Additional references (web)


Al-Nassir WN, Sethi AK, Nerandzic MM, Bobulsky GS, Jump RL, Donskey CJ. Comparison of clinical and microbiological response to treatment of *Clostridium*


Many thanks to the Reviewers and Editors for their constructive comments. Our responses are outlined below.

**Reviewer comments**

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<th>Comment</th>
<th>Response</th>
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<td>My main criticism is that the referencing needs to be improved – there is too much use of review articles instead of source studies. Also, the choice of which statements to reference is inconsistent, including whether ‘w’ or main references are utilised. Some (but not all) such instances are included below.</td>
<td>The references have been thoroughly expanded and revised, including utilisation of web vs. print citations. Specific instances are addressed below.</td>
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<td>Pg 3 '16-35% of hospital inpatients' Some studies have shown lower carriage prevalences – need to be careful when summarising such data, as the type of patient, hospital, length of stay etc will all potentially influence the data.</td>
<td>Paragraph revised, with additional references: C. difficile may be cultured from the stool of 3% of healthy adults, and as many as 35% of hospital inpatients. Some studies have shown lower rates of nosocomial colonisation, which may vary depending on patient population, length of hospital stay and local infection control procedures.</td>
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<td>Pg 4 'In suspected cases of ‘silent’ C. difficile infection, occurring without diarrhoea, other diagnostic procedures such as endoscopy or an abdominal CT scan may be required.' Should point out here that such cases may represent very severe infection associated with ileus/toxic megacolon.</td>
<td>Paragraph revised, with additional reference: The spectrum of gastrointestinal disease associated with C. difficile infection ranges from mild diarrhoea to fulminant colitis. Some ‘silent’ infections present with abdominal pain and distension, in the absence of significant diarrhoea. These features may indicate severe disease, causing ileus or toxic megacolon. See also response to Editor comment [6].</td>
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<td>Pg 5 'C. difficile infection has been estimated to increase the duration of hospital stay by an average of 21 days.' Old (but (NHS) data, not recently collected – may be shorter increased lengths of stay now.</td>
<td>Paragraph revised, with additional references: C. difficile infection has been estimated to increase the duration of hospital stay by an average of 21 days, although more recent studies have suggested a less pronounced effect.</td>
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<td>Pg 5. In the introductory paragraph to the Prevention section, there is no mention of the potential benefit of using molecular surveillance techniques to identify case clusters/transmission. There is circumstantial evidence that CDI reports in England have declined once there was widespread access to/uptake of this approach (as an adjunct to mandatory surveillance, which is also not mentioned). Hence, enhanced surveillance is an important part of CDI control (prevention).</td>
<td>Paragraph revised, with additional references: In the UK, reporting of C. difficile infections to the HPA is part of a mandatory surveillance scheme for healthcare associated infections. At a local level, surveillance of C. difficile infections is key to identifying outbreaks, and initiating control measures in a timely fashion. Typing of C. difficile isolates and molecular surveillance techniques may assist in the investigation of apparent increases in cases, and improve the understanding of the transmission of epidemic strains within and between health care institutions. Added to the Summary Points box: • Surveillance of C. difficile infection at national and local levels is critical for guiding the implementation of control measures</td>
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This should thus also be included in the summary points box.

