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## **Redefining *Clostridioides difficile* infection antibiotic response and clinical outcomes**

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# Redefining *Clostridioides difficile* infection antibiotic response and clinical outcomes



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With the approval and development of narrow-spectrum antibiotics for the treatment of *Clostridioides difficile* infection (CDI), the primary endpoint for treatment success of CDI antibiotic treatment trials has shifted from treatment response at end of therapy to sustained response 30 days after completed therapy. The current definition of a successful response to treatment (three or fewer unformed bowel movements [UBMs] per day for 1–2 days) has not been validated, does not reflect CDI management, and could impair assessments for successful treatment at 30 days. We propose new definitions to optimise trial design to assess sustained response. Primarily, we suggest that the initial response at the end of treatment be defined as (1) three or fewer UBMs per day, (2) a reduction in UBMs of more than 50% per day, (3) a decrease in stool volume of more than 75% for those with ostomy, or (4) attainment of bowel movements of Bristol Stool Form Scale types 1–4, on average, by day 2 after completion of primary CDI therapy (ie, assessed on day 11 and day 12 of a 10-day treatment course) and following an investigator determination that CDI treatment can be ceased.

## Introduction

From the earliest *Clostridioides difficile* infection (CDI) treatment trials in the 1980s, *C difficile* research has used various definitions for clinical response and disease outcomes. 40 years later, the medical community continues to grapple with how to define diarrhoea, how to define a patient's response to CDI therapy, how to define meaningful primary clinical outcomes, and how to measure relevant long-term outcomes in both the clinic and research. Definitions of diarrhoea have shifted from evidence of persistent diarrhoea (six or more unformed bowel movements [UBMs] over 36 h)<sup>1</sup> to less stringent measurements of diarrhoea, with several trials defining diarrhoea as three or more UBMs in 24 h.<sup>2–9</sup> Similarly, the definition of CDI initial cure has transformed from primarily clinical, which required improvement of symptoms over the course of treatment,<sup>1</sup> to more stringent definitions with the same measure of three or fewer UBMs per day for 24–48 h.<sup>3,7,8,10</sup> In clinical practice, no treatment guidelines provide a set number of UBMs at the end of therapy to determine treatment duration or recommendations for response to therapy.<sup>11–13</sup> Furthermore, the shift towards more restrictive definitions of CDI cure could have unintended consequences for people enrolled in clinical trials and for drug innovation. Overly restrictive definitions of initial clinical cure impact the ability to measure long-term outcomes such as sustained clinical response, which has historically been measured as initial clinical cure without recurrence of CDI within a specified time that is also not uniformly defined. With more restrictive initial clinical cure definitions, fewer people will attain a sustained clinical response, despite otherwise demonstrating a satisfactory clinical response to CDI therapy.

In this Personal View, we aim to explore the potential effect of current CDI trial definitions and to propose a novel definition grounded in clinically relevant, discrete,

and objective measures of CDI. Although we acknowledge the testing methods used to diagnose CDI have a large bearing on trial enrolment and outcomes, this Personal View focuses on how to define trial outcomes and will therefore not discuss diagnosis recommendations. Additionally, although we recognise the various therapies used for prevention of recurrent CDI that are approved and undergoing study, including monoclonal antibodies and live biotherapeutic products, our discussion focuses on primary antibiotic therapy for CDI. The positions and recommendations we offer, as a group of *C difficile* experts, are intended to establish a network of practical definitions that can be used from the bench to bedside for people enrolled in *C difficile* trials and for the primary antibiotic management of people with CDI.

