**Supplementary data**

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| Table A.1 MEDLINE Search strategy (1946-January 13 2015). |
| # | **Searches** | **Results** |
| 1 | exp *Clostridium difficile*/ | 5528 |
| 2 | exp Enterocolitis, pseudomembranous/ | 6388 |
| 3 | Clostridium diff\*.mp. | 9874 |
| 4 | C diff\*.mp. | 5470 |
| 5 | CDAD.mp. | 598 |
| 6 | or/1‐5 | 13979 |
| 7 | exp Practice Guideline/ | 19541 |
| 8 | exp Practice Guidelines as Topic/ | 82427 |
| 9 | Guideline\*.mp. | 289332 |
| 10 | Guidance\*.mp. | 66440 |
| 11 | Recommend\*.mp. | 417330 |
| 12 | (polic\* adj5 (statement\* or document\* or development\*)).mp. | 11030 |
| 13 | (consensus adj5 (statement\* or document\* or development\*)).mp. | 16449 |
| 14 | (Polic\* adj5 statement\*).mp. | 1831 |
| 15 | (Polic\* adj5 document\*).mp. | 1560 |
| 16 | (Polic\* adj5 development).mp. | 6718 |
| 17 | (Polic\* adj5 paper\*).mp. | 1822 |
| 18 | (Consens?s adj5 statement\*).mp. | 4316 |
| 19 | (Consens?s adj5 document\*).mp. | 1494 |
| 20 | (Consens?s adj5 development\*).mp. | 13016 |
| 21 | (Consens?s adj5 paper\*).mp. | 604 |
| 22 | or/7‐21 | 711495 |
| 23 | 6 and 22 | 720 |

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| Table A.2. Grey literature sources (inception to August 2015) |
| National Guidelines Clearinghouse (NGC; from the Agency for Healthcare Research and Quality in the United States, AHRQ) |
| Turning Research into Practice (TRIP) |
| Canadian Medical Association (CMA) |
| National Institute for Health and Care Excellence (NICE) |
| Scottish Intercollegiate Guidelines Network (SIGN) |
| Guidelines International Network (GIN) |
| Google Scholar |
| Centre for Disease Control (CDC) |
| European Centre for Disease Control (ECDC) |
| American Gastroenterology Association (AGA) |
| Institute for Clinical Systems Improvement (ICSI) |

| **Table A.3. AGREE II Instrument.** |
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| **Domain** | **Item** |
| **Scope and purpose** | 1. The overall objective(s) of the guideline is (are) specifically described.
 |
| 1. The health question(s) covered by the guideline is (are) specifically described.
 |
| 1. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
 |
| **Stakeholder involvement** | 1. The guideline development group includes individuals from all the relevant professional groups.
 |
| 1. The views and preferences of the target population (patients, public, etc.) have been sought.
 |
| 1. The target users of the guideline are clearly defined.
 |
| **Rigor of development** | 1. Systematic methods were used to search for evidence.
 |
| 1. The criteria for selecting the evidence are clearly described.
 |
| 1. The strengths and limitations of the body of evidence are clearly described.
 |
| 1. The methods for formulating the recommendations are clearly described.
 |
| 1. The health benefits, side effects and risks have been considered in formulating the recommendations.
 |
| 1. There is an explicit link between the recommendations and the supporting evidence.
 |
| 1. The guideline has been externally reviewed by experts prior to its publication.
 |
| 1. A procedure for updating the guideline is provided.
 |
| **Clarity of presentation** | 1. The recommendations are specific and unambiguous.
 |
| 1. The different options for management of the condition or health issue are clearly presented.
 |
| 1. Key recommendations are easily identifiable.
 |
| **Applicability** | 1. The guideline describes facilitators and barriers to its application.
 |
| 1. The guideline provides advice and/or tools on how the recommendations can be put into practice.
 |
| 1. The potential resource implications of applying the recommendations have been considered.
 |
| 1. The guideline presents monitoring and/ or auditing criteria.
 |
| **Editorial independence** | 1. The views of the funding body have not influenced the content of the guideline.
 |
| 1. Competing interests of guideline development group members have been recorded and addressed.
 |
| **Overall Guideline Assessment** | 1. Rate the overall quality of this guideline.