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<th>Pg 5 ‘Many authors have produced ‘hit-lists’ blaming different antibiotics for their potential to cause C. difficile infection, but this approach is not without problems.’ Should emphasise the confounding due to duration of antibiotics, numbers of antibiotics and, crucially, exposure to C. difficile (Wilcox MH, Freeman J. Epidemic Clostridium difficile. N Engl J Med 2006;354:1199-203). Paragraph revised, with additional references: Although the use of fluoroquinolones has been linked to the spread of the ribotype 027 strain, risk analyses have been confounded by antibiotic polypharmacy, duration of antibiotic treatment, and infection control practices. See also response to Editor comment [7].</th>
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<td>Pg 8 ‘but the study suffered from major methodological flaws limiting the generalisability of the results.’ This statement should ideally be referenced as these major drawbacks were published. Wilcox MH, Sandoe JA. Probiotics and diarrhea: Data are not widely applicable. BMJ 2007;335:171. Reference added, with thanks.</td>
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<td>Pg 6-7 ‘UK National Guidelines therefore make various recommendations … with significant reductions in rates of C. difficile infection.’ The use of a review article (w9) as the sole reference for these statements is not good practice. Key points should be individually referenced e.g. use of chlorine-containing cleaning agents, disposable thermometers, etc. Paragraph revised, with additional references: C. difficile spores can survive in the environment for months or years, and environmental contamination has been linked to the spread of C. difficile infection in healthcare settings. UK National Guidelines therefore make various recommendations for C. difficile prevention through environmental decontamination: cleaning of rooms or bed spaces of patients with C. difficile infection should be conducted daily using chlorine-containing cleaning agents; commodes, toilets and bathroom areas should be cleaned after each use; and when an infected patient has been discharged, the room and mattress should be thoroughly cleaned using chlorine-containing cleaning agents or vaporised hydrogen peroxide. Please note also expanded discussion of isolation measures, and responses to Editor comments [8] and [9] on hand washing and electronic thermometers.</td>
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<td>Pg 7 ‘In a large outbreak, it may not be possible to isolate affected patients in single rooms with en suite facilities, and it may then be necessary to cohort nurse them in a dedicated area of a ward.’ This may be true in high endemicity settings not just outbreaks. Also, should link here to the sub-optimal PPV mentioned earlier i.e. risk of managing false-positive cases with true</td>
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<td>Paragraph revised, with additional references: There is no RCT or systematic review evidence assessing the value of isolation measures in preventing C. difficile infection, but a systematic review of isolation in the hospital management of methicillin resistant Staphylococcus aureus (MRSA) suggested its effectiveness as part of a broader infection control strategy. UK National Guidelines recommend that patients with potentially infective diarrhoea should be moved immediately into a single room with en suite facilities, but this practice is not without difficulties. For example, moving frail elderly</td>
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cases. patients with C. difficile infection may increase the risk of delirium, and its associated adverse effects.\(^{16}\) In a large outbreak, or settings with high endemicity, it may not be possible to isolate affected patients in single rooms. The creation of C. difficile isolation wards in hospitals with high levels of disease proved successful in certain well-publicised outbreaks.\(^{6,21}\) Since the positive predictive value of C. difficile toxin immunoassays is sub-optimal, however, transferring patients to cohort areas runs the risk of putting individuals without C. difficile (false positives) at a greatly increased risk of acquiring the infection.

| Pg 9 'UK surveillance data supports the emergence of reduced susceptibility to metronidazole in some C. difficile isolates, but the clinical significance of this is unclear. w1 is not the source reference for this observation. | Reference added. | \(^{w23}\) |
| Pg 9 ‘Which antibiotics are used to treat C. difficile infection’ There is evidence that response time to vancomycin may be shorter than to metronidazole. This is not mentioned. | Paragraph revised, with additional references: Retrospective and prospective observational studies have also shown the response time to vancomycin to be shorter than to metronidazole, which may be important in patients with severe disease.\(^{24,25}\) |
| Pg 10 ‘and because there is concern that overuse of vancomycin may result in the selection of vancomycin resistant Enterococci’. Actually, there is reasonable evidence that metronidazole is a risk factor for vancomycin resistant enterococcal overgrowth. Again, w1 is not the correct reference for such a statement. | Paragraph revised, with additional reference: UK National Guidelines therefore still recommend oral metronidazole for initial treatment in these patient groups, because it is cheaper than oral vancomycin, and because of concern that overuse of vancomycin may result in the selection of vancomycin resistant Enterococci.\(^{1}\) Observational data suggest, however, that metronidazole, as well as vancomycin, may promote persistent overgrowth of vancomycin resistant Enterococci.\(^{28}\) |
| Pg 11 ‘The risk of recurrence following a single episode is significant, with up to 35% of patients experiencing at least a second episode after treatment with either metronidazole or vancomycin.’ This unreferenced rate is higher than is generally accepted (~20%). | Paragraph revised: The risk of recurrence following a single episode is significant, with 8-50% of patients experiencing at least a second episode after treatment with either metronidazole or vancomycin.' |
| ‘Risk factors include …’ Previous CDI should be included here. | Paragraph revised: Risk factors include previous relapses, age greater than 65 years, severe underlying illness, and additional antibiotic use after treatment for C. difficile infection has been stopped.\(^{29,30}\) |
| Pg 11 ‘Patients may continue to remain C. difficile toxin positive despite clinical cure’. Key point, but not referenced. | Reference added. \(^{31}\) |
| Pg 13 ‘Intravenous immunoglobulin may therefore benefit a small group of patients | Please see response to Editor comment [12]. |
with multiple recurrences, but there are no RCTs to support its adoption and issues such as cost and availability may preclude its use.’ No source references are supplied. Also, worth pointing out that this indication is included in the DoH list of indications for prescribing of iv immunoglobulin.