## Historical background

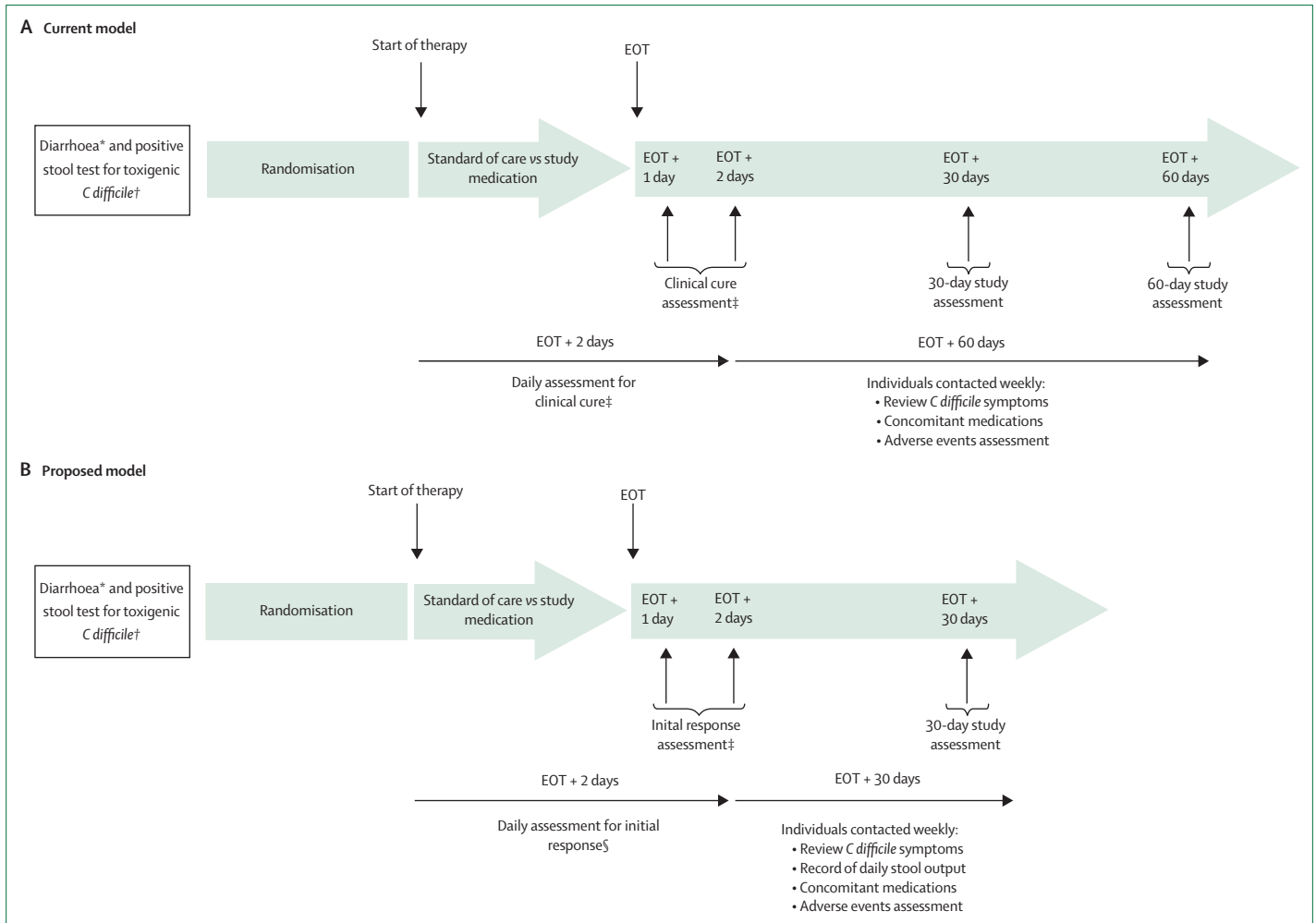
The evaluation of new antimicrobials typically includes measures of both bacteriological and clinical cure. However, these endpoints are not suited to the evaluation of anti-CDI therapies because routine cultures are not performed, organism and toxin presence in stool is not diagnostic of disease, antimicrobials do not eradicate spores from the host, and the complex interplay of pathogen and host microbiome is not accounted for, but is determinative for both immediate and long-term outcomes. Additionally, the rate of residual post-treatment positive stool culture has not shown a correlation with treatment success and far exceeds the rate of clinical CDI recurrence.<sup>14</sup> Instead, CDI clinical trials have relied heavily on clinical cure as the primary measure of efficacy (figure). This reliance emphasises the importance of measuring clinical outcomes in an externally valid way that captures true treatment effects. However, basic tenets such as how diarrhoea is defined, and subjectivity of diarrhoea as experienced and reported by the individual, undermine many efforts to do so.

