/82 (4)	5/90 (6)			
Wenisch, 1996[73]	3 subjects died within first days of therapy (treatment groups not noted)				
Teasley, 1983[76]	2/56 (4)	0/45			

All-cause mortality was significantly higher for combination metronidazole plus rifampin versus metronidazole alone (32 percent versus 5 percent).[71] There were no differences in all-cause mortality in any of the other treatment comparisons (Table 16).

Table 16. All-cause mortality (# subjects / # randomized) for all other standard treatment trials

Study	Vancomycin	Metronidazole	Nitazoxanide	Fidaxomicin	Bacitracin	Placebo
Musher, 2009[69]		Overall mortality was 4% (2/49 subjects) (treatment groups not noted)				
Lagrotteria, 2006[71]		1/20 (5) 6/19 (32) + Rif				
Musher, 2006[72]		1+/44*	3+/98*			
Fekety, 1989[75]	1/28 HD 1/28 LD					
Dudley, 1986[74]	0/31	1/31 (3)				
Young, 1985[77]	0/21	0/21				
Keighley, 1978[78]	0 “colitis”/12	0 “colitis”/12				
Louie, 2011[79†]	21/323 (7)			16/300 (5)		

* A total of 13 deaths (9 percent) occurred, but only the 4 deaths above were denoted by treatment arm. † Numbers based on safety population.

Other Outcomes

Where the outcomes were reported, no differences were found between vancomycin and metronidazole for clearance of toxin,[73] laboratory-confirmed relapse,[73] or persistence of the organism[76] (Table 17). The clinical relevance of these outcomes is uncertain.

Table 17. Other outcomes (# subjects / # assessed) for vancomycin versus metronidazole

Study	Vancomycin	Metronidazole	Relative Risk [95% CI]
Zar, 2007[70]	Not reported	Not reported	
Wenisch, 1996[73]	CT at day 6 22/31 (71)	CT at day 6 22/31 (71)	1.00 [0.73 to 1.37]
	LR at day 30 9/31 (29)	LR at day 30 9/31 (29)	1.00 [0.46 to 2.18]
Teasley, 1983[76]	P at day 21 11/43 (26)	P at day 21 14/35 (40)	0.64 [0.33 to 1.23]

CI = confidence interval; CT = clearance of toxin; LR = laboratory-confirmed-relapse; P = persistence

Pooled data of 104 subjects comparing vancomycin to bacitracin showed significantly higher rates of organism or toxin clearance for vancomycin.[74,77] No other differences were found in reported outcomes (Table 18).

Harms

Reported adverse events were relatively uncommon, minor, and not associated with one drug compared with the other. One study reported two episodes of intolerance (nausea and vomiting) leading to subject withdrawal, one in each treatment arm.[76] Another reported a subject with emesis that developed while on metronidazole, which resolved when treatment was changed to vancomycin; in the same study, another subject developed nausea while on vancomycin, which resolved when treatment was changed to metronidazole.[70] The third study reported "gastrointestinal discomfort" (which did not result in cessation of therapy) in 10 percent of subjects receiving metronidazole, compared to none with vancomycin, a difference that did not reach significance.

Disease Severity

Only one study stratified patients by disease severity at the time of screening.[70] Severity was dichotomized into two outcomes: mild or severe disease. This trial stratified treatment based on disease severity (mild versus severe). Sixty-nine subjects, 31 who received vancomycin and 38 who received metronidazole, met the prespecified definition of severe disease. Patients with two or more of the following were considered to be severe: 60 years old or older, temperature above 38.3 degrees Celsius, albumin level less than 2.5 mg/dL, or peripheral white blood count greater than 15,000 cells/mm^3 within 48 hours. Using a treatment-received analysis, the authors reported that initial cure was more common among those receiving vancomycin (97 percent versus 76 percent), with a relative risk for initial cure of 1.27 (95 percent CI, 1.05 to 1.53). In a subsequent response[181] to several letters,[182-184] they reported a revised result, which incorporated a modified intention-to-treat analysis (including subjects who died in the first 5 days of therapy), and reclassification of two subjects as being initially cured. This slightly changed the relative risk for initial cure to 1.28 (95 percent CI, 1.03 to 1.59). However, using a strict intention-to-treat analysis, which includes subjects intolerant of therapy, lost to followup, and early deaths, and the original classification of initial cure, the percentage cured with vancomycin versus metronidazole was 79 percent versus 66 percent. This corresponds to a relative risk for initial cure of 1.20 (95 percent CI, 0.92 to 1.57) (Table 9). This is minimally changed to 1.20 (95 percent CI, 0.93 to 1.54) if the two subjects initially classified as failures are reclassified as cures. No other significant differences in outcomes were found by disease severity.

C. difficile Strain

A single study assessed initial cure and recurrence by strain, categorized as North American pulsed-field gel electrophoresis type 1 (NAP1) versus non-NAP1.[79] Strain data was available for 324 of the 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 percent versus 28 percent; $P < 0.001$), whereas among patients with the NAP1 strain recurrence was similarly frequent regardless of treatment.

Patient Characteristics

Our search did not identify any evidence for comparative effectiveness by general patient characteristics such as age, gender, or treatment setting.

Resistance of Other Pathogens

The impact of treatment for CDI on other pathogens has not been addressed by the available studies that directly assigned subjects to different drugs. From observational studies, there is some evidence that treatment with either metronidazole or vancomycin can cause an increase in the incidence in the carriage of vancomycin resistant enterococci[185,186] however, the magnitude of this effect and the clinical significance are uncertain.

Table 18. Outcomes for all standard treatment trials

Study	Vancomycin	Metronidazole	Fidaxomicin	Nitazoxanide	Bacitracin	Placebo
	Clinical Initial Cure (# Subjects / # Randomized)					
Musher, 2009[69]	20/27 (74)			17/23 (74)		
Zar, 2007[70]	69/82 (84)	66/90 (73)				
Lagrotteria, 2006[71]		13/20 (65) 12/19 (63) + Rif				
Musher, 2006[72]		28/44 (64)		68/98 (69)		
Wenisch, 1996[73]	29/31 (94)	29/31 (94)			27/29 (93)	
de Lalla, 1992[187]	20/24 (83)					
Fekety, 1989[75]	22/28 (79) HD 24/28 (86) LD					
Dudley, 1986[74]	15/23* (65)				12/16* (75)	
Young, 1985[77]	18/21 (86)				16/21 (76)	
Teasley, 1983[76]	51/56 (91)	39/45 (87)				
Keighley, 1978[78]*	9/12* (75)					1/9* (11)
Louie, 2011[79]	265/313 (85)		253/289 (88)			
	Clinical Recurrence (# Subjects / # Initially Cured) for all Standard Treatment Trials					
Musher, 2009[69]	2/20 (10)			1/17 (6)		
Zar, 2007[70]	5/69 (7)	9/66 (14)				
Lagrotteria, 2006[71]		5/13 (38) 5/12 (42) + Rif				
Musher, 2006[72]		8/28 (29)		14/68 (21)		
Wenisch, 1996[75]	5/29 (16)	5/29 (16)			8/27 (30)	
de Lalla, 1992[186]	4/20 (20)					
Fekety, 1989[75]	4/22 (18) HD 5/24 (21) LD					
Dudley, 1986[74]	3/15 (20)				5/12 (42)	
Young, 1985[77]	6/18 (33)				5/12† (42)	
Teasley, 1983[76]	6/51 (12)	2/39 (5)				
Keighley, 1978[78]	Not reported	Not reported				
Louie, 2011[79]	67/265 (25)		39/253 (15)			
	All-cause Mortality (# Subjects / # Randomized) for all Standard Treatment Trials					
Musher, 2009[69]		Overall mortality was 4% (2/49 subjects) (treatment groups not noted)				
Zar, 2007[70]	3/82 (4)	5/90 (6)				
Lagrotteria, 2006[71]		1/20 (5) 6/19 (32) + Rif				
Musher, 2006[72]	1+/44‡			3+/98‡		
Wenisch, 1996[73]		3 subjects died within first days of therapy (treatment groups not noted)				
de Lalla, 1992[187]		2 subjects died within first days of therapy (treatment groups not noted)				

Table 18. Outcomes for all standard treatment trials (continued)

Study	Vancomycin	Metronidazole	Fidaxomicin	Nitazoxanide	Bacitracin	Placebo
Fekety, 1989[75]	1/28 HD 1/28 LD					
Dudley, 1986[74]	0/31	1/31 (3)			1/31 (3)	
Young, 1985[77]	0/21	0/21			0/21	
Teasley, 1983[76]	2/56 (4)	0/45				
Keighley, 1978[78]	0 “colitis”/12	0 “colitis”/12				
Louie, 2011[79]	21/323 (7)		16/300 (5)			
	Mean Days to Resolution of Diarrhea/Clinical Improvement					
Musher, 2009[69]	NR			Not reported		
Zar, 2007[70]	NR	Not reported				
Lagrotteria, 2006[71]		6.6 7.0 + Rif				
Musher, 2006[72]		Not reported		Not reported		
Wenisch, 1996[73]	3.1 ± 1.1	3.2 ± 1.1				
de Lalla, 1992[187]	3.6 ± 1.7					
Fekety, 1989[75]	4.3 ± 1.8 HD 3.8 ± 1.4 LD					
Dudley, 1986[74]	Not reported				NR	
Young, 1985	4.3 ± 1.8				4.8 ± 1.8	
Teasley, 1983[76]	2.8 ± 1.8	2.4 ± 1.9				
Keighley, 1978[78]	Not reported					Not reported
Louie, 2011[79]	Median 3.3		Median 2.4			
	Clearance of Organism (CO) / Toxin (CT) or Laboratory-confirmed-relapse (LR) / Persistence (P) for Evaluable Subjects					
Musher, 2009[69]	Not reported			Not reported		
Zar, 2007[70]	Not reported	Not reported				
Lagrotteria, 2006[71]		LR 2 LR 4 (+ Rif)				
Musher, 2006[72]		Not reported		Not reported		
Wenisch, 1996[73]	CT 22/31 (71) LR 9/31 (29)	CT 22/31 (71) LR 9/31 (29)			CT 14/29 (48) LR 15/29 (52)	
de Lalla, 1992[187]	P 9/20 (45)					
Fekety, 1989[75]	CO 4/10 (40) HD CO 5/9 (56) LD					
Dudley, 1986[74]	CO 11/14 (79) CT 12/14 (86)				CO 4/10 (40) CT 5/11 (45)	

Table 18. Outcomes for all standard treatment trials (continued)

Study	Vancomycin	Metronidazole	Fidaxomicin	Nitazoxanide	Bacitracin	Placebo
Young, 1985[77]	CO 17/21 (81) CT 15/18 (83)				CO 11/21 (52) CT 10/19 (53)	
Teasley, 1983[76]	P 11/43 (26)	P 14/35 (40)				
Keighley, 1978[78]	CO 11/12 (92) CT 12/12 (100)					CO 1/9 (11) CT 3/9 (33)
Louie, 2011[79]	Not reported		Not reported			

HD = high dose; LD = low dose; NR = not reported; Rif = Rifampin

* Subjects without demonstrable C. difficile cytotoxin and/or positive culture for C. difficile were removed and not included in the efficacy analyses.

† 4 subjects excluded with no reasons given.

‡ A total of 13 deaths (9 percent) occurred, but only the 4 deaths above were denoted by treatment arm.

Key Question 4. What are the Effectiveness and Harms of Nonstandard Adjunctive Interventions?

Search Results

A total of five RCTs on nonstandard adjunctive treatments of CDI (Table 19) and 13 studies that addressed prevention of CDI (Table 20) 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.[80-83] One study compared a nonstandard intervention with placebo.[84] All of the 13 prevention studies compared the nonstandard intervention to placebo rather than to another intervention, reflecting the current state of this area of science. Five of the 13 prevention studies analyzed antibiotic-acquired diarrhea as a primary outcome and CDI as a secondary outcome.[83,85,87,89,188] Numerous published case reports, as well as nonexperimental studies, describe additional nonstandard approaches for treatment of CDI and their possible harms (Table 21).

Due to the heterogeneity of the interventions, quantitative analysis was not possible. We therefore provide a narrative review of the literature.

Key Points

- Overall, study quality was low.
- *C. difficile* immune whey in one study of 38 patients was similar to standard antibiotic treatment with metronidazole in treating recurrent CDI.
- Colestipol plus metronidazole in one study was not more effective than placebo plus metronidazole.
- Administration of a probiotic to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any known benefit.
- There is low-strength limited evidence that the nonstandard 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.
- There is limited moderate-strength evidence from one study that monoclonal antibodies are effective in preventing recurrence of CDI.
- There is limited low-strength evidence from 6 case studies/series with 60 patients that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year.
- Data are inconclusive about the benefit of intravenous immunoglobulin as an adjuvant treatment for severe CDI.
- Definitions of CDI with regard to diarrhea, that is, number and consistency of stool, were inconsistent across studies.

Quality of the Studies

The level of the quality of the evidence is low. Several study limitations lowered the quality of their findings. Among the most common were lack of a power analysis, inadequate power to detect significant differences, lack of an intent-to-treat analysis, and failure to define allocation concealment. In one study, the findings of subjects with CDI at the start of a nonstandard

intervention were combined with those who developed CDI after the intervention.[84] The problem of a nonstandardized, incomplete, or unspecified definition of CDI has already been noted. In one study, a culture of *C. difficile* (which could have indicated a nontoxigenic strain of the organism) was accepted in place of, or in addition to, a toxin test for the definition of CDI for some patients.[84] Longer term followup for CDI incidence or recurrence sometimes relies on reports of diarrhea without retesting for *C. difficile* toxin. Although probiotics may have been intended solely for prevention of recurrent CDI in some studies, they were included among treatments for recurrent CDI because the probiotic was administered concurrently with a standard antibiotic during treatment and not after recurrent CDI was cured.[80,83] Thus, it is not possible to restrict the effect of the probiotic for prevention of future CDI recurrence only. Whether the results of CDI as a secondary outcome are weaker than the primary outcome of AAD due to an underpowered subgroup analysis cannot be determined. There was known lack of adequate power for the primary outcome in one of these studies,[87] and no power analysis for the primary outcome was reported in the other four studies.[83,85,89,188] There was lack of standardization of the active control in two studies, allowing subjects to receive an antibiotic for CDI as prescribed by their physicians.[91,95] Summaries of study quality and strength of evidence are provided in Appendix Tables C9 and C10.

Detailed Analysis

Defining the Outcome of CDI

The operative definition of diarrhea, which is part of the definition of CDI, varied among the studies for prevention and treatment of CDI (Tables 19 and 20). Six of the studies defined diarrhea as three or more loose or liquid stools per day for 2 days.[80,81,83-85,95] One study required that same number and consistency of stools but for only 1 day,[86] and another study did not require the three stools per day to be loose or liquid.[83] One study required two liquid stools on 3 or more days.[90] The most liberal definition of diarrhea was one to two loose stools per day.[91] Diarrhea due to *C. difficile* was not explicitly defined in four studies (6 percent).[82,87-89]

Treatment of CDI

The effectiveness of two types of nonstandard interventions were compared for treating CDI, agents that bind or absorb *C. difficile* toxins,[82,84] and probiotics that aim to recolonize the intestinal flora with nonpathogenic bacteria[80,81,83] (Table 19). All interventions were administered orally. Probiotics were the only intervention administered as an adjunct to standard antibiotic treatment for CDI;[80,81,83] the other nonstandard interventions were administered independently. The probiotic in two studies contained *Sacchromyces boulardii*[80,83] and in one it contained *Lactobacillus plantarum.*[81]

Subjects in the treatment studies had a mean age ranging from 58 to 67 years. Females comprised more than 70 percent of the sample in three of the six studies,[80,81,83] and, in one study, the age and gender of subjects were not reported.[84] Subjects were hospital inpatients in two studies.[80,83,84]

The findings of the studies in Table 19 are presented in the same direction, that is, as CDI resolution (versus treatment failure) to facilitate comparison and interpretation. In all studies of CDI treatment, the main outcome was the incidence of resolving CDI, which was defined as diarrhea in patients with a positive stool test for *C. difficile* toxin.