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| **Overall Guideline Assessment** | 1. I would recommend this guideline for use.
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| **Table A.4. Systems of evidence review and recommendation development used in guidelines** |
| **Guideline** | **System for summarizing evidence** | **System for assigning strength to recommendation** |
| **American Journal of Gastroenterology** | Modified GRADEHigh: if further research is unlikelyto change our confidence in the estimate of the effectModerate: if further research is likely to have an important impact and may change the estimate Low: if further research is very likely tochange the estimate | Modified GRADEStrong: when the evidence shows the benefit of the interventionor treatment clearly outweighs any riskConditional: when uncertainty exists about the risk – benefit ratio |
| **Association of Professionals in Infection Control and Epidemiology** | None | None |
| **European Society for Clinical Microbiology and Infectious Diseases** | OCEBM Levels of Evidence (2008) Level 1a: Systematic review (with homogeneity) ofrandomised controlled trialsLevel 1b: Individual randomised controlled trial (withnarrow confidence interval)Level 1c: Studies with the outcome ‘All or none’Level 2a: Systematic review (with homogeneity) of cohort studiesLevel 2b: Individual cohort study (including low-quality randomised controlled trials; e.g., <80% follow-up)Level 2c: ‘Outcomes’ research; ecological studiesLevel 3a: Systematic review (with homogeneity) of case–control studiesLevel 3b: Individual case–control studyLevel 4: Case series (and poor quality cohort and case–control studies)Level 5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or‘first principles’ | HICPAC categories for implementationIA: Strongly recommended for implementation andstrongly supported by well-designed experimental,clinical or epidemiological studiesIB: Strongly recommended for implementation andstrongly supported by some experimental, clinical orepidemiological studies and a strong theoreticalrationaleIC: Required for implementation, as mandated by federal and ⁄ or state regulation or standard (may vary among different states ⁄ countries)II: Suggested for implementation and supported bysuggestive clinical or epidemiological studies or atheoretical rationaleUnresolved issue: Practices for which insufficientevidence exists or no consensus regarding efficacy exists (no recommendation) |
| **Department of Health, Health Protection Agency** | Own system; combined evidence and recommendationA: Strongly recommended and supported by systematic review of randomised controlled trials (RCTs) or individual RCTsB: Strongly recommended and supported by non-RCT studies and/or by clinical governance reports and/or the CodeC: Recommended and supported by group consensus and/or strong theoretical rationale |
| **Infectious Diseases Society of America, Society for Healthcare Epidemiology of America** | Modified GRADEI. High: Highly confident that the true effect lies close to that of the estimated size and direction of the effect. Evidence is rated as high quality when there is a wide range of studies with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval.II. Moderate The true effect is likely to be close to the estimated size and direction of the effect, but there is a possibility that it is substantially different. Evidence is rated as moderate quality when there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide.III. Low The true effect may be substantially different from the estimated size and direction of the effect.Evidence is rated as low quality when supporting studies have major flaws, there is important variation between studies, the confidence interval of the summary estimate is very wide, or there are no rigorous studies, only expert consensus. | Own system(1) Basic practices: should be adopted by all acute care hospitals; potential to impact HAI risk clearly outweighs the potential for undesirable effects(2) Special approaches: can be considered for use in locations and/or populations within hospitals when HAIs are not controlled by use of basic practices; the intervention is likely to reduce HAI risk but where there is concern about the risks for undesirable outcomes, where the quality of evidence is low, or where evidence supports the impact of the intervention in select settings (eg, during outbreaks) or for select patient populations(3) Approaches that should not be considered a routine part of CDI prevention |