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**Figure: Timeline of *Clostridioides difficile* infection outcome assessments for clinical trials**  
 CDI=*Clostridioides difficile* infection. EOT=end of treatment. \*Diarrhoea defined as three or more loose stools in 24 h or fewer. †Diarrhoeal stool testing positive for toxigenic *C difficile*. Specimen collected within 48 h of randomisation and before anti-CDI treatment. ‡Clinical cure defined as resolution of diarrhoea (ie, three or fewer stools for 2 consecutive days) and maintenance of resolution requiring no further treatment for CDI within 2 days after completion of therapy. §Initial response defined as any significant improvement in diarrhoea (three or fewer unformed bowel movements per day, >50% reduction in unformed bowel movements per day, >75% decrease in stool volume for those with an ostomy, or attainment of bowel movements of Bristol Stool Form Scale types 1–4 on average) by day 2 after completion of CDI therapy.

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The absence of diarrhoea, defined as the inverse to the diarrhoea definition used for enrolment, has broadly served as the basis for designating a successful treatment outcome in all major CDI clinical trials since the approval of fidaxomicin, despite the absence of a validated definition for diarrhoea or CDI cure. As previously mentioned, the definition of diarrhoea has changed over time (appendix p 1). There are several underlying reasons for this change, including the development of diagnostic tests generating results in hours instead of days, an increase in CDI severity with some people progressing to fulminant CDI within 1–2 days of symptom onset<sup>15</sup> and, for clinical trials, the need to start people on a study drug within an acceptable timeframe to determine efficacy. The currently recommended definition of diarrhoea for diagnosing CDI in adults of three or more UBMs in 24 h

is intended to improve the specificity of *C difficile* diagnostic assays (vs fewer than three UBMs in 24 h) and to minimise the risk of delays in diagnosis, treatment, and isolation of people with CDI. This definition has also been applied to identify people for treatment trials as study participants currently cannot be on other CDI treatments for more than 24 h to remain eligible. Despite its use for clinical management of people and enrolment into clinical trials, this definition has never been validated in comparison with other definitions. It is also challenging to apply this definition of diarrhoea to infants and children younger than 3 years, as they might have stools with a softer or looser consistency at baseline, and the normal frequency of bowel movements during the first year of life is often higher than three per day, particularly in breastfed infants. Therefore, in this specific population, diarrhoea is

often defined in terms of a change in the usual stool frequency. Additionally, it can be unrealistic to expect sustained absence of diarrhoea in people who have a high frequency of bowel movements before CDI related to underlying comorbidities or treatment (eg, people with previous bowel or biliary surgery, people with irritable bowel syndrome, or those given magnesium supplementation or treatment involving lactulose). Likewise, people with fulminant CDI and who develop an ileus might not have diarrhoea consistently during disease progression, challenging the application of a diarrhoea-based measure of response.<sup>16,17</sup> CDI treatment studies have omitted people with underlying gastrointestinal disease or fulminant CDI for this reason.<sup>3–6,8,10,18</sup>

Furthermore, CDI is unique among infectious diseases, in that disease recurrence historically occurred in up to a third of people following standard-of-care antibiotic therapy.<sup>3–5</sup> As narrow-spectrum, microbiome-sparing CDI therapeutics have been developed, clinical trials of primary treatment agents have shifted from measuring initial clinical cure, which is assessed on completion of therapy, to the more holistic sustained clinical response at 30 days following the end of therapy as a primary endpoint.<sup>7,10,19</sup> This shift in emphasis towards sustained clinical response is highlighted by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults<sup>12</sup> and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2021 Update on the Treatment Guidance Document for *Clostridioides difficile* Infection in Adults,<sup>20</sup> which both suggest fidaxomicin as first-line therapy rather than vancomycin or metronidazole for both primary and recurrent CDI in adults. Although fidaxomicin and vancomycin result in similar rates of initial clinical cure for a primary infection, these recommendations reflect the 10.1% (95% CI 5.7–15.7) increase in sustained clinical response rate provided by fidaxomicin.<sup>12</sup> Currently available data in children suggest that fidaxomicin is safe and associated with higher frequency of sustained clinical response.<sup>9,21</sup> However, eligibility for sustained clinical response is dependent on first attaining an initial clinical cure from CDI treatment. Thus people with symptoms that do not meet initial clinical cure criteria might unnecessarily be excluded from sustained clinical response evaluation despite otherwise having had a satisfactory clinical response. These variations in CDI clinical trial endpoints and scarcity of associated validation present challenges to clinicians, investigators, and regulators in determining a drug's true effect.