Treatment of Primary CDI

The rate of resolution of CDI was the lowest in the study comparing an absorptive resin (25 percent of subjects) to placebo (21 percent of subjects); no statistical results were reported.[84] Resolution rates for probiotic (81 percent of patients) compared to placebo (76 percent of patients) were not statistically different in another study.[83]

Treatment of Recurrent CDI

In three comparative treatment studies the subjects recruited were treated for a recurrent (rather than an initial) episode of CDI.[80-82] A third study conducted a subanalysis of their subjects with recurrent CDI.[83] In all four studies, the nonstandard intervention was probiotic. There was no significant difference in the resolution of CDI between the interventions compared in three of the studies[80-82] based on reported statistics or those conducted by the reviewers. In the study that analyzed a subset of their patients with recurrent CDI, a significantly higher percentage of subjects on a standard antibiotic plus a probiotic resolved diarrhea compared to those on a standard antibiotic and a placebo.[83]

Prevention of Primary CDI

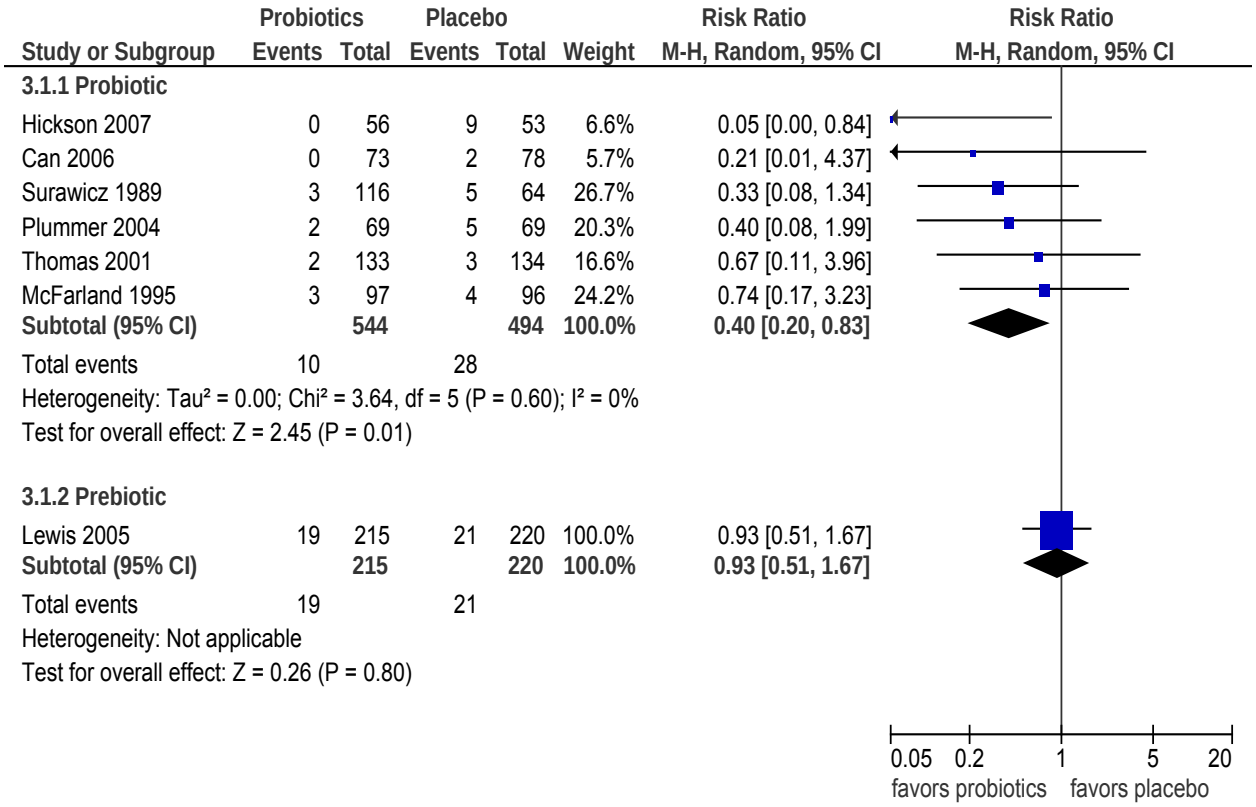
The nonstandard interventions investigated for preventing CDI were (1) probiotics,[85-90] (2) a prebiotic (oligofructose) that aims to support a normal ecology of bacteria,[91,92] and (3) a monoclonal antibody to *C. difficile* toxins[95] (Table 20). Six different probiotics were tested, and in two of the eight studies, the probiotic contained more than one strain of bacteria.[88,90] Seven of the 12 CDI prevention trials using nonstandard interventions focused on primary prevention, i.e., avoiding a first occurrence of CDI.[85-91] All of the studies of primary prevention of CDI investigated either a probiotic (six studies) or a prebiotic (one probiotic). Two studies that tested a nonstandard intervention for treating CDI also investigated its ability to prevent CDI recurrence.[80,81]

Subjects in the primary prevention studies had a mean age of 47 to 77 years. Females comprised less than one-third of the sample in two studies[85,89]and, in one study, the age and sex of the sample were not reported.[88] Subjects in all of the primary prevention studies were hospitalized patients.

The overall incidence of CDI across intervention groups was relatively low, ranging from 2 percent to 9 percent. Only one of seven studies, which investigated a mixture of two probiotics (*L. casei and S. thermophilus*), showed a significantly lower incidence of CDI diarrhea compared to placebo;[90] the investigators of this study acknowledged that the study was underpowered to detect a significant difference greater than by chance. In four studies, statistical testing was not reported.[86,87,89,91] Based on reported statistics, or those conducted by the reviewers, there was no significant difference in the recurrence of CDI between any of the interventions and placebo in the six other studies.[85-89,91]

There is disagreement in the research community regarding the appropriateness of pooling results of probiotics due to the heterogeneity of probiotic organisms used and variability in dosing. We provide a forest plot (Figure 5) of the effects of probiotics on overall incidence of CDI from the primary prevention probiotic trials for those who view such aggregation as reasonable. The pooled RR is 0.40 (95 percent CI, 0.20 to 0.83). The prebiotic trial showed no effect.

Figure 5. Overall incidence of CDI from probiotic primary prevention trials



CI = confidence interval; M-H = Mantel-Haenszel test

Prevention of Recurrence of CDI

Five studies investigated the effectiveness of a nonstandard intervention to prevent the recurrence of CDI (Table 20). Three studies investigated a probiotic,[80,81,83] one a prebiotic,[92] and one a monoclonal antibody to *C. difficile*.[95] The mean age of subjects ranged from 58 to 75 years. Females comprised 70 percent or more of the subjects in three studies.[80,81,83] Hospital inpatients comprised the sample in two studies[83,91] and were included along with nonhospitalized subjects in a second study.[80] The overall recurrence rate of CDI across intervention groups ranged from 6.5 percent to 34.5 percent.

A significantly lower rate of CDI recurrence was reported in two studies following administration of the prebiotic oligofructose[92] or a monoclonal antibody to *C. difficile* toxins A and B.[95] In both studies, the recurrence rate of CDI was approximately three times as great in subjects on placebo compared with the intervention. There was no significant difference in the recurrence of CDI in subjects taking probiotics[80,81] compared to controls. In one study comparing a probiotic versus placebo as adjuvants to standard antibiotics, no conclusions could be made since no statistical testing was conducted and findings of similar subgroups were not reported.[83] For example, patients with initial or recurrent CDI participated in the study but the recurrence rate was not reported by the type of CDI as enrollment for the probiotic group.[83]

Additional Nonstandard Approaches

In addition to the nonstandard interventions for CDI addressed in this review, case reports, or nonexperimental studies reveal numerous other approaches for treating or preventing CDI (See Table 21; Appendix Table C11 is the evidence table). Use of other probiotics (for example, yogurt containing live bacterial cultures)[93,189,190] and other cytotoxin absorbing resins[191,192] have been reported.

Another approach under investigation for treatment of recurrent or refractory CDI is fecal flora reconstitution, which instills feces from a healthy donor into the colon of a patient with CDI. Six case studies/series have been published,[96,97,128-130,193] four within the last 2 years. [128-130,193] Of a total of 60 patients; 52 patients (87 percent) resolved diarrhea and experienced no further relapse during followup. Two studies reported relapse of diarrhea in 7 of 34 patients (21 percent). Followup periods ranged from 3 weeks to 8 years.

Other nonstandard interventions include a monoclonal antibody to *C. difficile* toxin A,[194] intravenous immunoglobulin,[106,195-197] two nonstandard antibiotics, Tigecycline,[198] a *C. difficile* toxoid vaccine,[199] and a nontoxigenic strain of *C. difficile*.[200]

Potential Harms

Harmful effects of nonstandard interventions for CDI appear to be few, but not all studies or case reports included adverse effects in their finding (Tables 19–21). A serious potential harm associated with administration of probiotics for CDI in critically ill patients is fungemia.[93,94] In one review of an outbreak, previous medical charts, and the literature, 46 percent of 60 critically ill patients who developed fungemia had been administered a probiotic, and 28 percent subsequently died.[93] In addition, McFarland reported finding 12 cases of *Lactobacillus* bacteremia in patients (mostly children) taking a probiotic containing *Lactobacillus*.[11] Minor adverse symptoms of probiotics and prebiotics were abdominal symptoms such as nausea, bloating, and vomiting, and they have not differed significantly from those of subjects receiving placebo or an active control.[11,83,91] Headache (one subject), and abdominal pain, change in bowel habit, and polymyalgia rheumatica (one subject) occurred following *C. difficile* vaccination.[199] Hypotension, diarrhea, headache, nausea, and abdominal discomfort were reported after administration of a monoclonal antibody to *C. difficile* toxin A.[194]

Table 19. Nonstandard intervention for treatment of initial and recurrent CDI

Study	Sample	Intervention/ Comparison and Method	Resolution of CDI (Diarrhea and CD Toxin Positive Stool)	Other Outcomes	Study Quality
Nonstandard Intervention Versus Active Control for Recurrent CDI					
Mattila, 2008[82] Scand J Infect Dis FInland	40 adults with ≥2 episodes of CDI in past 3 months and stool positive for *C. difficile* toxin 38 completed the study (95%) Mean age: 61.3 (CDIW 56.4 vs. metronidazole 65.7) Gender: Male 47%	*C. difficile* immune whey (CDIW) CDIW 200 ml liquid and placebo tablets three times per day x 14 d (n=18) Metronidazole 400 mg tablets and placebo liquid three times per day x 14 days (n=20) CD culture and toxin on days 0, 14, and 28 followup x 7 days Daily stool and symptom diary daily for 42 days Followup after day 28 used stool and symptom diary only	Response to study drugs at day 14 CDIW: 89% (16/18) Metronidazole: 100% (20/20) No statistical testing reported, Fisher's Exact test performed by reviewers p=0.22	Response to study drugs at day 28 (14 days after treatment) CDIW: 61% (11/18) Metronidazole:60% (12/20)	Allocation concealment: not defined Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts adequately described: yes Notes: Sample size not achieved because of bankruptcy of sponsor Although CD culture and toxin were measured and stool diary data collected at day 14, the reported primary endpoint, "response to …study drugs" was not defined nor defined in relation to these measures; the same is true for sustained response at day 28 Secondary outcome of time to treatment failure through day 70 was measured by diarrhea only and not by CD toxin in stool CDIW had no local or systemic side effects

Table 19. Nonstandard intervention for treatment of initial and recurrent CDI (continued)

Study	Sample	Intervention/ Comparison and Method	Resolution of CDI* (Diarrhea and CD Toxin Positive Stool)	Other Outcomes	Study Quality
Adjuvant Nonstandard Intervention Versus Active Control for Recurrent CDI					
Surawicz, 2000[80] Clin Infectious Diseases United States	168 randomized adult inpatients and outpatients with recurrent CDI, 32 on high-dose vancomycin (This paper reported subgroup analysis of treatment of subjects on high-dose vancomycin only) *Recurrent CDI subjects* Mean age (years): 61.6 Gender: Male (M) 41%	Probiotic-*Sacchromyces boulardii* (1 g/d) + high dose oral vancomycin (2g/d) (n=16) Placebo (1 g/d) + high dose oral vancomycin (2g/d) (n=16) Probiotic/placebo started on day 7–day 28 CDI was defined as diarrhea (≥3 loose/watery stools/s x 2 days or >8 loose stools/day within 48 hours) and positive CD assay (culture then toxin A or B) measured at multiple time points	Probiotic and vancomycin: 13/16 (81.3%) Placebo and vancomycin: 8/16 (50%) Fisher's Exact test performed by reviewers p =0.06		Allocation concealment: adequate, centralized Blinding: double Intention-to-treat analysis: yes Withdrawals and dropouts adequately described: none reported

Table 19. Nonstandard intervention for treatment of initial and recurrent CDI (continued)

Study	Sample	Intervention/ Comparison and Method	Resolution of CDI* (Diarrhea and CD Toxin Positive Stool)	Other Outcomes	Study Quality
Wullt, 2003[81] Scan J Infect Dis Sweden	29 adult patients with recurrent disease from 9 centers (positive CD toxin assay within 6 days of enrollment at least 1 prior episode CD diarrhea within past 2 months and ongoing diarrhea). 8 patients (28%) lost to followup were not included in analysis, 21 completed trial (72%) Mean age: 63.8 Gender: Male 5%	Probiotic-*Lactobacillus plantarum* in fruit drink with oats fermented by L. plantarum 299v (5 x 10^{10} cfu) x 38 days and Metronidazole (400 mg three times per day po) x 10 d Placebo fruit drink with chemically acidified oats and metronidazole Toxin testing on days 11–13 followup about diarrhea on days 37–41 and 70–75 Clinical cure was defined as no diarrhea (≥3 loose stools x 2 days) on days 5-10 of treatment:	Probiotic and metronidazole: 92% (11/12) Placebo and metronidazole: 100% (9/9) No statistical testing reported, Fisher's Exact test performed by reviewers p=1.0		Allocation concealment: Not defined Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts adequately described: yes Notes: CD toxin not measured after day 11

Table 19. Nonstandard intervention for treatment of initial and recurrent CDI (continued)

Study	Sample	Intervention/ Comparison and Method	Resolution of CDI* (Diarrhea and CD Toxin Positive Stool)	Other Outcomes	Study Quality
McFarland, 1994[83] JAMA United States	124 in patients with active CDI and receiving standard antibiotic treatment (vancomycin or metronidazole) 104 (84%) completed the study Mean age 58.1 Gender: Male 23% 64 patients had initial CDI and 60 had recurrent CDI	Probiotic-Lyophilized *S. boulardii* $3x10^{10}$ cfu (1 g) orally in two 250 mg capsules/days x 4 weeks and standard therapy, vancomycin or metronidazole or both (n=57). Probiotic was given within 4 days of treatment Placebo and standard therapy, vancomycin or metronidazole or both (n=67). Both groups followed for 4 weeks and an additional 4 weeks CDI defined as diarrhea ≥3 stools/d x 2 consecutive days and 1 CD positive assay (culture, toxin A or toxin B) Treatment failure was defined as 2 consecutive days of diarrhea, and positive CD assay or pseudomembranes by endoscope at time of diarrhea, diarrhea no attributable to another cause	Resolution of CDI *Overall* (all subjects, n=124) Probiotic: 73.4% (42/57) Placebo: 55.2% (37/67) p = 0.05 *Subgroup analysis* Subjects treated for recurrent CD (n=60) Probiotic 65.4% (17/26) Placebo 35.3% (12/34) p=0.04 Subjects treated for initial CD (n=64) Probiotic 81.3% (25/31) Placebo 75.5% (25/33) p=0.86		Allocation concealment: Adequate, blinded study drug kits Blinding: double Intention-to-treat analysis: yes Withdrawals and dropouts adequately described: yes Notes: No difference in nausea, pain, or vomiting

Table 19. Nonstandard intervention for treatment of initial and recurrent CDI (continued)

Study	Sample	Intervention/ Comparison and Method	Resolution of CDI* (Diarrhea and CD Toxin Positive Stool)	Other Outcomes	Study Quality
Nonstandard Intervention Versus Placebo					
Mogg, 1982[84] Br J Surg United Kingdom	48 patients on a single surgical unit with severe diarrhea after antibiotic treatment 48 entered study and 10 withdrew (7 on resin and 3 on placebo), 38 analyzed (79%) No information on age and gender. Diarrhea defined as ≥3 loose stools/day or more than 1 L of drainage from colostomy Previous placebo group (n=22) from prior study of vancomycin and placebo on same unit.	Absorptive resin Colestipol 10 g every day mixed in fruit squash x 5 days (n=17) Placebo (sherbet) (n=21) Stool tested for CD cytotoxin at study start, on day 3 and last day of treatment (day 5) Outcome was defined as return of diarrheal stool to normal, (i.e., 2 solid stools in 24 hours) in stools that were positive for *C. difficile* OR its toxin	Colestipol: 3/12 (25%) Placebo: 3/14 (21%)		Allocation concealment: Possibly adequate ("identical placebo") Blinding: not reported Intention-to-treat analysis: no Withdrawals and dropouts adequately described: yes Notes: CD cytotoxin was not present in all subjects reported as cases No statistical testing Some historical controls included with concurrent controls CD treatment and prevention findings were combined (i.e., findings of subjects with *C. difficile* or its toxin in stool before receiving the intervention were combined with those who acquired these *during* the intervention)

CD = Clostridium difficile; CDI = Clostridium difficile infection

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Primary Prevention of Initial CDI						
Surawicz, 1989[85] Gastroenterology United States RCT	318 hospitalized patients given new antibiotics 180 completed study, 138 had *C. difficile* tested Mean age: 46.5 years Gender: Male 69%	Probiotic: *Sacchromyces boulardii* (250 mg capsule with 1 g S. boulardii bid (n=116) Placebo bid (n=64) Stools collected for CD culture at entry, day 5 then q 10 d, end of study, and when have diarrhea (diarrhea ≥3 loose/watery stools/s x 2 d); CD culture + stools were tested for cytotoxin; need 3 stools tested for CD and ≥8 days of monitoring for inclusion	Overall incidence of CDI: Probiotic: 3/116 (2.6%) Placebo: 5/64 (7.8%) Fisher's Exact test performed by reviewers p=0.13 Incidence of diarrhea in 48 patients had stools that were CD toxin+: Probiotic: 3/32 (9.4%) Placebo: 5/16 (31%), test of significance between groups p=0.07			Allocation concealment: not defined Blinding: double Intention-to-treat analysis*: no, 138 not evaluated (43%) Withdrawals and dropouts adequately described: yes
McFarland, 1995[188] Am J Gastroenterol United States RCT	193 hospitalized adult patients receiving new beta-lactam antibiotic with or without another antibiotic and no diarrhea 129 (67%) completed study Mean age: 42 years Gender: Male 65%	Probiotic: Lyophilized *S. boulardii* $3x10^{10}$ cfu (1 g) orally in two 250 mg capsules/d within 72 hours of antibiotic and until max of 28 days (n=97) Placebo 1 g (undefined) (n=96) Followup for 7 days after stopping drug	Overall incidence of AAD: Probiotic: 3/97 (3.1%) Placebo: 4/96 (4.2%) Fisher's Exact test performed by reviewers p=0.72 Development of ADD in 24 patients with positive CD assays: Probiotic: 3/10 (30%) Placebo: 4/14 (29%) (The power of detecting a significant difference based on the sample size of 24 and the above rates was less than 3%)			Allocation concealment: adequate (appearance and odor of the capsules of interventions were identical, done centrally Blinding: double Intention-to-treat analysis: yes Withdrawals and dropouts adequately described: yes Notes: 3 reviewers of diarrhea