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| **Table A.5. Rating evidence using the OCEBM system.** |
| **Question** | **Step 1 (Level 1\*)** | **Step 2 (Level 2\*)** | **Step 3 (Level 3\*)** | **Step 4 (Level 4\*)** | **Step 5 (Level 5\*)** |
| **How common is the problem?** | Local and current random sample surveys (or censuses) | Systematic review of surveys that allow matching to local circumstances\*\* | Local non-random sample\*\* | Case-series\*\* | n/a |
| **Is this diagnostic or monitoring test accurate? (Diagnosis)** | Systematic review of cross sectional studies with consistently applied reference standard and blinding | Individual cross sectional studies with consistently applied reference standard and blinding | Non-consecutive studies, or studies without consistently applied reference standards\*\* | Case-control studies, or “poor or non-independent reference standard\*\* | Mechanism-based reasoning |
| **What will happen if we do not add a therapy? (Prognosis)** | Systematic review of inception cohort studies | Inception cohort studies | Cohort study or control arm of randomized trial\* | Case-series or casecontrol studies, or poor quality prognostic cohort study\*\* | n/a |
| **Does this intervention help? (Treatment Benefits)** | Systematic review of randomized trials or n-of-1 trials | Randomized trial or observational study with dramatic effect | Non-randomized controlled cohort/follow-up study\*\* | Case-series, case-control studies, or historically controlled studies\*\* | Mechanism-based reasoning |
| **What are the COMMON harms? (Treatment Harms)** | Systematic review of randomized trials, systematic review of nested case-control studies, nof-1 trial with the patient you are raising the question about, or observational study with dramatic effect | Individual randomized trial or (exceptionally) observational study with dramatic effect | Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)\*\* | Case-series, case-control, or historically controlled studies\*\* | Mechanism-based reasoning |
| **What are the RARE harms? (Treatment Harms)** | Systematic review of randomized trials or n-of-1 trial | Randomized trial or (exceptionally) observational study with dramatic effect |
| **Is this (early detection) test worthwhile? (Screening)** | Systematic review of randomized trials | Randomized tria | Non -randomized controlled cohort/follow-up study\*\* | Case-series, case-control, or historically controlled studies\*\* | Mechanism-based reasoning |
| \* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.\*\* As always, a systematic review is generally better than an individual study. |

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| Table A.6. Hierarchy of Infection Prevention and Control Research. |
| Study design | **Level** |
| Systematic review of RCTs | 1 |
| Systematic review of observational studies (all kinds) | 2 |
| RCT (including cluster RCT) | 2 |
| ITS, control group | 2 |
| Non-systematic review | 3 or 4 |
| Non-randomized cross-over control | 3 |
| Before after, control group | 3 |
| ITS, historical control | 3 |
| Before after study, historical control  | 4 |
| Case control study; must be related to recommendation | 4 |
| Diagnosis or prevalence study; must be related to recommendation | 4 |
| Case review | 4 |
| RCT or ITS with control, but with a surrogate outcome  | 4 |
| Ecological study (e.g. bacterial sampling); studies that do not have CDI outcome as result (i.e. make recommendations based on indirect evidence), regardless of the design or quality of the study | 5 |
| Not relevant, e.g. study does not involve CDI or prevention of CDI even indirectly | 5 |
| ITS, Interrupted time series; RCT, Randomized controlled trial. Notes: A study conducted during an outbreak will be downgraded one level, but not lower than 4. An observational study with a large effect will be upgraded one level, but not if it is conducted during an outbreak or if it’s a before-after study. |

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| Table A.7.. Limitations and actions to improve guideline quality. |
| Guideline | **Key limitations** | **Actions to improve next update**  |
| All guidelines | Guideline authors’ contributions to the guideline are not discussed | Outline the role of each author in the guideline development panel |