### Potential negative impact on clinical trial design of current initial cure definition

Although sustained clinical response is a more comprehensive primary endpoint than initial clinical cure, it continues to rely on a measure of initial cure. As outlined

earlier, threshold-based definitions of initial cure have shifted in the last 10 years to more restrictive definitions that risk misclassifying CDI treatment response as failed. Continued use of these definitions, regardless of the emphasis placed on sustained clinical response, could therefore be a potential hindrance to the development of new CDI therapeutics.

For example, medication A is considered the gold standard for CDI treatment and is serving as the comparator for a new medication (B) in clinical trials. Medication A has an initial clinical cure rate of 86%, and 75% of those with initial clinical cure attain a sustained clinical response at 30 days after the completion of therapy. We expect, based on phase 2 trials, that medication B will have an initial clinical cure rate of 72%, with 90% of those cases with a sustained clinical response.

To appropriately power this hypothetical study, a large sample would be required to assess differences in the sustained clinical response rates between medications A and B since the 14–28% of the population without initial clinical cure would be excluded from sustained clinical response evaluation. This attrition of people would hinder the ability to detect a true difference in the rates of sustained clinical response, and bias the analysis towards finding no difference in primary outcomes. Refining an initial clinical cure definition to detect more clinically relevant measures of success could simultaneously lower the burden of enrolment and increase the number of people that are eligible for sustained clinical response evaluation, leading to fewer type II (false negative) errors as investigators would be more likely to appropriately reject a null hypothesis that medications A and B are equal, if true. Furthermore, a more inclusive initial clinical cure definition could increase the sensitivity of sustained clinical response as a primary outcome as people with CDI recurrence still would not attain sustained clinical response, making the risk of increasing type I (false positive) errors negligible.

To illustrate these points, if the previous example represented results from a head-to-head, phase 3 trial, and initial clinical cure was the primary outcome, medication B would not be considered non-inferior to medication A because the difference in the initial clinical cure rate would be more than 10%. If 1000 people received each medication, 860 people given medication A and 720 people given medication B would attain an initial clinical cure. However, sustained clinical response would occur in a similar number of people (645 people given medication A vs 648 given medication B) as a result of the higher rate of sustained clinical response with medication B. Although medication B would be considered non-inferior to medication A if sustained clinical response was measured as the primary endpoint, the exclusion of almost 300 people who did not attain initial clinical cure following medication B requires a substantial increase in sample size to find a significant association as a result.

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See Online for appendix

To underscore the decreased enrolment burden of a more clinically accurate initial clinical cure definition, we present an additional scenario in which initial clinical cure is compared with a more inclusive measure of initial response. In this scenario, if two drugs, medications C and D, both have initial clinical cure rates of 80%, but recurrence rates of 25% (C) and 10% (D), then a sample size of 243 people per group would be needed to detect this difference in sustained clinical response. However, if a more inclusive initial response measure was applied, which increased the initial response rate to 85% for both drugs (with the same recurrence rates), only 193 people per group would be required. Overall, 100 fewer people would need to be enrolled to show the same sustained clinical response difference through use of a less restrictive response definition.