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Lewis, 1998[86] J Infect United Kingdom RCT	72 Hospitalized elderly (≥65 years) patients started on antibiotics Mean age (range): 74 (70-85) years Gender not reported ("no difference between sex")	Probiotic: *S. boulardii* (113 mg) (Ultra-Levure, Biocodex, Montrouge, FR) 2x/day (n=33) Placebo (undefined) 2x/day (n=36) Stool sample sent to lab every 4th day or if diarrhea (≥3 loose stools in 24 hours) to test for CD toxin	<u>Overall incidence of CDI:</u> 4 patients had diarrhea stools that were CD toxin+ (not reported by treatment arm) No statistically significant difference in diarrhea stools with + CD toxin between probiotic and placebo (data and percents not reported)		CD toxin only Probiotic: 5/33 (15%) Placebo 3/36 (8%) No statistical testing done	Allocation concealment: adequate (pharmacy-controlled) Blinding: probably double, nursing staff blinded to treatment assignment Intention-to-treat analysis: no, 3 excluded Withdrawals and dropouts adequately described: yes
Thomas, 2001[87] Mayo Clinics United States RCT	302 hospitalized patients on antibiotics 267 (88%) completed study Mean age (range): 56 (18-93) years Gender: Male 54%	Probiotic*: Lactobacillus* GG (20×10^9 cfu + inulin filler) (CAG Functional Foods, Nebraska) 1 capsule 2x/d x 14 d (n=133) Placebo (inulin filler) (n=134)	<u>Overall incidence of CDI:</u> Only 5 patients (1.9%) with positive CD toxin: Probiotic: 2/133 (1.5%) Placebo: 3/134 (2.2%), p >0.99		CD toxin in 1st 21 days after enrollment per retrospective chart review data of patients with CD at hospital Probiotic: 5/133 (4%) Placebo: 3/134 (2%), no statistical testing	Allocation concealment: adequate (pharmacy-controlled) Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts adequately described: yes Notes: CD results by randomized chart review How tested for CD toxin not reported No association of diarrhea with CD toxin+

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Plummer, 2004[88] International Microbiol United Kingdom RCT	150 elderly hospitalized patients started on antibiotics 138 (92%) completed study Age and gender not reported	Probiotic: *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, 2 x 10^{10} cfu in 1 capsule/d (Cultech, Saansea) for at least 20 of antibiotic therapy (n=69) Placebo (n=69) Start therapy within 36 hours of antibiotics, probiotic = 1.12 days after antibiotics placebo = 1.10 day Stools were cultured for *C. difficile*, then if culture +, CD toxins A and B were tested - at start of study - if diarrhea - after antibiotics completed during hospitalization or discharge	<u>CD diarrhea, 1st testing, during diarrhea and antibiotic tx in hospital:</u> Probiotic: 2/69 (3%) Placebo: 5/69 (7%), no statistical testing reported, Fisher's Exact test performed by reviewers p=0.44 Proportion developing diarrhea positive for CD toxins was 4.35% lower in probiotic group (95% CI of –0.132 to 0.038). <u>CD diarrhea, 2nd testing of same patients after antibiotics completed or at discharge:</u> Probiotic: 2/69 (3%) Placebo: 6/69 (9%)			Allocation concealment: not defined Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts adequately described: no Notes: Diarrhea is undefined Study participation stopped if on antibiotics >20 days

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Lewis, 2005[91] Aliment Pharmacol Ther United Kingdom RCT	450 hospital patients ≥65 years prescribed a broad spectrum antibiotic within past 24 hours 15 (3.3%) patients withdrew or were withdrawn from study N=435 who finished Mean age (range): 77 (70–84) years Gender: Male 49%	Prebiotic: Oligofructose (12 g/d) (n=215) Placebo (sucrose 12 g/day) (n=220) Taken during antibiotics + 7 days after Follow up for additional 7 days *C difficile* toxin was measured if diarrhea (1-2 loose stools/day)	54 (12%) patients were culture-positive for *C. difficile* on study entry. Prebiotic: 19/213 (9%) Placebo: 21/220 (9.5%), no statistical testing reported, Fisher's Exact test performed by reviewers p=0.87			Allocation concealment: Unclear Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts adequately described: yes Notes: Subjects were withdrawn from study if they experienced significant diarrhea (>3 stools/day) Stated intent to treat but some % are for N=433 not 435 or 450 who enrolled No increase in bloating, stool form or interval between stools by prebiotic

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Can, 2006 [89] Med Sci Monit Turkey RCT	151 adult inpatients between 25–50 years who had chemotherapy and antibiotics Gender: Male 95%	Probiotic: *S. boulardii* + antibiotics (β lactam) (n=73) Placebo + antibiotics(n=78) 2x/day started 48 hours or less after antibiotic therapy started for duration of antibiotic tx CD toxin A tested in those with diarrhea	<u>Overall incidence of CDI:</u> 8 patients had diarrhea, only two CD toxin + (both in the placebo group Probiotic: 0/73 (0%) Placebo: 2/78 (2.6%) Fisher's Exact test performed by reviewers p=0.50			Allocation concealment: not defined Blinding: double Intention-to-treat analysis: yes Withdrawals and dropouts adequately described: none reported Notes: Duration of probiotic may have been variable Diarrhea is undefined

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Hickson, 2007[90] BMJ RCT	135 hospital patients taking antibiotics were given tx until tx was finished + 1 week; If discharged from hospital and stayed on antibiotics, they continued tx; CD testing and followup occurred for 4 weeks after tx ended 11/2002-1/2005 22 (16%) patients lost to followup and not included in the analyses 12 in probiotic group and 10 in placebo 4 pts not tested for CD (1 on probiotics and 3 on placebo) Mean age: 74 years Gender: Male 46%	Probiotic: *L. casei* DN-114 001 (L casei imunitass, 1 x 10^8 cfu/ml) + *S.thermophilus* (1 x 10^8 cfu/ml) + *L. bulgaris* (1 x 107 cfu/ml) in yogurt drink (Actimel, Danone, FR) (n=69) Placebo: sterile milkshake (Yazoo, Campina NE) (n=66) Drinks consumed during antibiotics therapy + 1 week CD toxins A and B tested in diarrheal stools CD diarrhea = CD toxins A and/or B and diarrhea stools (2 liquid stools/d x 3 or more days in an amount greater than normal for the patient)	<u>Overall incidence of CDI:</u> Probiotic: 0/57 Placebo: 9/53 (17%), p=0.001 Absolute risk reduction = 17% (95% CI 7% to 27%) NNT = 6 (4 to 14)			Allocation concealment: adequate (pharmacy - controlled) Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts adequately described: yes Notes: Good compliance with drink, 75% for probiotic and 79% placebo Type CD toxin not specified No adverse events from either drink

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Prevention of Recurrent CDI						
McFarland, 1994[83] JAMA United States	124 in patients with active CDI and receiving standard antibiotic treatment (vancomycin or metronidazole) 104 (84%) completed the study Mean age 58.1 Gender: Male 23% 64 patients had initial CDI and 60 had recurrent CDI	Probiotic-Lyophilized *S. boulardii* $3x10^{10}$ cfu (1 g) orally in two 250 mg capsules/days x 4 weeks and standard therapy, vancomycin or metronidazole or both (n=57). Probiotic was given within 4 days of treatment Placebo and standard therapy, vancomycin or metronidazole or both (n=67). Both groups followed for 4 weeks and an additional 4 weeks CDI defined as diarrhea ≥3 stools/d x 2 consecutive days and 1 CD positive assay (culture, toxin A or toxin B) Treatment failure was defined as 2 consecutive days of diarrhea, and positive CD assay or pseudomembranes by endoscope at time of diarrhea, diarrhea no attributable to another cause		Probiotic: 41.3% (51/124) subjects with no recurrence Placebo: 24.3% (8/33) with initial CDI had CDI recurrence and 64.7% (22/34) with recurrent CDI had another recurrence no statistical testing		Allocation concealment: Adequate, blinded study drug kits Blinding: double Intention-to-treat analysis: yes Withdrawals and dropouts adequately described: yes Notes: The absence of CDI recurrence for the probiotic group was reported as a percent of the entire sample and not of the probiotic group. No difference in nausea, pain, or vomiting

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Surawicz, 2000[80] CI Infectious Diseases United States RCT	32 randomized adult inpatients and outpatients, 32 with recurrent CDI *CD disease subjects* Age: 61.6 Gender: Male 41%	*CDI subjects* Probiotic: *S. boulardii* (1 g/d) + high dose oral vancomycin (2g/d) (n=16) Placebo (1 g/d) + high-dose oral vancomycin (2g/d) (n=16) Probiotic/placebo started on day 7 - day 28 CDI = diarrhea + (≥3 loose/watery stools/s x 2 days or >8 loose stools/day within 48 hours) and positive CD assay (culture then toxin A or B) measured at multiple time points		Recurrence: Probiotic: 3/18 (17%) Placebo: 7/14 (50%), p=0.05		Allocation concealment: adequate, centralized Blinding: double Intention-to-treat analysis: yes Withdrawals and dropouts adequately described: none reported
Wullt, 2003[81] Scan J infect Dis RCT	29 adult patients from 9 centers with + CD toxin assay within 6 days of enrollment at least 1 prior episode CDI diarrhea within past 2 months. And ongoing diarrhea 8 patients (28%) lost to followup were not included in analysis, 21 completed trial Mean age: 63.8 years Gender: Male 5%	Probiotic: *L. plantarum* in fruit drink with oats fermented by L. plantarum 299v (5×10^{10} cfu) x 38 days and Metronidazole (400 mg tid po) x 10 days Metronidazole + placebo fruit drink with chemically acidified oats	Clinical cure: no diarrhea (≥ 3 loose stools x 2 days) on days 5-10 of tx Probiotic: 11/12 (92%) Placebo: 9/9 (100%)	Total recurrences: Probiotic: 4/11 (36%) Placebo: 6/9 no statistical testing reported, Fisher's Exact test performed by reviewers p=0.37	CD toxin negative: Probiotic:7/12 (58%) Placebo: 5/9 (56%), p=.642	Allocation concealment: Not defined Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts adequately described: yes

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Lewis, 2005[92] Clin Gastroenterol Hepatol RCT	142 consecutive elderly (≥65 years) in patients with CDI and treated by their physician with metronidazole or vancomycin for 10 days (if treatment failure (diarrhea and CD toxin A and B) or intolerance with metronidazole). Mean age: 75 years Gender: Male 58%	Prebiotic: Oligofructose (12 g/d) (n=72) Placebo (sucrose 12 g/day) (n=70) Taken as soon as possible after dx of CD diarrhea and + 30 days after CDI diarrhea = 3 loose stools in 1 day and + CD toxin		Relapse of diarrhea (CD was not retested) Prebiotic: 6/72 (8.3%) Placebo: 24/70 (34.3%), p<0.0001		Allocation concealment: Not defined Blinding: single Intention-to-treat analysis: no, 1 was lost to followup and 8 never resolved diarrhea to be able to relapse and were excluded Withdrawals and dropouts adequately described: yes Notes: CD was not measured at diarrhea recurrence

Table 20. Probiotic or prebiotic interventions for prevention of initial and recurrent CDI (continued)

Study/ Design	Sample	Intervention/Comparison and Method	*C. difficile* Diarrhea (Diarrhea and CD Toxin +)	Later Recurrence of CD Diarrhea	CD Toxin+	Notes of Study Quality and Side Effects
Lowy, 2010[95] N Eng J Med United States and Canada RCT	200 inpatients and outpatients were ≥18 years of age with diarrhea associated with a positive stool test for CD toxin(s) in the 14 days prior to enrollment and who were receiving either metronidazole or vancomycin Mean age (range): 64 (20-101) years Gender: Male 34% White race: 88% Black race: 6% Severe disease at enrollment: 40%	Monoclonal antibodies: intravenous infusion of fully human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1) x 1 (n=101) Placebo (0.9% sodium chloride) x 1 (n=99) Recurrence of *C. difficile* infection, was defined as a new episode of diarrhea associated with a new positive stool toxin test after the resolution of the initial CDI diarrheal episode and after discontinuation of metronidazole or vancomycin. Diarrhea was defined as three or more unformed stools per day for at least 2 consecutive days or more than six unformed stools in 1 day		<u>Incidence of laboratory documented CDI - primary outcome):</u> Monoclonal antibodies: 7/101 (7%); inpatient = 7/50, outpatient = 0/51 Placebo: 25/99 (25%); inpatient = 13/52, outpatient = 12/47, p=0.0004 Recurrent diarrhea With/without laboratory confirmation of CDI and with/without antibiotic treatment for CDI Monoclonal antibodies: 28/101 (28%) Placebo: 49/99 (50%), p=0.0022		Allocation concealment: not defined Blinding: double and independent statistician and data and safety monitoring board Intention-to-treat analysis: yes Withdrawals and dropouts adequately described: yes Adverse events reported in 14 patients (antibody group = 9; placebo = 5) during infusion and in 11 patients (antibody group = 6; placebo = 5) during 2-hour period after infusion. All AE noted to be mild to moderate (headache reported most frequently) Death: antibody group = 7; placebo = 8 (p=0.79)

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

Table 21. Summary of case studies/series and potential harms of nonstandard interventions for CDI

Intervention	# of Reports	Patient N	Type of CDI Patient	Study Aim	Outcome	Reported Adverse Events
Fecal flora reconstitution	6[96,97,128-130,193]	60	Recurrent CDI	Treatment	73% – 100% symptom free, up to 1 year	1 case IBS
Cholestyramine	2[191,192]	2	CDI with PMC	Treatment, primary CDI	1 patient rapid symptom relief	Not reported
IV hemoperfusion, vancomycin	1[201]	2	CDI with PMC	Treatment, primary CDI	PMC resolved in 7 days	Not reported
Probiotics	3[93,189,190]	5 (plus 57 from literature review)	4 ICU patients,1 recurrent CDI (plus 41 patients with fungemia, 14 ICU)	Treatment		1 case S. pneumonaie and secondary L. rhamnosus septicemia and death. 46% fungemia patients previously given probiotics
Nontoxigenic *C. difficile* strain	1[200]	2	CDI patients failing antibiotic treatment	Treatment	Symptom decrease, 1 patient resolved	Constipation
Monoclonal antibody for *C. difficile* toxin A	1[194]	30	Healthy young adults	Safety study		3 moderate AE (low BP, diarrhea), 18 mild AE (headache, nausea, loose stools, abdominal discomfort BP changes)
Intravenous Tigecycline	1[198]	4	CDI with PMC	Treatment, severe refractory	Symptom decrease within 7 days	Not reported
C. difficile toxoid vaccines	2[199,202]	3 (plus 30 healthy adults)	First CDI relapse	Treatment (safety study)		Mild headache, mild abdominal pain, rash, 1 CDI relapse patient polyarthritis
Intravenous immunoglobulin	4[83,106,196,197]	37	CDI, recurrent, refractory, severely ill	Treatment	54% symptom resolution, of these, 20% patients had recurrence or toxin still present	1 case pulmonary edema

AE = adverse event; BP = blood pressure; CDI = *Clostridium difficile* infection; IBS = irritable bowel syndrome; ICU = intensive care unit; IV = intravenous; PMC = pseudomembranous colitis

Summary and Discussion

There is very limited high-quality evidence, to support the diagnostic, preventive, and treatment practices for *Clostridium difficile* infection (CDI) carried out by providers in hospital, long-term care, and outpatient settings. Inconsistency in definitions of diarrhea, severity, and resolution of symptoms contributes to the difficulty in drawing conclusions from the evidence. Table 22 provides a summary of the evidence and results presented in this review.

Diagnostic Testing (Key Question 1)

This review focused on comparing the sensitivity and specificity of diagnostic methods that rely, at least in part, on the most widely used commercial immunoassays for *C. difficile* toxin. Immunoassays that can detect both toxins A and B were of particular interest because hypothetically they are the most sensitive immunoassay for detecting toxins and they are very commonly used by laboratories in the United States. In addition, data from comparative evaluations that included newer commercial *C difficile* toxin gene detection tests were of interest.

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 direct comparisons of the immunoassay that are available in the literature. The possibility exists that future research could impact the findings. Further, one article that examined eight tests is the sole source for many of the comparisons. The available comparative data doesn't rule out the possibility of larger differences 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-based tests that used toxin B gene fragments tended to have better sensitivity than immunoassays for toxins A and B. Results, however, should be viewed with caution. Few studies contributed to the findings, and many direct comparisons were not found. Further, as mentioned above, the methodological differences between studies, including use of different reference tests, might have affected the toxin immunoassays more than the gene detection tests. Perhaps variation in the stability of the toxins in stool specimens as they were collected, stored, and processed contributed to the observed variation between studies in the estimates of the immunoassay's sensitivities, whereas detection via amplification of gene fragments could be less susceptible to specimen degradation. Use of a more sensitive toxigenic culture as the reference test may impact the estimated sensitivity of the immunoassays more than the toxin gene detection tests.[203]

These 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.[98] and Crobach et al.[99] encountered difficulty comparing the sensitivities and specificities of the diagnostic tests in large part because there was too much variation between studies in the estimates of sensitivity and specificity of a particular test. Planche et al. used logistic regression with dummy variables to represent each immunoassay and found significant differences in sensitivity and specificity; however, the regression model did not include any covariates to try to account for the substantial heterogeneity between studies. 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 and 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, along with estimates of the prior probability of CDI (using Bayes formula) into their patient care decisions is not clear.

Clinical diagnosis is important in outpatient settings, and primary care in particular, as well as inpatient settings. Outpatient clinicians will need to be alert to the possibility of CDI, given that CDI can manifest several months after hospital exposure or antibiotic use.

Prevention (Key Question 2)

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.[41] 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.[100] Clindamycin resistance was identified soon after the role of *C. difficile* in pathogenesis was discovered.[46,101,102] More recently, quinolones have assumed greater importance because strains have become more resistant over time.[103]

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, health care quality, and 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 bundled prevention strategies to determine which ones are essential or what might be added.