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<td><strong>Comment</strong></td>
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<td>1. Please read this letter in conjunction with a word document that I shall send attached to a separate email. The document is a copy of your submitted manuscript, in which I have used the ‘track changes’ word tool to reduce the word count, to indicate some style changes that we would like you to make and to ask questions at relevant points. Questions, explanations and requests for further information are enclosed in [square brackets] and may be highlighted.</td>
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<td>2. In the first sentence of the introduction please qualify whether you refer to incidence of C. diff infection or diarrhea increasing.</td>
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<td>3. In the introduction you mention the previously uncommon but highly virulent strain, but then you do not mention it again, which is odd. Perhaps it would be better to omit mention of it at all.</td>
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<td>4. We suggest bringing up one point from the conclusion and putting it in the introduction. “Many cases of infection could be prevented by the combination of prudent antibiotic prescribing and vigorous application of infection control measures.”</td>
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<td>5. In the section on who becomes infected please change ‘up to’ to ‘as many as’. A reader has repeatedly criticized us for using the term ‘up to’, which he says is a journalistic term, so we try to avoid using it now. Are you able to give readers an estimate of the prevalence of C. diff colonization in the community?</td>
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6. In the section “How does C. difficile infection present and how is it diagnosed?” please mention how ‘silent’ infection presents in the first part after describing the spectrum of GI disease. At the end of the section please say what endoscopy and/or CT would be expected to show in C. diff infection.

Paragraph revised:
In suspected cases of ‘silent’ C. difficile infection, an endoscopy or abdominal CT scan may be required. Characteristic findings include thickening of the colonic wall, dilatation and pseudomembrane formation.

Please also note response to Reviewer comment on paragraph headed: How does C. difficile infection present and how is it diagnosed?

7. Under “…antibiotic stewardship…” please tell us which agents within the fluoroquinolone class have been associated with higher likelihood of C. diff infection. (“The contribution of fluoroquinolones to C. difficile infection is still debated, but observational data suggest that different agents within this class have different propensity to cause C. difficile infection.”)

Paragraph revised, with additional references:
In addition, observational data suggest that different fluoroquinolones may have different propensities to cause C. difficile infection, with gatifloxacin associated with the highest risk.

8. Where you say, “Alcohol-based hand gels are less effective at reducing contamination with C. difficile spores than washing with soap and water,” please either say what studies have shown this or say who recommends it….the reference w1 is to Department of health guidelines, which doesn’t give the reader an idea of the strength of evidence underlying the statement.

Paragraph revised, with additional references:
Hand washing is paramount in the prevention of most hospital-acquired infections (http://www.npsa.nhs.uk/cleanyourhands). Alcohol-based hand gels are highly effective against non-spore forming organisms, but they do not kill C. difficile spores or remove them from the hands. Experimental studies examining different hand hygiene methods have shown that alcohol-based hand gels are significantly less effective at reducing contamination with C. difficile spores than washing with soap and water. UK National Guidelines therefore recommend that healthcare workers wash their hands before and after contact with patients with suspected or proven C. difficile infection, and that disposable gloves and aprons be used whenever handling body fluids and caring for such patients.

As stated, the recommendation comes from UK National Guidelines, and the National Patient Safety Agency CleanYourHands campaign.

9. Where you talk about replacing digital thermometers with disposable thermometers because this has been associated with ‘significant reductions’ in C. diff infection rates please can you tell the reader what sort of study showed this, how big the reduction in infection was and if the results can be generalised.

Paragraph revised, with additional references:
Replacing electronic oral and rectal thermometers (which may become contaminated with C. difficile spores, and then inoculate them directly into the gastrointestinal tract) with disposable thermometers has been associated with significant reductions in rates of C. difficile infection.