These limitations of non-clinically relevant initial clinical cure definitions have been presented in CDI clinical trials since 2011, based on the date enrolment was commenced.<sup>22–25</sup> Cadazolid did not demonstrate non-inferiority to vancomycin in one of its two phase 3 trials with a definition of initial cure consisting of fewer than three UBMs per day maintained for at least two consecutive days at the end of treatment.<sup>8</sup> However, predefined exploratory analyses with investigator-assessed measures of clinical cure and sustained response determined cadazolid would be non-inferior to vancomycin if these different endpoints were applied, bringing into question the validity of the current endpoints.<sup>26</sup> The phase 3 trials assessing use of adjunctive bezlotoxumab versus placebo with standard-of-care antibiotics help to show that a strict definition of fewer than three UBMs per day for initial clinical cure might not be appropriate to establish response to CDI treatment.<sup>27,28</sup> In the MODIFY I trial,<sup>22</sup> initial clinical cure was attained in 299 (77%) of 386 people receiving bezlotoxumab and 327 (83%) of 395 people receiving placebo (adjusted difference  $-5.3\%$ ; 95% CI  $-10.9$  to  $0.3$ ) whereas initial clinical cure was attained in 326 (83%) of 395 people receiving bezlotoxumab and 294 (78%) of 378 people receiving placebo in the MODIFY II trial<sup>22</sup> ( $4.8\%$ ;  $-0.9$  to  $10.4$ ). As the direction of non-inferiority related to bezlotoxumab was equal and opposite across the two trials,<sup>22</sup> bezlotoxumab is unlikely to have influenced these differences. However, since the 95% CIs crossed the  $-10\%$  threshold used to establish non-inferiority in MODIFY I and MODIFY II, both trials found standard-of-care treatment for CDI was not non-inferior to standard-of-care treatment. Although initial clinical cure was an exploratory endpoint in these trials, it was also defined conservatively as less than or equal to two UBMs per 24 h for two consecutive days after the end of treatment. Both the lack of agreement between the trials and their underlying inability to capture similar initial clinical cure outcomes in two groups of standard-of-care antibiotics underscore the limitations of restrictive initial clinical cure definitions.

### Considerations for a clinical trial definition

Much of the knowledge gained in the field of CDI research over the past 40 years can, and should, help to inform new measures of clinical success in clinical trials. First, the appropriateness of a standardised threshold for UBMs per day in determining success should be questioned. People with a wide range of UBMs per day are typically included in clinical trials, yet baseline stool frequency is not considered in assessing cure. Whether the application of the same stool frequency threshold makes intuitive clinical sense when assessing an individual with more than ten UBMs per day at enrolment, or an individual with four UBMs per day should be carefully considered. Second, the pathogenesis of persistent symptoms at the end of treatment requires attention. Continued diarrhoeal movements of any number within 2 days of completing treatment has been considered a failure of antibiotic therapy, yet various disease processes can influence the response time even in the presence of effective antibiotics: toxin-induced colonic mucosal damage and inflammation,<sup>29</sup> microbiome disruption resulting in reduced resorption of water,<sup>30–32</sup> transient functional bowel disorder, or some combination of these factors yet to be discovered. Although CDI can present with several associated symptoms beyond diarrhoea, such as abdominal cramping, pain, bloating, and nausea, determination of cure objectively relies on diarrhoeal resolution rather than patient-reported outcomes or a global clinical assessment. Consideration should be given to broadening our measures of short-term outcomes to capture a well rounded clinical picture. Third, an emphasis on including long-term outcomes, such as recurrence, in the primary efficacy outcome of clinical trials should be considered. The shift towards assessing for a sustained clinical response has partly achieved this goal, but its reliance on initial clinical cure still limits the ability of sustained clinical response in its current form to accurately capture outcomes. Increased attention is warranted to better define which people should undergo an evaluation for a sustained clinical response, to increase the sensitivity of this measure.

### Recommendations for new definitions

Here we propose the use of a new set of clinical trial endpoints: initial response and sustained response (panel). Although we acknowledge the importance of measuring short-term outcomes, we support use of a less restrictive definition of initial response to increase the validity of sustained response. We recommend defining initial response as any substantial improvement in diarrhoea (three or fewer UBMs per day,  $>50\%$  reduction in UBMs per day,  $>75\%$  decrease in stool volume for people with ostomy, or attainment of bowel movements of Bristol Stool Form Scale types 1–4, on average) by day 2 after completion of primary CDI therapy (ie, assessed on day 11 and day 12 of a 10-day treatment

course) and following an investigator determination that CDI treatment can be ceased.<sup>5-7,18,33</sup> This determination can take into consideration the resolution of other CDI-related symptoms that could be considered as secondary trial outcomes (appendix p 2). We highlight the use of the term response in this short-term outcome assessment since we prefer to reserve the term cure for people who do not have any recurrence. Hence, we define sustained response as people with initial response and without the need for retreatment of CDI by day 30 after the completion of primary CDI therapy (ie, assessed on day 40 of a 10-day treatment course).<sup>34,35</sup> Although some people might have CDI recurrence up to 8 weeks after primary infection,<sup>36</sup> we acknowledge that a range of events could occur in an 8-week follow-up period that confound the investigators' ability to discern a given antibiotic's treatment effect, such as exposure to non-CDI treatment antibiotics. We use the term sustained not to denote the absence of recurrence, but instead to avoid confusion with the past varied use of the terms clinical cure or cure within the comprehensive body of CDI literature. Although this set of definitions could be applied to all individuals with CDI outside of the context of a clinical trial, the purpose of these definitions are to assess CDI treatment antibiotic response outcomes for clinical trials. Therefore they are not intended to be applied to populations typically excluded from clinical trials (eg, patients with fulminant CDI).<sup>3-6,8,10,18</sup>