The realities of the environment and the habits of people who occupy those environments are complicated, and care must be taken to avoid assuming the effectiveness of preventive practices based on apparent logic. For example, handwashing is a logical and simple sounding strategy. Studies[103,133,204] have shown that surfaces in and near the bed of a patient with CDI are often contaminated with *C. difficile*, and it is easy for health care workers to recontaminate their hands by touching one of these surfaces. However, if handwashing is performed using the same facilities as the patient, depending on the state of cleanliness in the room, handwashing may be negated the moment a surface is touched by the freshly washed hands. Further, *C. difficile* spores may persist for up to 5 months on some surfaces.[205] This very issue of complexity is in part what drives the aforementioned practice of adding prevention components with what might be, under other conditions, considered minimal available evidence.

Standard Treatment (Key Question 3)

There is moderate evidence that the two most commonly used treatments, metronidazole and vancomycin, are similary effective for the initial cure of CDI. Our results build upon, and are consistent with, the Cochrane Review completed by Bricker et al.[107]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.

In addition, there is moderate-strength evidence, based on a single large study, that fidaxomicin and vancomycin are similarly effective for initial cure of CDI, but that fidaxomicin use leads to significantly fewer recurrences. This difference in recurrence was observed only among non-NAP1 strains of *C. difficile*. 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, that is, 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 trialused a prespecified analysis, and the severity classification appears to have been made before treatment allocation.[70] However, the superiority of vancomycin over metronidazole does not persist when a strict intention-to-treat analysis is used. An argument can be made that even small increases in effect size are important to a high-risk patient population where time is of the essence.[104] A study that has been presented in abstract form only would add to the data available for comparing metronidazole with vancomycin, but it has not yet been published in a peer-reviewed journal (See Table 23, study NCT00196794).

Outcome definitions varied significantly. For the assessment of initial cure, methods varied between only assessing symptoms, to a combination of symptoms and either laboratory values (stool studies, C-reactive protein levels, peripheral blood leukocyte count) or a physiologic measure (temperature). Similarly, definitions of resolved diarrhea ranged from greater than three formed stools in a 24-hour period[70] to greater than two formed stools daily[76] to "no loose stools."[73] Assessment of recurrence in these studies was similarly complicated by variable definitions, followup periods (21 days in two, 30 days in the other), and lack of detail regarding whether active or passive surveillance was used to detect recurrence.

None of the randomized controlled trials (RCT) studies included data regarding any other organisms, either with regard to colonization or subsequent clinical infection. Selection of vancomycin-resistant enterococci (VRE) in particular has long been a concern when treating CDI; usually this concern has involved the use of vancomycin, but increasingly it has been recognized that other antimicrobials can also select for increased rates of VRE carriage.

Nonstandard Treatment (Key Question 4)

We sought to document the range of treatments under investigation for treatment and prevention of CDI, particularly recurrent CDI. Overall, definitions of CDI, interventions and measured outcomes are variable across the nonstandard prevention and treatment literature.

In attempts to expand treatment options for high rates of treatment nonresponse, treatment failure,[206] relapse, and recurrence, researchers and clinicians are examining a number of potential lines of treatment options. 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. Administration of a probiotic to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any established benefit.

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. Indeed, the majority of ongoing trials accessed through ClinicalTrials.gov are of this type of research. (See the Future Research Needs section and Table 23 following this section.)

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 moderate 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. Study designs in which probiotics are administered along with standard antibiotics for recurrent CDI result in a combined treatment for recurrent CDI and do not allow for restricted investigation of probiotics as a prevention of CDI recurrence only.

There were five systematic reviews[207-210] and one meta-analysis[211] about the effectiveness of probiotics for treating CDI, one systematic review about immunoglobulin treatment of CDI,[212] and one systematic review included studies about prevention of CDI using probiotics[210] (Appendix Table C12).

The five systematic reviews on the effectiveness of probiotics for treating CDI included three to six studies. The authors of the systematic reviews determined that the variability in methods, such as types of probiotics, outcome measures, and types of subjects, did not support pooling estimates in a meta-analysis. The conclusions of the systematic reviews were that there was no evidence (two reviews), sparse evidence (two reviews), and insufficient evidence (one review) of any benefit of probiotics for CDI. The systematic review on probiotics that also addressed prevention of CDI included only one prevention study and concluded there was sparse evidence supporting this use of probiotics. The one meta-analysis of using probiotics for CDI included six studies[211] and has been met with criticism. The criticism noted, among other points, the combination of findings from studies of treatment and prevention of adults and children, conducting a pooled analysis on results from heterogeneous outcome measures, analysis of results of studies with low quality due to flawed designs or methods, and lack of independent review as the investigator reviewed their own studies. The conclusion from the meta-analysis was that there was benefit in using a probiotic, especially one containing *S. boulardii,* for reducing recurrence of CDI. The one systematic review of immunoglobulin was based on four retrospective studies and five case reports and concluded no recommendations could be made.[212] This conclusion is supported by the findings of a recent retrospective case series with the largest sample size to date, which showed a higher mortality rate than previously reported.[106] The authors suggested that the effect of immunoglobulin may be dependent upon the extent of systematic involvement in CDI.[106]

Caution is recommended regarding new, nonstandard treatments, and not extrapolating study findings beyond the data. For example, one cannot assume if a probiotic treatment is effective for antibiotic-associated diarrhea that 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. During a Technical Expert Panel call it was noted that some intensive care units have banned probiotics in order to avoid the potential for fungemia and bacteremia in very ill patients.

Future Research

There are a number of important questions to be addressed regarding: (1) how to control both endemic infections and outbreaks; (2) what to do to prevent transmission after occurrence; (3) how to diagnose; (4) how to treat; and (5) how to change prevention strategies with outbreaks. Table 24 provides a summary of 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. Estimates of sensitivity and specificity for many diagnostics tests for toxigenic *C. difficile* can vary greatly between laboratories. Further, there is no high-grade evidence from direct, within-laboratory comparisons of the performance of currently available diagnostic tests. The reviewed comparative studies did not clearly define the testing scenario, including the setting, disease prevalence, patient selection criteria, patient characteristics, or the 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 and patient outcomes.[213]

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 gene amplification and detection tests are more consistent across laboratories, and more sensitive than the currently used toxin immunoassays 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. It happens as a comprehensive approach for 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 data sets and followup periods, and definitions of interventions are agreed to in order to facilitate pooling data across organizations. Efforts to establish and define minimum datasets for surveillance purposes have been undertaken jointly by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America.[110] Lessons learned from this experience can guide future work in establishing expert and evidence-based minimum dataset projects, aligned with the needs of decisionmakers, consumers, and other stakeholders. 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. Another approach to addressing lack of data to support prevention recommendations is to conduct studies that model *C. difficile* transmission and the impact the intervention has on interrupting transmission. This may have the additional benefit of identifying new, potentially more effective methods to prevent transmission

as well. The nature of the decisions faced by infection control professionals is qualitatively different than 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 know 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. Findings of one fecal flora reconstitution case show that the colonic microbial profile of the donor temporarily resembles that of the normal donor, which might explain its beneficial effect.[126] Guidelines related to screening for safety and selecting donors that would need to be considered in future studies have been outlined.[214] 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 or few strains of bacteria, and thus may be insufficient to correct alterations in the complex and extensive microbiome to the extent needed 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.[215,216] 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*. Colonization with nontoxigenic *C. difficile* in hamsters protects against *C. difficile* disease after challenge with a toxigenic strain. The nontoxigenic strain of *C. difficile* is thought to directly compete with toxigenic strains 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.[105,106] 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 effects 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, 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. For example, studies in hamsters indicate that timing of administration of a nontoxigenic strain of *C. difficile* for successful colonization as potential protection against disease differs depending on whether the animal is receiving antibiotics to which *C. difficile* is susceptible or resistant.[217]

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.

Other organizations have also examined research gaps based on literature reviews and expert opinion. Key research issues identified during the *Clostridium difficile* Symposium on Emerging Issues and Research, convened in 2004, provides further information on research gaps.[152] While many of the issues identified in the symposium are beyond the scope of this review, they merit mention. Table 23 provides a list of 23 relevant ongoing or recently completed trials not yet published for the diagnosis, prevention, and treatment of CDI. While there is considerable activity, none of the studies listed is expected to provide a definitive answer for any of the research needs discussed above. More studies that compare toxin gene detection tests to other diagnostic tests for toxigenic *C. difficile* are forthcoming and may support the notion that the gene detection tests are generally more sensitive.

Table 22. Summary of evidence

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Key Question 1 - Diagnostics		
Immunoassays for toxins A and B	Low to moderate	Ten studies directly compared at least two 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, i.e. specificity, were not found among the tests that were compared.
Gene detection tests vs. 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.
Key Question 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 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 for 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 is insufficient to draw conclusions. Harms were not reported.

Table 22. Summary of evidence (continued)

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Key Question 3 - Antibiotic Treatment		
Vancomycin versus Metronidazole	Moderate for clinical cure, low for all other outcomes	There were three head to head trials with a total of 335 subjects. Trials used various definitions of CDI patient and cure definitions, especially with regard to stool count and consistency. No significant differences in outcomes, including initial cure, clinical recurrence, mean days to resolved diarrhea, were found. Our results build upon, and are consistent with, the Cochrane Review completed by Bricker et al.[106]
Severe disease, vancomycin versus metronidazole	Insufficient	One RCT examined a prespecified subgroup of 69 subjects with severe CDI; improved clinical cure based on per-protocol analysis, but not with strict intention-to-treat analysis
Fidaxomycin versus vancomycin	Moderate	One large, high-quality RCT demonstrated decreased recurrence among those receiving fidaxomicin.
All other comparisons of standard treatments	Moderate for vancomycin vs. 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 versus vancomycin) demonstrated deecreased 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.
Key Question 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.
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 six case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year (3 weeks to 8 years).
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

Table 23. Trials from ClinicalTrials.gov and other sources

Intervention Comparator	Last Update, Estimated Completion	Sponsor	Study Design	Population	Primary Outcome	Code
Not yet Recruiting – Diagnostic						
PCR, EIA, or cytotoxin assay	Feb 2010, 2010	Hamilton Health Science, McMaster C. Lee, PI	Comparative	N=500 12+ years stool specimens	Test performance	NCT01066221
Not yet Recruiting – Prevention						
I: Lactobacillus acidophilus/ rhamnosus complex C: placebo	Jan 2010, 2012	Vancouver Island Health Authority, C. Harder	RCT double blind	N=200 60+ patients on antibiotics	CDI incidence	NCT01048567
I: Colostrum derived antibodies C: placebo	Aug 2009, 2012	Hadassah Medical Organization	RCT double blind 60 day followup Phase II, III	N=300 18+ patients symptomatic patient, lab-confirmed CDI	Recurrent CDI, new cases in close proximity	NCT00747071
Recruiting – Prevention						
I: Saccharomyces Boulardii C:Placebo	July 2012	Bernhard Nocht Institute for Tropical Medicine S. Ehrhardt, PI	RCT double blind, Phase III	N=1,520 18+ hospitalized patients	CDI incidence	NCT01143272
I: toxoid vaccine C: placebo	Apr 2011	Sanofi-Aventis	RCT double blind 9 week followup	N=650 18+ patients with one CDI episode within last 10 days, not currently treated for recurrent	Recurrent CDI	NCT00772343
I: Lactobacillus casei probiotic C: placebo	Apr 2010, 2012	University of Sussex, C. Rajkumar, PI	RCT double blind, 28 days, Phase II	N=1,200 55+ patients receiving antibiotics	Incidence and presence of toxin, prevent recurrence	NCT01087892
I: Clostridium butyricum MIYAIRI 588 Strain (CBM588 C: placebo)	Feb 2010, 2011	Osel, Inc. P. Lee, PI	RCT double blind, Phase II	N=200 18+ patients treated with vancomycin or metronidazole for CDI	Recurrent CDI	NCT01077245
I: Probiotic VSL#3 C: placebo	Sept 2009, Sept 2010	NHS, UK N. Haslam, PI	RCT double blind, 28 days, Phase II, III	N=450 18+ patients on antibiotics	CDI incidence	NCT00973908

Table 23. Trials from ClinicalTrials.gov and other sources (continued)

Intervention Comparator	Last Update, Estimated Completion	Sponsor	Study Design	Population	Primary Outcome	Code
I: Recombinant human lactoferrin C: placebo	Sept 2006	John Hopkins W. Greenough, PI	RCT double blind	N=300 18+ LTC patients on enteral tube feeding	Not reported	NCT00377078
I: Hospital ward physical design C: traditional ward design	Mar 2009	University of Calgary W. Ghali, PI	Prospective controlled trial	N=3,600 18+ patients	CDI incidence	NCT00563186
Recruiting – Treatment						
I: CB-183,315 two doses tested C: Vancomycin	Apr 2010, 2011	Cubist Pharmaceuticals	RCT double blinded, 3 arms, Phase II	N=210 18+ patients symptomatic patients, lab-confirmed, index or 1st recurrence	Not clear	NCT01085591
I: Loperamide (Imodium) C: placebo	Jan 2008, Dec 2009	VA Houston, D. Musher, PI	RCT double blind, Phase IV	N=120 18+ patients on antibiotics	Symptomatic treatment of diarrhea	NCT00591357
I: Nitazoxanide C: NA	Mar 2006	VA Houston, D. Musher, PI	Open label compassionate use Phase III	N=100 18+ patients with CDI who failed therapy	Resolution of symptoms	NCT00304356
Fecal bacteriology	Mar 2006	VA Houston D. Musher, PI	Retro observational cross-sectional	N=80 18+ patients with CDI, patients lab-confirmed without CDI, patients who fail therapy, hospitalized patients on antibiotic with no diarrhea		NCT00304876
Completed – Prevention						
I: Bio-K+ CL-1285 probiotic, Lactobacillus acidophilus, Lactobacillus casei C: placebo	Aug 2009	Bio-K Plus International, Inc. G. XingWang, PI	RCT double blind, Phase III	N=255 50-70 years, patients on antibiotic therapy	CDI incidence	NCT00958308

Table 23. Trials from ClinicalTrials.gov and other sources (continued)

Intervention Comparator	Last Update, Estimated Completion	Sponsor	Study Design	Population	Primary Outcome	Code
I: Lactobacillus acidophilus and casei C: placebo	Sept 2008	Bio-K Plus International, Inc. J. Dylewski, PI	RCT double blind	N=480 18+ patients on antibiotics	CDI incidence	NCT00328263
I:Polycationic disinfectant C: alcohol-based gel and regular disinfectant with quat/chloramines	Aug 2008	Helsinki University Soft protector TEKES, M. Kanerva, PI	Open label, parallel active control 6 months	3 experimental wards plus control wards	CDI incidence	NCT00566306
Completed – Treatment						
I:GT160-246 C: Vancomycin	Jul 2009	Genzyme	RCT double blinded, Phase II	N=300 18+ patient with mild to moderate CDI	Not reported	NCT00034294
I: Rifaximin C: Vancomycin	Dec 2009	Salix Pharmaceuticals A. Shaw, PI	RCT double blind, Phase III	N=300 18+ lab confirmed CDI	Resolution of baseline, recurrence	NCT00269399
I: OPT-80 C: Vancomycin	Feb 2010	Optimer Pharmaceuticals, YK Shue, PI	RCT double blind, Phase III	N=536 16+ patients with CDI	Cure rate, recurrence rate	NCT00468728
I: Lactobacillus CL placebo (both arms used metronidazole)	Mar 2006	VA Houston D. Musher	RCT double blind Phase IV	N=70 18+ patients lab confirmed CDI	Response to treatment	NCT00304863
Not ClinicalTrials.gov						
FECAL trial I: bacteriotherapy C: Standard antibiotic treatment		ZonMW, the Netherlands Organisation for Health Research and Development van Nood, PI	RCT, 10 week followup	N=120 18+ patients, proven relapse of CDI. Exclude ICU, immuno-compromised	Response to treatment	Netherlands. Non-citizens accepted if travel to Amsterdam

C = comparator; CDI = Clostridium difficile infection; EIA = enzyme immunoassay; I = intervention; ICU = intensive care unit; PCR = polymerase chain reaction; PI = Principal Investigator; RCT = randomized controlled trial

Table 24. Future research recommendations

Key Question	Research Gaps	Types of Studies Needed to Answer Questions	Future Research Recommendation
Key Question 1. How do different methods for detection of toxigenic *C. difficile* compare in their sensitivity, specificity, and predictive values?	Few direct comparisons are available. Methodological heterogeneity is an obstacle. Unknown what differences in sensitivity and specificity would alter clinician decisionmaking and patient outcomes. Unknown influence of patient and stool characteristics on differences in test sensitivity and specificity.	Comparison of diagnostic tests using same clinical samples in the same labs. Multicenter studies with well-documented patient samples.	Document stool sample characteristics, patient selection criteria, patient characteristics, signs and symptoms of suspected CDI and effects of differences on patient outcomes.
Key Question 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 data sets for observational data points that can inform models.
Key Question 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.
Key Question 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.

CDI = Clostridium difficile infection

References and Included Studies

(The references below correspond to the footnotes in the body of the report. There is a separate set of references at the end of the evidence tables in Appendix C.)

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Abbreviations

AAD	Antibiotic-associated disease
AE	Adverse effects
AHRQ	Agency for Healthcare Research and Quality
AMED	Allied and Complementary Medicine
CDI	*Clostridium difficile* infection
CI	Confidence interval
GDH	Glutamate dehydrogenase enzyme
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
ICU	Intensive care unit
MeSH	Medical Subject Headings
MRSA	Methicillin-resistant Staphylococcus aureus
PCR	Polymerase chain reaction
RCT	Randomized controlled trial
RR	Relative risk
TEP	Technical expert panel
VRE	Vancomycin-resistant enterococci
WMD	Weighted mean differences

Glossary of Terms

CDI – *C. difficile* infection.

Colonization – *C. difficile* becomes established in the intestine. Technically, colonized individuals may or may not have CDI, since an individual with an infection is necessarily colonized by the organism. However, the term is often used in the literature to denote asymptomatic colonization.

False Negative Fraction – Fraction of tested stool specimens that had a positive reference test and a negative result for the diagnostic method being evaluated. The false negative fraction is equal to one minus the sensitivity.