A prospective randomised crossover study involving 20 nursing units reported a significantly lower rate of nosocomial C. difficile infection with disposable thermometer use (0.16 per 1,000 patient days) compared with electronic thermometer use (0.37 per 1,000 patient days, relative risk [RR] = 0.44; 95% confidence interval 0.21-0.93), and a similar reduction was reported from an observational study comparing rates before and after the introduction of tympanic thermometers.

10. Please include more points in your ‘summary points’. We suggest the following four points:
• The incidence of Clostridium difficile infection has increased in the last decade
• Strategies to control C. difficile infection

Changes accepted, but instead of...
• Strategies to control C. difficile infection depend largely on prevention
... we have included the following, as requested by the Reviewer comment on the paragraph headed: Prevention.
depend largely on prevention.
• C. difficile infection may be prevented by prudent antibiotic prescribing, correct hand hygiene and use of personal protective equipment, environmental decontamination and isolation / cohort nursing
• Nationally agreed protocols provide recommend treating C. difficile infection initially with oral vancomycin or metronidazole according to severity of disease, and escalating treatment in the event of non-response
• Surveillance of C. difficile infection at national and local levels is critical for guiding the implementation of control measures

Please note the paragraph headed: Medical Management. This is an important point. Patients with C. difficile infection are prone to developing electrolyte imbalance, dehydration, malnutrition and pressure sores, and it is therefore essential to optimise their supportive medical care. Following outbreaks at Maidstone and Tunbridge Wells NHS Trust in 2005-6, the UK Healthcare Commission was critical of the quality of general management of patients with C. difficile infection, including inadequate monitoring and doctor review, poor fluid replacement and nutritional support, and lack of multi-disciplinary assessment.

11. Please look at the third point in the "tips for non specialists box". If you do not mention this aspect of management in the main text then please remove this point.

12. We trust that you have seen the recent NEJM editorial and RCT on this subject. The editorial makes the important point about the management of C. difficile infection that it’s an antibiotic-associated condition for which antibiotics are the mainstay of treatment, and that although antibiotics are effective at inhibiting C. difficile and treating symptoms, they prevent the reestablishment of normal bowel flora, which means that a substantial proportion of patients suffer recurrent infections after the cessation of treatment. You might make this link in your article. The RCT examines two neutralizing human monoclonal antibodies against C. difficile toxins A and B. Might you update your treatment section to mention this RCT?

Updated Ongoing Research box to include monoclonal antibodies:
• There is considerable interest in the development of monoclonal antibodies and toxin-specific vaccines for the prevention or treatment of C. difficile infection, and Tolevamer, a novel toxin-binding polymer, is undergoing clinical trials

Revised paragraph headed: How do recommendations differ for recurrent disease?
Low levels of serum antibodies against C. difficile Toxin A correlate with the risk of recurrent C. difficile infection, and a recent phase 2 RCT demonstrated a significant reduction in C. difficile recurrence in patients treated with experimental monoclonal antibodies against toxins A and B. Pooled intravenous immunoglobulin may also be able to neutralise these toxins, and a small case series reported a successful clinical response to intravenous immunoglobulin in 3 out of 5 patients with recurrent C. difficile infection. Although recommended in the UK Department of Health Clinical Guidelines for Immunoglobulin Use, for selected patients with multiply recurrent C. difficile infection in whom all other treatments have failed or are inappropriate, there are no RCTs to support the use of intravenous immunoglobulin, and issues such as cost and availability may preclude its widespread adoption.

Revised paragraph headed: How is recurrent C. difficile infection diagnosed?
Paradoxically, the antibiotics used to treat C. difficile infection may themselves interfere with the re-establishment of the normal colonic flora, contributing to the propensity for recurrent disease.

13. General point: Due to space constraints in the print journal we set the word limit at 2000 words (excluding text in boxes, tables, figure sections which may be removed to shorten the print version to around 2000 words have been highlighted in grey. Please note that this inevitably includes some
Often after addressing our and reviewers’ points authors find that the review exceeds 2000 words. Often that’s okay; it may be printed in its entirety on bmj.com but you will need to highlight discrete chunks that could be omitted in the print version. Please do not supply us with a long and a short version. We require only one version but if it is too long possible cuts should be identified.

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<th>areas expanded in response to Reviewer and Editor comments. Please also note that the reference list will be affected if the highlighted areas are excised!</th>
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