|  | No views and preferences sought of target population | Engage with patient advocacy groups |
|  | Limited or no systematic search for evidence, and selection criteria for studies (except Vonberg et al 2009) | Conduct a formal systematic review to find all available evidence |
|  | Limited or no description of strengths and limitations of evidence body and formal method of assigning strengths of recommendations | Adopt systematic method of guideline development, preferably GRADE |
|  | Limited discussion of health benefits, side effects, and risks of recommendations | Present details of discussions regarding benefits and harms during development of recommendations |
|  | The link between evidence and recommendations is not explicit | Be transparent about the quality of evidence used to support recommendations, and discuss the authors’ confidence regarding the potential impact that future research may have on recommendation; limit drawing conclusions about the effectiveness of single strategies from studies that implemented bundle strategies |
|  | No procedure for updating the guideline (except for Dubberke et al 2014) | Define criteria for updating guidelines, such as number of years of if large studies are published that may change current recommendations |
|  | Guidelines have a limited discussion on how to disseminate the guideline, and do not discuss potential barriers to its implementation | Obtain feedback from key stakeholders  |
|  | Limited discussion of resource implications of implementing guidelines | Conduct cost effectiveness analysis; if resources are limited, discuss previously conducted cost effectiveness analyses on relevant recommendations |
| AJG 2013 | Guideline was not peer reviewed prior to publication | See Hawkey 2008 |
|  | No advice or tools on how to put recommendations into practice | Include an implementation section to the guideline, with tools such as checklists, how-to manuals, etc. |
|  | No monitoring or auditing criteria for assessing the effect of the guideline have been described | Include a section on criteria to assess the implementation of guidelines, description of what and how often should be measured, etc. |
| APIC 2013 | Target users of guideline are not clearly defined | Specify which recommendations apply to which users  |
|  | Key recommendations are not easily identifiable | Summarize key recommendations in a single, clearly specified table |
|  | Views of funding body may have influenced the guideline | Be transparent about what influence the sponsor may have had on guideline development and reporting |
| ESCMID 2009 | Limited monitoring or auditing criteria for assessing the effect of the guideline have been described | See Surawitz 2013 |
|  | The recent guideline, published in 2014, only updated the treatment section, and additional research has been published on the subject | See Hawkey 2008 |
| HPA/DH 2008 | Guideline was not peer reviewed prior to publication | Conduct formal peer review, including the description of reviewers, their suggestions, and how their advice was used (if at all) in further development |
|  | None of the authors listed competing interests | For each author, list all potential financial and other conflicts of interest |
|  | The recent guideline, published in 2013, only updated the treatment section, and additional research has been published on the subject | Include a review of prevention strategies to update recommendations |
| SHEA/IDSA 2014 | See advice in “all guidelines” |  |
| ACG, American College of Gastroenterology; APIC, Association of Professionals in Infection Control and Epidemiology; DH, Department of Health; ECDC, European Centre for Disease Control and other collaborators; ESCMID, European Society for Clinical Microbiology and Infectious Diseases; HPA, Health Protection Agency; IDSA, Infectious Diseases Society of America; PHE, Public Health England; SHEA, Society for Healthcare Epidemiology of America. |

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| **Table A.8. Strength of recommendations, author-generated evidence assessment, and reviewer-generated evidence assessment for each recommendation made by each guideline.** |
|  | **AJG 2013** | **APIC 2013** | **ESCMID 2009** | **HPA/DH 2008** | **SHEA/IDSA 2014** |