False Positive Fraction – Fraction of tested stool specimens that had a negative reference test and a positive result for the diagnostic method being evaluated. The false positive fraction is equal to one minus the specificity.

Gene Detection Test – Methods of amplifying (replicating) specific parts of genetic material (DNA) in samples usually using the polymerase chain reaction (PCR) followed by detection of the highly replicated gene fragment.

Hypersporulation – Accelerated rate of spore production.

Hypervirulent – Strains of CDI that include increased toxin production, an additional binary toxin, hypersporulation, and high-level resistance to fluoroquinolone antibiotics.[27]

Immunoassay – Test that is based on interactions between added animal antibodies against the specific substance to be detected, e.g. *C. difficile* toxins or glutamate dehydrogenase. Different tests use varying methods to isolate and detect the antibody/antigen complexes formed in the specimen being tested. Commonly referred to as enzyme immunoassay (EIA) in the literature.

Negative Predictive Value – Fraction of tested stool specimens that were negative for the diagnostic method being evaluated and negative on the reference test. Depends on the prevalence of toxigenic *C. difficile* in the tested specimens.

Nonstandard Therapy – Therapies other than treatment with antibiotics for CDI, such as probiotics, prebiotics, monoclonal antibodies, and fecal flora reconstitution.

Positive Predictive Value – Fraction of tested stool specimens that were positive for the diagnostic method being evaluated and positive on the reference test. Depends on the prevalence of toxigenic *C. difficile* in the tested specimens.

Prebiotics – Nondigestible foods that create environments healthy for bacteria growth.

Probiotics – Living microorganisms, including bacteria or yeast, which are believed to restore microbial balance to gastrointestinal flora when administered in adequate amounts.

Recurrent CDI – Recurrence of symptoms within 8 to 10 weeks after cessation of specific antibiotic therapy, with exclusion of other enteropathogens and a positive diagnostic test for toxigenic *C. difficile*.[119]

Sensitivity – Fraction of tested stool specimens that had a positive reference test and a positive result for the diagnostic method being evaluated. Sensitivity is also called the true positive fraction.

Severe CDI – Definitions vary in the literature, but generally refer to a CDI diagnosis in combination with more complex manifestations of disease or in patients with other significant risk-factors such as age, signs of infections, or comorbidities.

Specificity – Fraction of tested stool specimens that had a negative reference test and a negative result for the diagnostic method being evaluated. Specificity is also called the true negative fraction.

Appendix A. Technical Expert Panel Members and Affiliation

Marcel Salive, M.D., M.P.H.	Division of Medical and Surgical Services Centers for Medicare and Medicaid Services Baltimore, Maryland
Erik Dubberke, M.D., SHEA	School of Medicine Washington University St. Louis, Missouri
Christina Surawicz, M.D.	Professor of Medicine University of Washington School of Medicine Seattle, Washington
Dale Gerding, M.D.	Associate Chief of Staff Hines VA Hospital Hines, Illinois
Michael Wilson, M.D.	Department of Pathology & Laboratory Services Denver Health Medical Center Denver, Colorado

Appendix B. Search Strategies

Search string for C Difficile (general)

Database: Ovid MEDLINE
Search Strategy:
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1 difficile.mp.
2 limit 1 to (english language and humans)
3 limit 2 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
4 randomized controlled trial.pt.
5 controlled clinical trial.pt.
6 randomized.ab.
7 placebo.ab.
8 drug therapy.fs.
9 randomly.ab.
10 trial.ab.
11 groups.ab.
12 or/4-11
13 (animals not (humans and animals)).sh.
14 12 not 13
15 3 and 14
16 limit 15 to (addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits)
17 15 not 16
18 Cohort studies/ or comparative study/ or follow-up studies/ or prospective studies/ or risk factors/ or cohort.mp. or compared.mp. or groups.mp. or multivariate.mp.
19 limit 18 to (comment or editorial or historical article or interview or letter)
20 18 not 19
21 3 and 20
22 17 or 21

Search string for C Difficile (Diagnostic)

Database: Ovid MEDLINE
Search Strategy:
---

1 difficile.mp.
2 diagnostic accuracy.mp.
3 (enzyme adj2 immunoassay$).mp.
4 Immunoenzyme techniques/
5 enzyme linked immunosorbent assay/
6 feces/
7 faeces analysis.mp.
8 fecal.mp.
9 stool culture.mp.
10 exp "Sensitivity and Specificity"/
11 cytotoxicity test, immunologic/
12 cell cytotoxicity assay.mp.
13 pcr.mp. or polymerase chain reaction/
14 immunochromatography.mp.
15 or/2-14
16 1 and 15

17 limit 16 to (english language and humans and ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))
18 limit 17 to (addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits)
19 limit 17 to in vitro
20 17 not (18 or 19)

Appendix C. Evidence Tables

Appendix Table C1. Summary of matched comparisons of select† assays for *C. difficile* toxins

Study	Patients/ Site	Tested Specimens	Reference Standard/ % Positive in Sample	Tests Compared	True Positive/ False Positive‡	PPV/ NPV
Swindells 2010[1]	n=? Patients over 65 yrs old who developed diarrhea at least 48 hrs after admission Birmingham City Hospital, UK ?spectrum ?selection	n=150 fresh liquid stool specimens stored < 48 hrs at 2-8 ^{o} C ; Independent, blinded operators; No tests were repeated	Toxigenic culture using CTA on cultured organisms 12.0%	GeneOhm C. difficile (tcdB), Becton Dickinson GeneXpert *C.difficile* (tcdB), Cepheid VIDAS *C. difficile* Tox A/B, bioMerieux	17/18=94.4% 1/132=0.8% 18/18=100% 1/132=0.8% 8/18=44.4% 0/132=0%	17/18=94.4% 131/132=99.2% 18/19=94.7% 131/131=100% 8/8=100% 132/142=93.0%
Kvach, 2010[2]	n=341 in hospital with suspected CDI; Yale-New Haven Hospital, CT ?spectrum ?selection	n=400 fresh liquid or semisolid that were either GDH positive or negative; Some frozen at -20^{o} C for < week after two-step GDH/CTA to do other tests; Excluded if patient being treated for CDI or retested within 7 days; ?blinded	If not all positive or negative on 3 tests, then toxigenic culture using Premier Toxin A/B test of cultured organisms 26.2%	GeneOhm C. difficile (tcdB), Becton Dickinson Tox A/B II, Techlab	96/105=91.4% 0/295=0% 70/105=66.7% 1/295=0.3%	96/96=100% 295/304=97.0% 70/71=98.6% 294/329=89.4%
Alcala 2010[3]	n=412 ?suspected CDI Madrid, Spain ?spectrum ?selection	n= 487 ?fresh ?consistency ?blinded equivocal results were called negative	CTA followed by toxigenic culture if negative 12.7%	Premier ImmunoCard Toxins A&B, Meridian VIDAS *C. difficile* Tox A/B, bioMerieux	42/62=67.7% 21/425=4.9% 43/62=69.4% 8/425=1.9%	42/63=66.7% 404/424=95.3% 43/51=84.3% 417/436=95.6%

Appendix Table C1. Summary of matched comparisons of select† assays for *C. difficile* toxins (continued)

Study	Patients/ Site	Tested Specimens	Reference Standard/ % Positive in Sample	Tests Compared	True Positive/ False Positive‡	PPV/ NPV
Eastwood, 2009[4]	?n CDI suspected with some previously diagnosed CDI; Leeds Teaching Hospitals, London, UK ?spectrum ?selection	n=600 only 558 for GeneOhm test; fresh, unformed refrigerated except for GeneOHm that were frozen at -20 ^{o} C for < 8 months; ?blinded;	CTA of specimen and cultured organisms when stool CTA was negative 20.8%	GeneOhm C. difficile (tcdB), Becton Dickinson Premier Toxin A&B, Meridian Premier ImmunoCard Toxins A&B, Meridian Tox A/B II, Techlab Tox A/B Quik Chek, Techlab ProSpecT Toxin A/B, Remel Xpect Toxin A/B, Remel VIDAS *C. difficile* Tox A/B	92/103=89.3% 16/449=3.6% 101/125=80.8% 12/475=2.5% 86/115=74.8% 2/444=0.4% 100/125=80.0% 19/475=4.0% 93/125=74.4% 3/473=0.6% 102/125=81.6% 32/475=6.7% 86/117=73.5% 3/475=0.6% 100/116=86.2% 2/464=0.4%	92/108=85.2% 433/444=97.5% 101/113=89.4% 463/487=95.1% 86/88=97.7% 442/471=93.8% 100/119=84.0% 456/481=94.8% 93/96=96.9% 470/502=93.6% 102/134=76.1% 443/466=92.9% 86/89=96.6% 472/503=93.8% 100/102=98.0% 462/478=96.6%
Novak-Weekley, 2009[5]	n = 432 suspected CDI; patients under 2 years old excluded; Southern CA Permanente Medical Labs; ?spectrum ?selection	n = 432 ?fresh Unformed, refrigerated; ?blinded;	Toxigenic culture using CTA on cultured organisms 16.7%	GeneXpert *C.difficile* (tcdB), Cepheid Premier Toxins A&B, Meridian 1st C. difficle CHEK-60 (GDH), Techlab; if positive, then Premier Toxins A&B	68/72=94.4% 13/356=3.7% 42/72=58.3% 19/360=5.3% 40/72=55.6% 6/360=1.7%	68/81=84.0% 343/347=98.8% 42/61=68.9% 341/371=91.9% 40/46=87.0% 354/386=91.7%

Appendix Table C1. Summary of matched comparisons of select† assays for *C. difficile* toxins (continued)

Study	Patients/ Site	Tested Specimens	Reference Standard/ % Positive in Sample	Tests Compared	True Positive/ False Positive‡	PPV/ NPV
Alcala, 2008[6]	n=305 mixture of suspected CDI and positive samples by CTA; Hospital General Universitario Gregorio Maranon, Madrid, Spain ?spectrum ?selection	n=367 fresh refrigerated; ?consistency ?blinded ?indeterminate results	CTA of specimen and cultured organisms when direct CTA was negative 27.8%	ImmunoCard Toxins A&B, Meridian Xpect *C. diff*. toxin A/B, Remel TOX A/B QUIK CHEK, Techlab	68/102=66.7% 13/265=4.9% 50/102=49.0% 11/265=4.2% 56/102=54.9% 12/265=4.5%	68/81=83.9% 252/265=88.1% 50/61=81.9% 254/306=83.0% 56/68=82.4% 253/299=84.6%
Miendje Deyi, 2008[7]	n=91 Age 65-99 avg. 81 yrs; suspected CDI; 2 university hospitals in Brussels, Belgium; 1 hospital had recent outbreak of *C. difficile;* ?spectrum ?selection	n=100 frozen at -70° C; ?consistency tested blindly on same day in same lab ?indeterminate results	CTA 23.0%	ImmunoCard Toxins A&B, Meridian Xpect *C. diff*. toxin A/B, Remel TOX A/B QUIK CHEK, Techlab	21/23=91.3% 0/77=0% 21/23=91.3% 0/77=0% 22/23=95.7% 0/77=0%	21/21=100% 77/79=97.5% 21/21=100% 77/79=97.5% 22/22=100% 77/78=98.7%
Samra, 2008[8]	n=200 hospitalized patients with diarrhea; Rabin Medical Center, Israel ?spectrum ?selection	n= 200 fresh or refrigerated diarrhea; randomly selected from positive and negative results; ?blinded ?indeterminate results	In-house PCR for toxin B gene 47.0%	Tox A/B II, Techlab Tox A/B Quik Chek, Techlab Immmunocard Toxin A&B, Meridian	88/94=93.6% 6/106=5.7% 89/94=94.7% 3/106=2.8% 89/94=94.7% 3/106=2.8%	88/94=93.6% 100/106=94.3% 89/92=96.7% 103/108=95.4% 89/92=96.7% 103/108=95.4%

Appendix Table C1. Summary of matched comparisons of select† assays for *C. difficile* toxins (continued)

Study	Patients/ Site	Tested Specimens	Reference Standard/ % Positive in Sample	Tests Compared	True Positive/ False Positive‡	PPV/ NPV
Sloan, 2008[9]	n=200 suspected CDI; Mayo Clinic, Rochester, MN ?spectrum ?selection	n=200 soft or liquid; fresh or frozen < 48 hrs. ?blinded; ?indeterminate results	Toxigenic culture using toxin A and B gene detection for cultured organisms 22.0%	Premier Toxin A&B, Meridian ImmunoCard Toxin A&B, Meridian Xpect *C. diff*. toxin A/B, Remel	21/44=47.7% 3/156=1.9% 21/44=47.7% 2/156=1.3% 21/44=47.7% 25/156=16.0%	21/24=87.5% 153/176=86.9% 21/23=91.3% 154/177=87.0% 21/46=45.6% 131/154=85.1%
Musher, 2007[10]	?n inpatients suspected CDI; Michael E. DeBakey VA Medical Center, Houston, TX ?spectrum ?selection	n=446 ?fresh ?consistency ?blinded ?indeterminate results *Part 2* n=131 Convenience sample; Fresh; ?consistency ?blinded ?indeterminate results	CTA 17.0% CTA 41.2%	Premier Toxin A&B, Meridian ImmunoCard Toxin A & B, Meridian …… Premier Toxin A&B, Meridian C. difficile TOX A/B II, TechLab ProSpecT Clostridium difficile toxin A/B, Remel	75/76=98.7% 10/370=2.7% 73/76=96.1% 4/370=1.1% …….. 52/54=96.3% 5/77=6.5% 52/54=96.3% 10/77=13.0% 49/54=90.7% 2/77=2.6%	75/85=88.2% 360/361=99.7% 73/77=94.8% 366/369=99.2% …… 52/57=91.2% 72/74=97.3% 52/62=83.9% 67/69=97.1% 49/51=96.1% 75/80=93.8%
van den Berg, 2007[11]	n=450 all with diarrhea, some suspected CDI others not but inpatients for at least 72 hours; from 4 medical centers in The Netherlands; ?spectrum ?selection	n=547 diarrhea frozen at -20^{o} C; ?blinded	CTA 5.7%	Premier Toxins A&B, Meridian VIDAS C. difficile Tox A II, bioMerieux Vitek	30/31=96.8% 29/509=5.7% 26/31=83.8% 15/509=2.9%	30/59=50.8% 480/481=99.8% 26/41=63.4% 494/499=99.0%

Appendix Table C1. Summary of matched comparisons of select† assays for *C. difficile* toxins (continued)

Study	Patients/ Site	Tested Specimens	Reference Standard/ % Positive in Sample	Tests Compared	True Positive/ False Positive‡	PPV/ NPV
Turgeon, 2003[12]	n=1003 Consecutive samples, all suspected CDI; Childrens, university & cancer centers in Seattle, WA; 45% stem cell transplant patients ?spectrum ?selection	n=1003 any consistency; fresh for CTA, rest frozen at -20° C; ?interim time ?blinded ?indeterminate results	CTA 10.1%	Premier Cytoclone A/B, Meridian *C. diff* Tox A/B, Techlab	74/101=73.3% 8/898=0.9% 78/101=77.2% 5/902=0.6%	74/82=90.2% 890/917=97.1% 78/83=94.0% 897/902=99.4%
O'Connor, 2001[13]	n=133 Adults, consecutive samples, CDI suspected; Multiple health centers in Galway County area of Ireland ?spectrum ?selection	n=200 92% liquid or unformed; -20° C for CTA, then frozen at 84° C; ?blinded	CTA 30.5%	Premier Toxins A&B, Meridian *C. diff* Tox A/B II, Techlab	50/61=82.0% 1/139=0.7% 49/61=80.3% 1/139=0.7%	50/51=98.0% 138/149=92.6% 49/50=98.0% 138/150=92.0%

CDI = C. difficile infection; CTA = cytotoxicity assay using cultured test cells, true + is sensitivity/false + is 1 – specificity; PPV/NPV = positive/negative predictive value based on prevalence of C. difficile in tested sample; GDH = glutamate dehydrogenase.

? Iindicates issues identified by the quality assessment of diagnostic accuracy studies (QUADAS) criteria.

‡Varying numbers of indeterminate results are excluded from estimates of true and false positives when possible, thus denominators are not constant for all methods compared within a study.

† Presumably available and used in the United States, and at least one comparator is an immunoassay for toxins A and B.

Appendix Table C2. Grade of evidence for comparisons of diagnostic tests for toxigenic *C. difficile*

Comparison	Difference in Sensitivity (True Positives)		Difference in False Positives (1 – Specificity)	
	Ratings†	Overall Evidence Grade	Ratings†	Overall Evidence Grade
Immunoassays for Toxins A & B				
Premier Toxin A&B, Meridian Tox A/B II, TechLab	Consistent, Imprecise	Low	Inconsistent, Precise	Low
Tox A/B QUIK CHEK, TechLab ImmunoCard A&B, Meridian	Consistent, Imprecise	Low	Consistent, Precise	Moderate
Premier Toxin A&B, Meridian ImmunoCard A&B, Meridian	Consistent, Imprecise	Low	Consistent, Precise	Moderate
Tox A/B QUIK CHEK, TechLab Xpect Toxin A/B, Remel	Consistent, Imprecise	Low	Consistent, Precise	Moderate
Tox A/B QUIK CHEK, TechLab Tox A/B II, TechLab	Consistent, Imprecise	Low	Consistent, Imprecise	Low
Premier Toxin A&B, Meridian ProSpecT Toxin A/B, Remel	Consistent, Imprecise	Low	Inconsistent, Imprecise	Low
Premier Toxin A&B, Meridian Xpect Toxin A/B, Remel	Consistent, Imprecise	Low	Inconsistent, Imprecise	Low
Tox A/B II, TechLab ImmunoCard A&B, Meridian	Consistent, Imprecise	Low	Consistent, Imprecise	Low
Premier Toxin A&B, Meridian C. diff Tox A/B, VIDAS	Inconsistent Imprecise	Low	Consistent Precise	Moderate
Premier Toxin A&B, Meridian Tox A/B QUIK CHEK, TechLab	Single study, Imprecise	Low	Single study, Precise	Low
Tox A/B QUIK CHEK, TechLab ProSpecT Toxin A/B, Remel	Single study, Imprecise	Low	Single study, Imprecise	Low
Tox A/B QUIK CHEK, TechLab C. diff Tox A/B, VIDAS	Single study, Imprecise	Low	Single study, Precise	Low
Xpect Toxin A/B, Remel ProSpecT Toxin A/B, Remel	Single study, Imprecise	Low	Single study, Imprecise	Low
Xpect Toxin A/B, Remel C. diff Tox A/B, VIDAS	Single study, Imprecise	Low	Single study, Precise	Low
ProSpecT Toxin A/B, Remel C. diff Tox A/B, VIDAS	Single study, Imprecise	Low	Single study, Imprecise	Low
ImmunoCard A&B, Meridian C. diff Tox A/B, VIDAS	Single study Imprecise	Low	Single study, Imprecise	Low
Gene Detection Tests vs. Immunoassays for Toxins A & B				
GeneOhm, Becton Dickinson Tox A/B II, TechLab	Inconsistent, Imprecise	Low	Consistent, Precise	Moderate
GeneOhm, Becton Dickinson C. diff Tox A/B, VIDAS	Inconsistent, Imprecise	Low	Inconsistent, Imprecise	Low
GeneOhm, Becton Dickinson Premier Toxin A&B, Meridian	Single study, Imprecise	Low	Single study, Imprecise	Low
GeneOhm, Becton Dickinson ImmunoCard A&B, Meridian	Single study, Imprecise	Low	Single study, Imprecise	Low
GeneOhm, Becton Dickinson Tox A/B QUIK CHEK, TechLab	Single study, Imprecise	Low	Single study, Imprecise	Low
GeneOhm, Becton Dickinson ProSpecT Toxin A/B, Remel	Single study, Imprecise	Low	Single study, Imprecise	Low
GeneOhm, Becton Dickinson Xpect Toxin A/B, Remel	Single study, Imprecise	Low	Single study, Imprecise	Low

Appendix Table C2. Grade of evidence for comparisons of diagnostic tests for toxigenic *C. difficile* (continued)

Comparison	Difference in Sensitivity (True Positives)		Difference in False Positives (1 – Specificity)	
	Ratings†	Overall Evidence Grade	Ratings†	Overall Evidence Grade
GeneXpert, Cepheid Premier Toxin A&B, Meridian	Single study, Imprecise	Low	Single study, Imprecise	Low
GeneXpert, Cepheid 2-Stage test using CHEK-60 for GDH, then if positive Premier Toxin A&B, Meridian	Single study, Imprecise	Low	Single study, Imprecise	Low

† Consistency refers to the variation between estimates from different studies. Precision refers to the width of the overall confidence interval. The risk of bias was considered to be low for all comparisons. All the evidence is only indirectly related to clinical decisions and the effect of differences on patient health outcomes is not known.

Appendix Table C3. Description of studies evaluating risk factors for CDI

Study/ Origin	Study Type	Objective	Population	Methods	Results
Peled, 2007[14] Israel	Prospective cohort study	Compare the clinical characteristics of patients who developed CDI versus patients with a negative stool assay for *C. difficile* toxin	217 patients with ADD. *C. difficile* toxin positive (n=52): n=52; mean age 72 years; Male-female ratio 1:26 *C. difficile* toxin negative (n=165): mean age 66 (p=0.21 vs. toxin pos.); Male-female ratio 1:11	Diarrhea was defined as the passage of ≥3 unformed stools for ≥2 consecutive days. Toxin assay: enzyme immunoassay for *C. difficile* toxin A/B (TechLab). Analysis (controlling for confounding): Stepwise logistic regression	Significant factors for CDI: watery diarrhea (OR=17.1, p=0.000), functional capacity score of 2 or 3 (requiring assistance in daily activities or bedridden) (OR=9.14, p=0.000), use of a proton pump inhibitor (OR=6.1, p=0.024), hypoalbuminemia (OR=3.8, p=0.001), histamine blocker (OR=3.1, p=0.024) leukocytosis (OR=2.7, p=0.004). Stepwise logistic regression analysis predicted a positive result for *C. difficile* toxin with 95% specificity and 68% sensitivity.
Samore, 2006[15] United States	Prospective case series	Analyze *C. difficile* susceptibility results and genotypes in relation to antibiotic exposures that precipitated CDI	83 patients with nosocomial CDI. Mean age 66 years; female 43% Median length of stay before onset of CDI was 10 days (range, 2–95). *C. difficile* isolates were recovered from patients in 10 different hospital wards and 3 intensive care units. The wards with the largest number of cases were vascular surgery (n=15) and general surgery/liver transplantation (n =14).	Prospective surveillance and collection of stool isolates. Isolates were genotyped by pulsed-field gel electrophoresis and restriction enzyme analysis. Analysis: multivariable logistic regression	Clindamycin exposure was strongly associated with CDI caused by isolates that exhibited multiple resistance to clindamycin, erythromycin, and trovafloxacin (prevalence OR 4.2; 95%CI: 1.1 to 16.8)

Appendix Table C3. Description of studies evaluating risk factors for CDI (continued)

Study/ Origin	Study Type	Objective	Population	Methods	Results
Yearsley, 2006[16] United Kingdom	Prospective case-control	Association between acid suppression therapy and risk of CDI	N=308 hospital inpatients. CDI group (n=155): Mean age 79 years (range 37–102); Female 61% Received antibiotics: 92% Received PPI: 40% Received acid suppression: 41% Control group (n=153): Mean age 79 years (range 43–99); female 55% Received antibiotics: 50%, p<001 (vs. case) Received PPI: 25%, p=0.004 Received acid suppression: 26%, p=0.005	Cases with CDI were mostly were recruited from general medical wards. Control was chosen as a person on the same ward whose birthday was closest to that of the index patient. Analysis: Logistic regression	CDI was independently associated with: antibiotic use (OR 13.1, 95%CI: 6.6 to 26.1); acid suppression therapy (OR 1.90, 95%CI: 1.10 to 3.29); and female gender (OR 1.79, 95%CI: 1.06 to 3.04).
Vesta, 2005[17] United States	Prospective observational case control, multicenter, study	Risk factors associated with the development of nosocomial CDI, particularly with the use of antibiotics	144 hospitalized patients with diarrhea requiring a *C. difficile* toxin test as part of their routine clinical workup, Cases (n=72) Mean age 56 years; Female 43% Controls (n=72) Mean age 56 years; Female 43%	Case patients had nosocomial diarrhea and positive *C. difficile* toxin tests. Control were patients with stool negative for *C. difficile* toxin and were individually matched with cases based on hospital, sex, age (within 4 years), and duration of hospital stay up to the time of stool sampling (within 4 days). Analysis: multivariate logistic regression analysis to identify independent risk factors for the development of CDI (not performed)	There were no significant differences in antibiotic use between cases and controls. Patient severity, classified by Horn's Index, was significantly different between cases and controls (p=0.0022).

Appendix Table C3. Description of studies evaluating risk factors for CDI (continued)

Study/ Origin	Study Type	Objective	Population	Methods	Results
Kyne, 2002[18] United States	Prospective cohort series	Determine the diagnostic accuracy of an index of underlying disease severity (Horn's index) in identifying patients with a high probability of having nosocomial CDI as a complication of antimicrobial therapy	252 inpatients and receiving antibiotics. Mean age 74 years; female 60%; Disease severity (Horn's index) 1 (mild) 30% (n=76) 2 (moderate) 37% (n=93) 3 (severe) 22% (n=55) 4 (extremely severe) 11% (n=28) 28 (11%) of the patients had CDI	CDI defined as diarrhea (≥3 unformed stools for ≥2 days) not attributed to any other cause that occurred in association with a positive stool test for *C. difficile.* Horn's index as a measure of the severity of underlying disease at the time of admission to the hospital, rated as follows: mild=1; moderate =2 (more severe disease but uncomplicated recovery expected); severe (major illness or complications or multiple conditions requiring treatment) =3; extremely severe (catastrophic illness that may lead to death) =4. Analysis: stepwise multivariable logistic regression	Extremely severe underlying disease was associated with CDI (OR 17.6 95%CI: 5.8 to 53.5). Sensitivity, specificity, and positive and negative predictive values of a Horn's index score of 3 or more (severe to extremely severe disease) as a predictor of nosocomial *C. difficile* diarrhea were 79%, 73%, 27%, and 96%, respectively.
Mody, 2001[19] United States	Prospective case control	Evaluate risk factors and clustering of CDI cases over 2 years	252 patients from a Veterans Affairs Medical Center with unformed stools and positive stool *C difficile* cytotoxin assays over the 24-month period; 98 patients served as control. No information on age. 45 cases (17.8%) and 19 controls (19.4%) were HIV-infected.	Cases were patients with CDI. Controls were patients with unformed stools and *C. difficile* negative toxin test. Stools for cytotoxin assays were frozen and sent on ice to a reference laboratory. Analysis: logistic regression	Third-generation cephalosporins were the antibiotics most strongly associated with CDI (OR 3.63 95%CI 1.56 to 9.80). The association of third-generation cephalosporin use was particularly striking in HIV-infected patients (p=0.0004 when HIV status was included in the model). 34 (76%) of 45 HIV-infected patients with CDI died during their hospitalization.

Appendix Table C3. Description of studies evaluating risk factors for CDI (continued)

Study/ Origin	Study Type	Objective	Population	Methods	Results
Schwaber, 2000[20] Israel	Prospective case control	Determine factors associated with the development of nosocomial diarrhea and the acquisition of CDI	136 hospital inpatients, 98 with nosocomial diarrhea and 38 controls. 59.9 ±17.5 years, whereas that of the controls was 56.3 ±19.9 years *Clostridium difficile* toxin B was identified in the stool of 13 cases.	Diarrhea defined as ≥3 loose or watery stools in a 24 h, lasting for ≥ 3 days, beginning ≥ 2 days after admission. Toxin assay: cell-culture cytotoxin test in a culture of human fibroblasts. Analysis: No multivariate analyses reported.	Factors associated with the presence of *C. difficile* toxin B as compared to other causes of nosocomial diarrhea were: greater number of individual antibiotics used during hospitalization (p=0.02); cephalosporin use (p=0.03), more specifically, a third generation cephalosporin (p=0.02). Among patients with nosocomial diarrhea, those who *C. difficile* toxin positive had a significantly higher total antibiotic burden (as antibiotic days) than those with diarrhea due to other causes (p=0.01).
Katz, 1997[21] United States	Prospective case series	Develop predictors for diagnosis of CDAD	609 adult inpatients tested for *C. difficile* cytotoxin *C. difficile* toxin positive (n=49) Mean age 58 years; Female 57% *C. difficile* toxin negative (n=49) Mean age 58 Female 57%	Relevant clinical symptoms, signs, and antibiotic exposure were recorded before reporting of assay results. Toxin assay: procedure by Chang Analysis: logistic regression	Potential contributing causes of diarrhea (toxin+ vs. toxin-) Antibiotic use past 30 days: 98% vs. 84% (p=0.009) Cephalosporin use: 73% vs. 49% (p=0.001) Antibiotic use prior to admission/transfer: 51% vs. 32% (p=0.009) Antacid use: 20% vs. 10%, p=0.04. Prior antibiotic use and significant diarrhea were significantly greater in *C. difficile* toxin positive patients.

ADD = antibiotic-associated diarrhea; ASA = American Society of Anesthesiologists; CDI = C. difficile infection; HIV = Human immunodeficiency virus; OR = odds ratio; PPI = proton pump inhibitor

Appendix Table C4. Evidence table for standard antibiotic treatments

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
1. Newly Identified Trials				
Louie 2011[22] Region: Canada and USA Funding source: Industry The first draft of the manuscript was written by one of the authors who is a part-time employee of the study sponsor, Optimer Pharmaceuticals	Population: Adults with acute symptoms of CDI and a positive result on a stool toxin test Mean age: 62 % women: 56 Inclusion criteria: 16 years of age or older with a diagnosis of CDI, defined by the presence of diarrhea (a change in bowel habits, with >3 unformed bowel movements in the 24-hour period before randomization) and *C. difficile* toxin A, B, or both in a stool specimen obtained within 48 hours before randomization.	N=629 Intervention 1: Fidaxomicin 200 mg 2 times/day (n=302) Intervention 2: Vancomycin 125 mg 4 times/day (n=327) Treatment duration: 10 days Followup period: 30 days	a. Clinical cure, defined by the resolution of diarrhea (i.e., three or fewer unformed stools for 2 consecutive days), with maintenance of resolution for the duration of therapy and no further requirement (in the investigator's opinion) for therapy for CDI as of the second day after the end of the course of therapy. b. Clinical recurrence, defined by the reappearance of more than three diarrheal stools per 24-hour period within 4 weeks after the cessation of therapy; *C. difficile* toxin A or B, or both, in stool; and a need for retreatment for CDI c. Median time to resolution of diarrhea d. All-cause mortality e. Adverse events	Allocation concealment: adeqaute Blinding: double Intention-to-treat analysis: modified (subjects with-drawing before treatment, had ≤3 bowel motions in 24 hours, or tested negative for *C. difficile* toxin were excluded Withdrawals and dropouts reported: yes

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
Musher, 2009[23] Region: USA Funding source: Department of Veterans Affairs	Population: Mild or severe symptomatic inpatient adults with comorbid conditions Mean age: 63 % women: 35 Ethnicity: White 69%; black 31% (45% in nitazoxanide group, 19% in vancomycin group) Inclusion criteria: EIA results positive for *C. difficile* toxin (Premier Toxins A & B; Meridian Bioscience), ≥3 loose stools within 24 h and ≥1 of the following additional findings: fever (temperature, 138.37C), abdominal pain, and/or leukocytosis Severity: patients with ≥2 points were considered to have severe CDI based on an assessment score developed for this study. One point each was given for age ≥60 years, >7 stools/day, temperature >38.3°C, albumin level <2.5 mg/dL, or peripheral WBC count >15,000 cells/mm^3	N=50 (severe 41%, n=20) Intervention 1: Vancomycin 125 mg 4 times/day (n=27) Intervention 2: Nitazoxanide 500 mg 2 times/day + placebo pill (n=23) Treatment duration: 10 days Followup period: 21 days	a. End-of-treatment response (cure), # of patients (defined as complete resolution of all symptoms and signs attributable to CDI during the 3 days after completion of therapy) b. Relapse, # of patients (defined as a return of symptoms after an initial response but within 31 days after the onset of treatment with *C. difficile* toxin detected in stool by EIA or patient was re-treated empirically for CDI and responded to treatment. c. All-cause mortality d. Adverse events	Allocation concealment: adequate (sequentially numbered identical packages) Blinding: double Intention-to-treat analysis (all subjects randomized included in the analyses): partially, one subject was found to have IBD (an exclusion criteria) and was removed Withdrawals and dropouts reported: 9 (18%)

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
Zar, 2007[24] Region: USA Funding source: none stated	Population: Mild or severe symptomatic inpatient adults with comorbid conditions Mean age: 58 (47% <60 years) % women: 45 Inclusion criteria: *Clostridium difficile*-associated diarrhea (CDI), testing positive for *C. difficile* cytotoxin Severity: patients with ≥2 points were considered to have severe CDI based on an assessment score developed for this study. One point each was given for age >60 years, temperature >38.3°C, albumin level <2.5 mg/dL, or peripheral WBC count >15,000 cells/mm^3 within 48 h of enrollment. Two points were given for endoscopic evidence of pseudo-membranous colitis or treatment in the intensive care. All patients had received antimicrobial treatment prior to onset of CDI (>90% within 14 days)	N=172 (mild 54%, severe 46% based on 150 patients completing trial) Intervention 1: Vancomycin (liquid) 125 mg 4 times/day + placebo pill (n=82) Intervention 2: Metronidazole (oral) 250 mg 4 times/day plus placebo liquid (n=90) Treatment duration: 10 days Followup period: 21 days	a. Cure, # of patients (defined as resolution of diarrhea by day 6 of treatment and a negative result of a *C. difficile* toxin A assay at days 6 and 10 of treatment) b. Relapse, # of patients (defined as recurrence of *C. difficile* toxin A-positive diarrhea by day 21 after initial cure) c. All-cause mortality	Allocation concealment: adequate (controlled by pharmacy) Blinding: double Intention-to-treat analysis: no, completers only Withdrawals and dropouts reported: 22 (13%)

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
2. Trials Included in Cochrane Systematic Review[24]				
Lagrotteria, 2006[26] Region: Canada Funding source: The Physicians' Services Incorporated Foundation	Population: Symptomatic adults (95% inpatients and 5% outpatients) Mean age: 69 years women: 59% Inclusion criteria: diagnosis of CDI on the basis of the Society for Healthcare Epidemiology of America definition, laboratory confirmation of the presence of *C. difficile* toxins A and B using an enzyme immunoassay, and no other etiology for diarrhea	N=39 Intervention 1: Metronidazole 500 mg 3 times/day (n=20) Intervention 2: Metronidazole 500 mg 3 times/day and rifampin 300 mg 2 times/day (n=19) Treatment duration: 10 days Followup period: 30 days	a. Clinical improvement (cure) at study day 10, # (%) of patients (defined as becoming asymptomatic during the treatment course. Failure defined as persistent symptoms and signs after 10 days of antimicrobial therapy) b. Experienced relapse by study day 40, # (%) of patients (defined as recurrence of diarrhea in the followup period for those patients who initially experienced a clinical cure) c. Laboratory-confirmed relapse by study day 40, # of patients d. Time to clinical improvement (days) e. Time to relapse (days) f. All-cause mortality g. Adverse events	Allocation concealment: unclear (numbered packages) Blinding: single (study staff) Intention-to-treat analysis: yes Withdrawals and dropouts reported: 7 (18%)