|  | **Strength** | **Evidence A** | **Evidence R** | **Evidence R** | **Strength** | **Evidence A** | **Evidence R** | **Strength + Evidence A** | **Evidence R** | **Strength** | **Evidence A** | **Evidence R** |
| EDUCATION |
| Educate HCPs, staff, patients, and their families on CDI | - | 2,3,4,5 | IA | 1a,2b,4,5 | 4 | B | 3 | 1 | III | 2,3,4 |
| DIAGNOSIS AND SURVEILLANCE |
| Only test diarrheal patients for *C. difficile*, unless ileus present | S | H1 | 4,5 | - | IB | 2b,3b,4 | 4,5 | B | - | 3 | II | 5 |
| Do not repeat testing, unless recurrence is suspected | - | - | IB | 3b,4 | 4,5 | B | - | 3 | III | - |
| Determine baseline rate and threshold to identify high incidence | - | 3,5 | IB | 2b,2c | 4,5 | B | 4 | 1 | III | 3,4 |
| Store fecal samples from CDI cases for typing; compare isolates | - | - | IB | 1b,3b,4 | 5 | C | 5 | - |
| ANTIMICROBIAL STEWARDSHIP |
| Use antimicrobial stewardship; monitor CDI patients’ antibiotics | S | H | 3,4,5 | 3,4,5 | IB | 1a,2b,3b,4 | 2,3,4 | B | 2,3,4,5 | 1 | II | 2,3,4,5 |
| Minimize prescription of high-risk antimicrobials | - | - | - | - | 2 | II | 2,4 |
| HAND HYGEINE |
| Use alcohol based hand rubs | - | 3,4,5 | IB | 2b,2c | 4,5 | B | 3,4,5 | 12 | III | 3,4,5 |
| Use soap and water | - | 3,4,5 | IB | 2a,2b,2c,4 | 3,4,5 | A | 3,5 | 1 | III | 3,4,5 |
| Use soap and water only | - | 3,4,5 | - | - | 2 | III | - |
| PATIENT ISOLATION AND PERSONAL EQUIPMENT |
| Suspected or known CDI patients should be in a private room or with other CDI patients | S | H | 5 | 2,4,5 | IB | 1b,2b,4 | 3,4 | B | 5 | 1 | III | - |
| Isolation can be discontinued 48 hours after symptoms resolve | - | - | II | 4 | 4,5 | C | 5 | 1 | III | 5 |
| Isolate all patients with diarrhea while awaiting test result | - | 4,5 | - | B | 5 | 2 | III | 5 |
| Consider isolating CDI patient until discharge | - | 5 | - | - | 2 | III | - |
| Cohorted patients should be managed by designated staff | - | - | IB | 1b,4 | 3,4 | - | - |
| Use disposable equipment; dedicate non-disposable equipment | S | M | 23 | 3 | IA3,IB | 1b,2b,2c,4 | 23,3,4,5 | - | 1 | III | 3,5 |
| GLOVE AND PROTECTIVE CLOTHING USE |
| Gloves and gowns for staff of known or suspected CDI patient | S | M | 34 | 3,4,5 | IB | 1a,1b,2b,4 | 3,4,5 | B | - | 1 | II4, III | 3,4 |
| Gloves and gowns for visitors of known or suspected CDI patient | S | M | 34 | 2,4,5 | - | A5 | - | - | - | 2 |
| ENVIRONMENTAL CLEANING |
| Use EPA registered disinfectant with *C. difficile*-sporicidal label claim or 1,000 ppm chlorine-containing cleaning agents | S | H | 3,4,5 | 2,3,4,5 | IB | 2b,2c,4 | 3,4,5 | B | 3,4,5 | 2 | III | 4 |
| Use bleach solution for daily disinfection and discharge cleaning | - | 2,3,4,5 | - | B | 3,4,5 | 2 | III | 4 |
| NOVEL STRATEGIES |
| Use of alternate methods of disinfection (ultiraviolet light, HPV) | - | 3,4,5 | - | B | 4 | - | - | 3,4,5 |
| Use probiotics for prophylaxis | S | L | 2 | - | - | - | 1,2 | - | 1,2 | - | - | 1,2 |
| The APIC 2013 guideline did not assign a strength to each recommendation, nor did the authors assign evidence quality for each recommendation; thus, these were omitted. The HPA/DH guideline had a joint measure of evaluating both the strength and evidence assessment; thus, these are combined. EvidenceA, Evidence assigned by authors (refer to supplementary for description of systems); EvidenceR, Evidence assigned by reviewers (Oxford Centre for Evidence Based Medicine Levels of Evidence).1, Authors combined recommendation for not screening (OCEBM level 4 and 5) with not treating asymptomatic patients (OCEBM level 2); 2, Considered an area of controversy; 3, Referring to disposable thermometers only; 4, Referring to gloves only; 5, Part of combined recommendation of glove/apron use and handwashing; likely the higher evidence grade is for handwashing.ABHR, Alcohol-based hand rubs; ACG, American College of Gastroenterology; APIC, Association of Professionals in Infection Control and Epidemiology; CDI, *Clostridium difficile* infection; DH, Department of Health; ECDC, European Centre for Disease Control; EPA, Environmental Protection Agency; ESCMID, European Society for Clinical Microbiology and Infectious Diseases; H, High quality of evidence; HCPs, Healthcare Professionals; HPA, Health Protection Agency; HPV, Hydrogen Peroxide Vapour; IDSA, Infectious Diseases Society of America; L, Low quality of evidence; M, Moderate quality of evidence; S, Strong recommendation; SHEA, Society for Healthcare Epidemiology of America. |