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
Musher, 2006[27] Region: USA Funding source: Romark Pharmaceuticals	Population: Symptomatic adults, a substantial proportion had severe, comorbid conditions Mean age: 68 women: 24% Ethnicity: White 77%; black 17%; Hispanic 6% Inclusion criteria: inpatients >18 years of age with diarrhea (defined as ≥3 unformed stools within a 24-h period), an enzyme immunoassay result positive for *C. difficile* toxin, and ≥1of the following findings: fever, abdominal pain, or leukocytosis	N=142 Intervention 1: Metronidazole 250 mg 4 times/day (n=44) Intervention 2: Nitazoxanide 500 mg 2 times/day for 7 days (n=49) Intervention 3: Nitazoxanide 500 mg 2 times/day (n=49) Treatment duration: 10 days unless noted Followup period: 31 days	a. Response to therapy, assessed 3 ways: (1) time to resolution of symptoms of colitis; (2) complete clinical response at the end of 7 days of treatment, defined as return of normal stool pattern and absence of fever, abdominal pain, or leukocytosis, unless some other explanation was apparent; and (3) sustained clinical response 31 days after the beginning of treatment b. All-cause mortality c. Adverse events	Allocation concealment: not defined Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts reported: 32 (23%)
Wullt, 2004[28] Noren 2006[29] Region: Sweden Funding source: Region Skåne and the Scandinavian Society of Antimicrobial Chemotherapy, and Leo Pharma AB	Population: Symptomatic adult inpatients (51%) or outpatients (49%) on enrollment Mean age: 59 % women: 39 Inclusion criteria: age >18 years, lack of hypersensitivity to fusidic acid or metronidazole, a positive *C. difficile* toxin assay from feces within 6 days before enrolment, and a history of ongoing diarrhea (diarrhea defined as three or more loose stools per day for at least 2 days)	N=131 Intervention 1: Metronidazole 400 mg 3 times/day (n=64) Intervention 2: Fusidic acid 250 mg 3 times/day (n=67) Treatment duration: 7 days Followup period: 33 days	a. Clinical cure (defined as cessation of diarrhea within 5–8 days of initiating treatment, and clinical failure as persistence of diarrhea on days 5–8) b. Clinical recurrence, defined as the reappearance of diarrhea on days 8–40 in clinically cured patients who had completed 7 days of treatment c. Adverse events	Allocation concealment: adequate (coded containers of identical appearance) Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts reported: 17 (13%)

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
Wenisch, 1996[30] Region: Austria Funding source: none stated	Population: Symptomatic adults hospitalized for a minimum of 5 days Mean age: 42 % women: 48 Inclusion criteria: age of >18 years and the presence of CDI. Diarrhea was defined as >3 loose stools per day. CDI was diagnosed on the basis of the results of a *C. difficile* toxin assay and/or endoscopic evidence of typical colitis, with the finding of granulocytes in stools	N=126 Intervention 1: Metronidazole 500 mg 3 times/day (n=31) Intervention 2: Fusidic acid 500 mg 3 times/day (n=29) Intervention 3: Vancomycin 500 mg 3 times/day (n=31) Intervention 4: Teicoplanin (injection) 400 mg 2 times/day (n=28) Treatment duration: 10 days Followup period: 30 days	a. Clinical cure, # of patients (defined as no loose stools, gastro-intestinal symptoms, or fever and normalization of serum levels of C-reactive protein and leukocyte counts) b. Clinical failure (defined as persistence of diarrhea after 6 days of treatment c. Clinical relapse (defined as the reappearance of CDI and other symptoms during the followup period) d. Adverse events	Allocation concealment: not defined Blinding: none stated, teicoplanin administered as an injection, the other drugs orally Intention-to-treat analysis: no Withdrawals and dropouts reported: 7 (6%)
de Lalla, 1992[31] Region: Italy Funding source: none stated	Population: Symptomatic adult inpatients Mean age (range): 47 (18 to 83) % women: 70 Inclusion criteria: age of >18 years, presence of symptoms (diarrhea, sometimes combined with fever and abdominal pain), and stool culture and/or a rapid diagnostic test positive for *C difficile* and/or colonoscopic demonstration of the typical endoscopic picture of pseudomembranous colitis	N=51 Intervention 1: Vancomycin 500 mg 4 times/day (n=24) Intervention 2: Teicoplanin 100 mg 2 times/day (n=27) Study duration: 10 days Followup period: 30 days	a. Cure, # of patients (defined as elimination of symptoms and signs were) b. Failure, # patients (defined persistence of diarrhea after 6 days of treatment) c. Relapse (defined as reappearance of diarrhea and other symptoms in the 1-month followup period) d. All-cause mortality e. Adverse events	Allocation concealment: not defined Blinding: none stated Intention-to-treat analysis: no Withdrawals and dropouts reported: 5 (10%)

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
Fekety, 1989[32] Region: USA Funding source: NIH and Upjohn Company	Population: Moderately or severely ill symptomatic inpatients adults (plus one infant) Mean age/range: 54 (1 to 76) % women: gender not reported Inclusion criteria: antibiotic associated diarrhea plus at least one stool specimen that demonstrated both *C difficile* and its cytotoxin. All patients were moderately or severely ill, or unresponsive to supportive therapy (patients with mild illness as judged physicians were treated supportively, and not entered into the study)	N=56 Intervention 1: Vancomycin 500 mg 4 times/day (n=22) Intervention 2: Vancomycin 125 mg 4 times/day (n=24) Study duration: 10 days Followup period: up to 6 weeks after treatment	a. Treatment response (cure) based diarrhea resolution (defined as patients stating their bowel function is normal, or when they were having ≤3 movements a day and their stools were semiformed) Patients whose diarrhea ceased within 7 days after treatment were considered to have a good response; patients whose diarrhea ceased but after 7 days of treatment were considered simply to have responded b. Mean duration of symptoms, days c. Adverse events	Allocation concealment: not defined Blinding: physicians were blinded to treatment assignment Intention-to-treat analysis: no Withdrawals and dropouts reported: 10 (18%)
Dudley, 1986[33] Region: USA Funding source: Upjohn Company	Population: Symptomatic adult inpatients Mean age: 69 % women: 60 (evaluable subjects (n=30) only for age and gender) Inclusion criteria: antibiotic associated diarrhea (≥4 loose stools were passed for ≥2 consecutive days, signs and symptoms of *C difficile*-induced diarrhea and its cytotoxin	N=62 Intervention 1: Vancomycin 500 mg 4 times/day (n=31) Intervention 2: Bacitracin 25,000 mg 4 times/day (n=31) Study duration: 10 days Followup period: up to 60 days	a. Treatment response (cure) based diarrhea resolution (defined as ≤4 loose stools were passed for ≥2 consecutive days) b. Treatment failure (defined as diarrhea and other symptoms worsened and were crossed over to the alternative drug in a blinded manner. Patients worsening after 5 days of the crossed over therapy were considered failures and removed from the study) c. All-cause mortality d. Adverse events	Allocation concealment: adequate (coded amber bottles prepared by pharmacy) Blinding: double Intention-to-treat analysis: no Withdrawals and dropouts reported: 32 (52%)

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
Young, 1985[34] Region: Australia Funding source: Upjohn Company and the McGauran Trust	Population: Symptomatic adult inpatients Mean age: 62 (gender not reported) Inclusion criteria: antibiotic associated diarrhea (≥4 loose stools were passed for ≥2 consecutive days, signs and symptoms of *C difficile*-induced diarrhea and its cytotoxin	N=42 Intervention 1: Vancomycin 125 mg 4 times/day (n=21) Intervention 2: Bacitracin 20,000 mg 4 times/day (n=21) Study duration: 7 days Followup period: 28 days	a. Treatment response (cure) based diarrhea resolution (defined as <3 times/day by the time the last capsule was given. Day of resolution defined as first day of <3 stools, provide frequency did not go above >2) b. Treatment relapse c. Mean days to 50% improvement	Allocation concealment: adequate (identical red capsules and sealed codes held in pharmacy) Blinding: double Intention-to-treat analysis: yes for initial therapy Withdrawals and dropouts reported: all completed initial treatment
Teasley, 1983[35] Region: USA Funding source: Veterans Affairs and Searle Laboratories	Population: Symptomatic inpatient adults Mean age: 65 % women: 1 Inclusion criteria: *C difficile*-associated diarrhea and its cytotoxin. All patients had received antimicrobial treatment 14-55 days prior to diarrhea	N=101 Intervention 1: Vancomycin 500 mg 4 times/day (n=56) Intervention 2: Metronidazole 250 mg 4 times/day (n=45) Study duration: 10 days Followup period: 21 days	a. Cure (defined as diarrhea resolved within 6 days of treatment, toleration of complete treatment course, and no relapse in the 21-day followup period) b. Treatment response based diarrhea resolution (defined as <2 stools formed /day) c. Treatment failure (defined as ≤4 loose stools/day after 6 days of treatment. d. Treatment relapse (defined as recurrence with 21 days of diarrhea with ≤4 loose stools/day for a minimum of 2 days)	Allocation concealment: not defined Blinding: none stated Intention-to-treat analysis: no Withdrawals and dropouts reported: 7 (7%)

Appendix Table C4. Evidence table for standard antibiotic treatments (continued)

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control (s) / Study Duration	Outcomes Evaluated	Study Quality
Keighley, 1978[36] Region: UK Funding source: none stated	Population: Symptomatic adult inpatients. Subjects with evidence of cytotoxins separated with from subjects with *C difficile* on culture Age and gender not reported Inclusion criteria: postoperative diarrhea (≥3 loose stools/day or colostomy output >1 liter/day. All patients had received antimicrobial treatment prior to diarrhea	N=44 Intervention: Vancomycin 125 mg 4 times/day (n=22) Control: Placebo (n=22) Study duration: 5 days Followup period: unclear, up to 29 days in the control group	a. Treatment response based diarrhea resolution (defined as normal stool, improved, same, or worse. Normal was defined as 1 solid stool/day, the others were not described) b. Adverse events	Allocation concealment: adequate (identical looking placebo and based code held in pharmacy) Blinding: unclear if double ("identical looking placebo") Intention-to-treat analysis: yes Withdrawals and dropouts reported: all completed initial treatment

Appendix Table C5. Assessment of study quality of individual metronidazole trials

Study	Allocation Concealment	Blinding	Intention-to-Treat Analysis	Withdrawals and Dropouts Reported	Study Quality Good, Fair, or Poor
Versus Vancomycin					
Zar 2007[24] (n=172), subset with severe disease (46% based on 150 completing trial)	Adequate	Double	Completers only	22 (13%)	Fair
Wenisch 1996[30] (n=62)	Not defined	None stated	No	7 (6%)*	Poor
Teasley 1983[35] (n=101)	Not defined	None stated	No	7 (7%)	Poor
Versus Nitazoxanide					
Musher 2006[27] (n=142)	Not defined	Double	No	32 (23%)	Poor
Versus Metronidazole Plus Rifampin					
Lagrotteria[26] (n=39)	Unclear (numbered packages but no further detail)	Single (study staff)	Yes	7 (18%)	Fair

* Based on all subjects, 4-arm trial.

Appendix Table C6. Assessment of study quality of individual vancomycin trials

Study	Allocation Concealment	Blinding	Intention-to-Treat Analysis	Withdrawals and Dropouts Reported	Study Quality Good, Fair, or Poor
Versus Metronidazole					
Zar, 2007[24] (n=172), subset with severe disease (46% based on 150 completing trial)	Adequate	Double	No, completers only	22 (13%)	Fair
Wenisch, 1996[30] (n=62)	Not defined	None stated	No	7 (6%)*	Poor
Teasley, 1983[35] (n=101)	Not defined	None stated	No	7 (7%)	Poor
Versus Nitazoxanide					
Musher, 2009[23] (n=50), subset of 20 with severe disease	Adequate	Double	Partially, one subject removed	9 (18%)	Good
Versus Fidaxomicin					
Louie, 2011[23]	Adequate	Double	Partially	33 (5%)	Good
Versus Bacitracin					
Dudley, 1986[33] (n=62)	Adequate	Double	No	32 (52%)	Fair
Young, 1985[34] (n=42)	Adequate	Double	Yes for initial therapy	None	Good
Versus Placebo					
Keighley, 1978[36] (n=44)	Adequate	Unclear (“identical placebo”)	Yes	All completed initial treatment	Good

* Based on all subjects, 4-arm trial.

Appendix Table C7. Summary of strength of evidence for CDI—Key Question 3c: vancomycin studies

Key Question, # Studies (# Participants)	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/ Conclusion
Versus Metronidazole						
Initial clinical cure; 3 (335)	RCT	High	Consistent	Direct	Imprecise	Low
Clinical recurrence; 3 (283)	RCT	High	Consistent	Direct	Imprecise	Low
Initial clinical cure, severe disease; 1 (69)	RCT	Medium	Unknown	Direct	Precise	Low
Clinical recurrence, severe disease; 1 (59)	RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Versus Nitazoxanide						
Initial clinical cure; 1 (50)	RCT	Low	Unknown	Direct	Imprecise	Low
Clinical recurrence; 1 (37)	RCT	Low	Unknown	Direct	Imprecise	Low
Initial clinical cure, severe disease; 1 (20)	RCT	Low	Unknown	Direct	Imprecise	Insufficient
Clinical recurrence, severe disease; 1 (15)	RCT	Low	Unknown	Direct	Imprecise	Insufficient
Versus Fidaxomicin						
Initial clinical cure; 1 (629)	RCT	Low	Unknown	Direct	Precise	Moderate
Clinical recurrence; 1 (518)	RCT	Low	Unknown	Direct	Precise	Moderate
Versus Bacitracin						
Initial clinical cure; 2 (81)	RCT	Low	Consistent	Direct	Imprecise	Low
Clinical recurrence; 2 (37)	RCT	Low	Consistent	Direct	Imprecise	Low
Versus Placebo						
Initial clinical cure; 1 (21)	RCT	Low	Unknown	Direct	Precise	Moderate

RCT = randomized controlled trial

Appendix Table C8. Summary of strength of evidence for CDI—Key Question 3c: metronidazole studies

Key Question, # Studies (# Participants)	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/ Conclusion
Versus Vancomycin						
Initial clinical cure; 3 (335)	RCT	High	Consistent	Direct	Imprecise	Low
Clinical recurrence; 3 (283)	RCT	High	Consistent	Direct	Imprecise	Low
Initial clinical cure, severe disease; 1 (69)	RCT	Medium	Unknown	Direct	Precise	Low
Clinical recurrence, severe disease; 1 (59)	RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Versus Nitazoxanide						
Initial clinical cure; 1 (142)	RCT	High	Unknown	Direct	Imprecise	Low
Clinical recurrence; 1 (97)	RCT	High	Unknown	Direct	Imprecise	Low
Versus Metronidazole Plus Rifampin						
Initial clinical cure; 1 (142)	RCT	Medium	Unknown	Direct	Imprecise	Low
Clinical recurrence; 1 (97)	RCT	Medium	Unknown	Direct	Imprecise	Low

RCT = randomized controlled trial

Appendix Table C9. Assessment of study quality of individual nonstandard treatment trials

Study	Allocation Concealment	Blinding	Intention-to-Treat Analysis	Withdrawals and Dropouts Adequately Described	Study Quality *Good, Fair or Poor*
Adjuvant Probiotics (With Standard Therapy) Versus Placebo (With Standard Therapy)					
Wullt, 2003[37] (n=29)	Not defined	Double	No	Yes	Fair
Surawicz, 2000[38] (n=168, 32 with recurrent CDI)	Adequate	Double	Yes	Yes (none reported)	Good
McFarland, 1994[39] (n=124)	Adequate	Double	Yes	Yes	Good
C. difficile Immune Whey Versus Active Control (Metronidazole)					
Mattila, 2008[40] (n=40)	Not defined	Double	No	Yes	Fair
Absorptive Resin Versus Active Placebo					
Mogg, 1982[41] (n=48)	Possibly adequate	None stated	No	Yes	Fair

CDI = Clostridium difficile infection

Appendix Table C10. Summary of evidence for CDI—Key Question 4

Key Question, # Studies (# Participants)	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/ Conclusion
Probiotics and Prebiotics (Adjuvant to Standard Care) Versus Placebo and Standard Care						
Resolution of CDI; 3 (185*)	RCT	Low	Consistent	Direct	Imprecise	Low
Prevention of CDI; 8 (1756)	RCT	Low	Consistent	Direct	Imprecise	Low
Prevention of recurrence of CDI; 3 (339)	RCT	Medium	Consistent	Direct	Imprecise	Low
Monoclonal Antibodies (Adjuvant to Standard Care) Versus Placebo and Standard Care						
Prevention of recurrence of CDI; 1 (200)	RCT	Medium	Unknown	Direct	Imprecise	Low
Resolution of CDI; 1 (n=40)	RCT	Medium	Unknown	Direct	Imprecise	Low
Colestipol (an Absorptive Resin) Versus Placebo						
Resolution of CDI; 1 (n=48)	RCT	Medium	Unknown	Direct	Imprecise	Low

CDI = C. difficile infection; RCT = randomized controlled trial

* Includes only patients with C. difficile positive stools. Some trials, particularly the prevention studies, enrolled patients who were negative for C. difficile.

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
McDonald, 1984[42] Treatment	Male, age 76 years Tx for diarrhea and PSC per sigmoidoscopy	Cholestyramine (toxin absorbing resin) 12 grams(g)/day (d)orally	PMC resolved at autopsy	CD toxin + stools for 1 month after symptomatic relief CD culture + stools for 1 month	Cholestyramine particles in arterial and venous vessel walls at autopsy Ulcerated esophagus was likely portal
Kunimoto, 1986[43] Treatment for recurrent CDI	Female, age 38 years with PMC and CD cytotoxin and 4 recurrences of symptoms after vancomycin and metronidazole	Cholestyramine 12 day/orally x 12 months.	"Rapid symptoms relief"		Not reported
Kimura, 2007[44] Treatment	2 men, age 71 and 54 years with PMC by colonoscopy, CD toxin A and septic shock	IV "hemoperfusion" agent: Vancomycin (2 g/d) orally + polymixin B-immobilized fiber 80–100 mg/d IV x 7–14 days		CD toxin became negative after 7 days PMC resolved after 7 days	Not reported
Tvede, 1989[45] Treatment for chronic relapsing CDI	6 patients with chronic relapsing CDI 1 male and 5 females, age 6–72 years 6 previously treated with vancomycin, 1 treated with cholestyramine and vancomycin and 5 were treated with metronidazole also	Fecal flora reconstitution: enema of fresh feces from a healthy relative 1 patient Enema of mixture of 10 strains of bacteria: E. coli (1109 & 1108-1), *Cl innocuum, Cl ramosum, Bact. Ovatus, Bact. vulgatus, Cl bifermentans, Bact. Thetaiotao-micron, Peptostrepto-coccus productus, Cl bifermentans*		All had stools negative for CD toxin after enema and at 1 yr followup All had stools negative for CD culture after enema and at 1 yr followup	Not reported

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI (continued)

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
Persky 2000[46] Treatment for recurrent CDI	Female, age 60 years who failed vancomycin treatment of CDI	Fecal flora reconstitution: enema of fresh feces from a healthy relative 1 patient	Diarrhea resolved	Stools negative for CD toxin	Not reported
Macconnachie, 2009[47] Treatment for recurrent CDI	15 patients with recurrent CDI which was defined as relapse of loose stool following antibiotic treatment for CD toxin positive stool 14 females, age = 81.5 (68-95) years (median [range]) 11 were inpatients and 4 were newly readmitted after recent discharge; all had several comorbidities and were seriously ill Retrospective chart review	Fecal flora reconstitution: Stool from healthy relatives administered by nasogastric tube Donors were administered a proton pump inhibitor and oral vancomycin (125 mg 4 times/d) up to 12 hours prior to reconstitution	11 (73%) with diarrhea were symptom free of diarrhea at followup and 4 had a relapse of diarrhea Followup was at 16 (4–24) weeks (median [range])		Reported as none
Rohlke, 2010[48] Treatment for recurrent CDI	19 patients with recurrent CDI defined as CD toxin positivity and symptoms after at least 3 courses of antibiotic treatment 17 females, mean age = 49 years	Fecal flora reconstitution: Stool from healthy relatives, partners, or housemates administered via colonoscopy	18 (95%) became free of symptoms after initial treatment for 6–60 mos. 3 (17%) redeveloped symptoms after 6–48 mos.		Not reported

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI (continued)

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
Yoon, 2010[49] Treatment for recurrent or refractory CDI	12 patients with refractory or recurrent CDI Defined as having diarrhea and symptoms of cramps and fever and a history of a positive CD toxin assay despite treatment with antibiotics 9 females; age = 66 (30–68) years (mean (range) Retrospective chart review	Fecal flora reconstitution: Stool from healthy relatives or friend administered via colonoscopy	12 (100%) had cessation of diarrhea and other symptoms within 3–5 days. Follow-up ranged 3 wks to 8 years. No relapse reported.		Reported as none
Silverman, 2010[50] Treatment for recurrent CDI	7 patients recurrent CDI defined as with diarrhea after a positive stool toxin test and antibiotic treatment 50% females, age range = 30–88 years; all lived at home after developing CDI in hospital Patients were treated with a standard antibiotic and probiotic (*S. boulardii*) up to 24–48 hours before procedure	Fecal flora reconstitution: Donor stools from relatives were infused by low-volume enema by self or family member	7 (100%) were free of diarrhea for up to 14 mos. followup		One patient developed infectious irritable bowel symptoms (alternating constipation and diarrhea) but *C. difficile* toxin test was negative

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI (continued)

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
MacGregor, 2002[51] Treatment	Female, age 42 years with multiple health problems then respiratory failure and critically ill Developed CDI, toxin positive Failed metronidazole switched to vancomycin and yogurt added	Probiotic: yogurt with live cultures (supermarket brand) + vancomycin			*S. pneumonaie* and secondary *L. rhamnosus* septicemia and death
Pakyz, 2007[52] Treatment for recurrent CDI	Female, age 87 years with recurrent diarrhea and *C. difficile* antigen in stool	Probiotic: lactinex (lactobacillus) 1 g orally 3x/day + Metronidazole	Loose watery stools continued for 5 days	CD antigen in stools remained even with symptomatic relief on vancomycin. Switched to oral vancomycin with symptomatic relief	Not reported
Munoz, 2005[53] Treatment	Case studies + Retrospective chart review of ICU pts + review of 57 patients literature review. 3 ICU patients 3 ICU patients (females in 70s) with *S. cerevisiae* fungemia Charts of 41 (with 14 ICU) patients over 1 month of fungemia outbreak were reviewed	Probiotic: 3 cases were treated with Ultralevura for CDI 2/41 patients without fungemia received probiotic		Probiotic cultures grew heavy yeast (>1 million cfu/ml) Mortality: 28% (17/60)	60 patients total with fungemia, 28/47 (60%) in ICU, 26 (46%) were treated with the probiotic

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI (continued)

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
Seal, 1987[54] Treatment	2 patients, age 88 and 76 years, with CDI toxin positive, who failed antibiotic treatment.	Nontoxigenic strain of *C. difficile* (M-I) previously shown to protect hamsters One ml was suspended in 50 ml of milk to yield ~10 7 CFU *of C. difficile/*ml. Given as a single oral dose on 3 successive days.	Symptoms decreased in 2 patients and CD toxin was (1) eventually 1 patient had a relapse of CD toxin and diarrhea x 2d 17 d after improvement		Constipation in 1 patient
Taylor, 2008[55] Phase 2 safety study	30 subjects, mean age 27.5 years (range 20-53) 33% male 5 cohorts of 6 subjects each	Monoclonal antibody to CD toxin A (CDAI)			No serious AEs possibly, probably or definitely associated to CDI 3 moderate severity AEs (low BP, diarrhea) 18 mild severity (headache, nausea, loose stools, abdominal discomfort, BP changes)
Herpers, 2009[56] Treatment for severe refractory CDI	4 patients with diarrhea, positive *C. difficile* toxin stool and pseudomembranes as well as septic or hypovolemic shock and other serious health problems 2 males, 59 and 36 years old and 2 females, 36 and 82 years old	Intravenous tigecycline 100 mg x 1 dose then 50 mg twice/day for 7-24 days 3 patients were treated with standard antibiotics along with tigecycline		Clinical signs (e.g., diarrhea) improved within 7 d *C. difficile* toxin became negative in 3 patients within 7 d and after continued oral vancomycin in 1 patient in 2 weeks No recurrence was reported in 3 weeks	

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI (continued)

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
Sougioultzis, 2005[57] Treatment CD Vaccine	Subject 1: Male, age 51 years Subject 2: Female, age 71 years Subject 3: Female, age 33 years All had ≥3 unformed bowel movements per day for ≥2 days, associated with a positive stool toxin test for *C. difficile* (either tissue culture cytotoxin assay or toxin A or B enzyme immunoassay) that occurred within 30 days of discontinuation of therapy with metronidazole or oral vancomycin that had been administered for treatment of a prior episode of CDI	*C difficile* toxoid vaccine form purified toxins A and B, injected IM at the deltoid region on 4 occasions, on days 0, 7, 28, and 56.		Subjects discontinued treatment with oral vancomycin after their fourth and final inoculation with the *C difficile* toxoid vaccine One of the 3 subjects did not show increase in serum antitoxin antibodies or serum toxin neutralizing activity	No AE that were definitely or probably related to vaccination. Adverse events that were possibly related to vaccination included a mild headache (subject 1) and mild abdominal pain (subject 2). Subject 2 also reported transient polyarthralgia after the fourth inoculation and later developed atypical polyarthritis with a normal erythrocyte sedimentation rate, a negative rheumatoid factor test, and slightly elevated C-reactive protein. Approximately 2 months after completion of the study, a clinical diagnosis of polymyalgia rheumatica was made by a rheumatologist

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI (continued)

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
Kotloff, 2001[58] Randomized, double-blind, Phase 1 study of CD vaccine	30 healthy adults (no ages reported)	Vaccine, 6.25, 25 or 100 mg given IM Five subjects at each dose level received soluble toxoid vaccine, and five subjects received an equivalent dose of toxoid adsorbed to alum.			No serious adverse events during the study: rash = 8 (subjects); abdominal pain = 6; athralgia = 2; diarrhea = 2 All subjects had local pain at injection site, especially those who received toxoid adsorbed to alum, pruritus (without urticaria) at the site of injection n = 6
McPherson, 2006[59] Treatment for recurrent or refractory CDI	14 patients with diarrhea and *C. difficile* toxin positive stools despite standard antibiotics Age = 79 (54–91) years (median [range])	Intravenous immunoglobulin (IVIG) 150–400 mg/kg x 1-2 doses	9 /14 (64%) resolved diarrhea 3/9 surviving had a recurrence		Reported as none
Murphy 2006 [60] Treatment for recurrent CDI	1 female age 57 years with recurrent and refractory diarrhea and *C. difficile* toxin-positive stools after standard antibiotics and S. boulardii probiotic	IVIG 400 mg x 3 days	Diarrhea resolved but stools remained positive for *C. difficile* toxin		Reported as none

Appendix Table C11. Case studies/series and potential harms of nonstandard interventions for CDI (continued)

Study/ Study Focus	Subject/Study Details	Interventions	Clinical Diarrhea Outcomes	CD Toxin, CD Culture, or Other	Adverse Effects (AE) Harms
Hassoun 2007[61] Treatment	1 male age 72 years with diarrhea, abdominal pain, nausea and ulcerative colitis by colonoscopy after chemotherapy for cancer Treatment included numerous antibiotics including oral vancomycin	IVIG 400 mg for I dose	Diarrhea and clinical symptoms and bowel dilatation resolved within 7 days	Hassoun 2007 Treatment	1 male age 72 years with diarrhea, abdominal pain, nausea and ulcerative colitis by colonoscopy after chemotherapy for cancer Treatment included numerous antibiotics including oral vancomycin
Abougergi, 2010[62] Treatment	21 patients with *C. difficile* colitis defined as *C. difficile* cytotoxin positive feces + diarrhea + other symptoms of abdominal pain and/or distention or fever +a leukoid reaction (white blood count of 20,000 cell/mm^3 or more) + radiographic evidence of colitis or pseudomembranes by colonoscopy or sigmoidoscopy 13 females and 8 males; age = 68 years (13) (mean [SD]) All patients were seriously ill with sepsis and other comorbidities Retrospective chart review	IVIG as an adjuvant treatment to standard antibiotics Dose: mode of 250 mg/kg for 1–3 days (dose range = 200–1,250 mg/kg)	9 patients (43%) survived with resolution of clinical symptoms of *C. difficile* colitis		Pulmonary edema in 1 patient

CD = C. difficile; CDI = C. difficile infection; IM = intramuscular; IVIG = intravenous immunoglobulin; PMC = PMC = pseudomembranous colitis

Appendix Table C12. Reviews and meta-analyses

Study	Title/Question Patient Population	# of Studies Patient N	Comparators	Outcomes Followup	Results
Diagnosis					
Planche, 2008[63] Searched 1994 to Nov 2007	Diagnosis of *Clostridium difficile* infection by toxin detection kits. Toxins A & B All inpatients	18 trials N=62 to 2,891 Meta-analysis	ELISA (Meridian, Techlab), Rapid antigen capture (Techlab), Rapid CI (Remel), EIA (BioMerieus) Rapid EIA (Meridian) compared to cell culture w/neutralisable toxin	Sensitivity, specificity	No test met acceptable criteria (sensitivity IQR >90%, and false positivity below 3%). No difference in diagnostic performance of commercially available tests. Most had higher specificity than sensitivity. Differences between tests likely due to assay threshold cutoff.
Prevention					
Garey, 2008[64] Searched 1966 to Aug 2007	Assess risk factors for recurrent CDI Adult inpatients	3 RCT, 9 observational Meta-analysis	Patients with recurrent versus patients with one episode only.	Studies generally 1 to 3 months	Continued use of non-*C. difficile* antibiotics after CDI diagnosis: OR 4.23 (2.10-8.55), use of antacid medication: OR 2.15 (1.13-4.08), older age: OR 1.62 (1.11 – 2.36). (Many risk factors not included in analysis due to limited literature.)
Bignardi, 1998[65] Searched to March 1996	Assess risk factors for CDI NR	49 studies	*C. difficile* cases versus individuals without diarrhea	CDI, *C. difficile* carrier	Risk factors with "substantive" evidence: age, severity of underlying diseases, nonsurgical gastrointestinal procedures, nasogastric tube, anti-ulcer medications, ICU, LoS, duration of antibiotic course, multiple antibiotics
Leonard, 2007[66] Searched 1966 thru 2005	Risk of enteric infection in patients taking acid suppression Primarily inpatient	25 observational studies N=1,382 Meta-analysis	Use of PPI or H2RA versus multiple control group types	Presence of enteric infection	PPI: OR 2.05 (1.47-2.85); H2RA: OR 1.48 (1.06 – 2.06); Overall: OR 1.95 (1.48-2.58). Significant heterogeneity between studies. ORs for other enteric infections were even greater. Index cases?
Kramer, 2006[67] Searched 1966 through 2005	How long do nosocomial pathogens persist on inanimate surfaces	NR number Experimental data		Range of reported duration of persistence	CDI spores: 5 months. Overall, high inoculum in cold rooms with higher humidity persist longest. No quality check.
Thomas, 2001[68] Searched 1966 to 2001	Antibiotics and hospital-acquired *C.difficile*-associated diarrhea Adult inpatients	48 observational studies	Use of antibiotics versus multiple control group types	Study quality	General study quality precludes meta-analysis of observational studies for relationships between antibiotics and C. diff. 2 studies provide valid evidence for cephalosporin, penicillin, and clindamycin.

Appendix Table C12. Reviews and meta-analyses (continued)

Study	Title/Question Patient Population	# of Studies Patient N	Comparators	Outcomes Followup	Results
Davey, 2005[69] Cochrane Searched Jan 1980 thru Jul 2005	Interventions to improve antibiotic prescribing practices for hospital inpatients Hospitals/units for all inpatients	66 studies, RCT to time series	60 interventions to improve prescribing practices versus usual processes	Presence of Gram negative-resistant bacteria, CDI, vancomycin-resistant enterococci, MRSA	Both persuasive and restrictive interventions were effective overall.
Treatment					
Koo, 2009[70] Searched thru Dec 2007	Antimotility agents for CDI treatment Adult inpatients	1 retrospective 19 case reports/series N = 55	With or without antibiotic use	Adverse events, clinical resolution	All patients with documented complications or mortality received antimotility drugs alone initially. 23 patients who received concurrent antibiotics did not experience complications. (Use of antimotility did not appear to shorten disease course in the 23 patients.)
Pillai, 2008[71] Cochrane Searched 1966 thru Oct 2007	Probiotics for treatment of *C. difficile*-associated colitis in adults Adults with recurrent CDI	4 trials	Use of probiotics, multiple forms, versus placebo	Resolution of diarrhea, negative stool for toxin assay or culture	Insufficient evidence to support use. Studies were small and lacked power.
Eddins, 2008[72] Jan 1996 thru Sept 2007	Probiotic or symbiotics for ADD, CDI, or radiation-induced diarrhea All patients	CDI:1 systematic review, 6 trials	Narrative		Sparse evidence may reduce risk for CDI or recurrence.
Segarra-Newnham, 2007[73] Searched 1970 thru March 2007	Probiotics for *C. difficile*-associated diarrhea: focus on *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii*	7 articles, care report to blinded trials	Narrative		Sparse evidence. Risks may outweigh benefits for debilitated and immunosuppressed patients, which are those most at risk for recurrent CDI.
McFarland, 2006[74] Searched 1977 to 2005	Probiotics for prevention of antibiotic associated diarrhea and treatment of *C. difficile* disease Primarily inpatient	31 trials; ADD 25, CDI 6 N = 3,164 Meta-analysis	Use of probiotics, multiple forms, versus placebo	New diarrhea episode associated with positive culture or toxin assay within 1 month of antibiotic exposure	ADD prevention: RR 0.43 (0.31–0.58). CDI treatment: RR 0.59 (0.41–0.85) Most benefit in CDI seen in treatment of patients with recurrent CDI, *S. boulardii* was effective agent.

Appendix Table C12. Reviews and meta-analyses (continued)

Study	Title/Question Patient Population	# of Studies Patient N	Comparators	Outcomes Followup	Results
Dendukuri, 2005[75] Searched up thru Mar 2005	Probiotic therapy for the prevention and treatment of *C.difficile*-associated diarrhea Adult inpatients	1 prevention trial, 3 treatment	Probiotics versus placebo; *L. acidophilus*, *L. plantarum*, *L. GG*, *Bifidocaterium bifidum*, *S. boulardii* (5)	Prevention of AAD 11 days to 8 weeks	No differences between groups for prevention. Only one found improvement for treatment. Subgroup analysis suggests limited to recurrent CDI. Dose was same as used in pediatric studies with positive results. Variability in CDI definition.
Nelson, 2007[25] Cochrane Searched 1966 thru April 2007	Antibiotic treatment for *C. difficile*-associated diarrhea (and need for stopping causative) in adults Inpatients	12 trials Meta-analysis	8 antibiotics, 1 placebo controlled	Resolution/ negative tests, recurrence/ positive tests, surgery, death	No single antibiotic clearly superior; teicoplanin showed some benefits over vancomycin, fusidic acid, metronidazole. Mild cases may be self-limiting without treatment. For prevention of spread, teicoplanin showed best bacteriologic cure.
Zimmerman, 1997[76] Searched 1978 thru 1996	Antibiotic treatment of *C. difficile* infection	9 trials Meta-analysis	5 antibiotics, 2 placebo controlled	Clinical resolution of diarrhea, relapse, negative test for toxin Average 1 month	Colestipol no better than placebo, but of other 4, no significant differences between types or doses of antibiotics for clinical resolution. Teicoplanin better than fusidic acid for relapse. Unclear if higher dose of teicoplanin reduces relapse.

References for Appendix Tables

Note that reference numbers for evidence tables in this appendix are different from those in the body of the report.

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Appendix D. Excluded Studies

Excluded References – C Difficile (General Search)

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