Age-based criteria for CDI trial enrolment should be applied to paediatric studies. We recommend that enrolment of children in CDI treatment trials is restricted to patients aged 2 years and older. This recommendation is made for several reasons. First, children younger than 2 years have higher rates of *C difficile* colonisation, and evidence for *C difficile* causing clinical disease in infants is scarce.<sup>37</sup> Due to the need for further evidence that there is an unmet need to treat CDI in this population, experts question the ethics and feasibility of including children younger than 2 years in clinical trials of CDI antibiotic treatments.<sup>38</sup> These observations are supported by findings in the fidaxomicin phase 3 paediatric trial showing differences in age-related efficacy. The subgroup of children younger than 2 years did not attain treatment efficacy; these children were probably colonised but not infected with *C difficile*.<sup>9</sup> If children younger than 2 years are included in studies for the purposes of generating paediatric safety data, we strongly recommend excluding data from participants from primary analyses of treatment efficacy.

As the clinical goals have shifted for the treatment of CDI, so too should the definitions that guide clinical trials. The set of definitions proposed here will capture clinical success more accurately and highlight the need for further research. These definitions are intended to capture the treatment effects of primary antibiotic therapy. As CDI management continues to progress to include vaccination, faecal microbiota transplantation,

#### Panel: Proposed outcome definitions for *Clostridioides difficile* infection (CDI) clinical trials

##### Initial response

- Any significant improvement in diarrhoea by day 2 after completion of primary CDI therapy plus investigator determination that CDI treatment can be stopped
- Improvement in diarrhoea measured as any one or more of the following: three or fewer unformed bowel movements per day; more than 50% reduction in number of stools; more than 75% decrease in stool volume (ostomy or rectal collection device); or attainment of bowel movements of Bristol Stool Form Scale types 1–4, on average

##### Sustained response

- Attained if initial response present with no need to retreat for CDI by day 30 after completion of primary CDI therapy

microbiota-based biotherapeutics, and non-toxicogenic *C difficile*, among other approaches, continued efforts are needed to ensure the accurate measurement of each treatment's effect, either alone or in combination with other therapies.

##### Contributors

AJG-L, AMS, and CDA were involved in writing the original draft of the manuscript, designing the project method, data validation, data curation, and provision of resources. AJG-L and CDA were also involved in project administration and AJG-L, AMS, and KWG contributed through data visualisation and figure creation. TGJdM, RJD, LKK, and TJS contributed to writing of the original draft and data validation. MHW participated in project supervision, data validation, and the review and edit of the writing. ERD conceptualised the project and was additionally involved in project supervision, method design, data validation, data curation, provision of resources, and the review and edit of the writing. All other authors contributed to data validation, and the review and edit of the writing.

##### Declaration of interests

AMS is supported by career development awards from the US Veteran Affairs and Institute for Translational Medicine, serves on an advisory board for Recursion Pharmaceuticals, and has accepted honoraria from the American Society of Healthcare Pharmacists and the Academy for Continued Healthcare Learning. CDA has been supported by an investigator-initiated grant from Merck; serves on advisory boards for Cidara Therapeutics, Merck, and AiCuris; and has accepted honoraria from the American Society of Healthcare Pharmacists and the Academy for Continued Healthcare Learning. OAC has grants from Amplyx, Basilea, German Federal Ministry of Education and Research, Cidara, German Center for Infection Research, Commission's Directorate-General for Research and Innovation (101037867), F2G, Gilead, Matinas, MedPace, Merck Sharp & Dohme, Mundipharma, Octapharma, Pfizer, and Scynexis, has accepted consulting fees from AbbVie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, Mycoses Study Group Education & Research Consortium, Noxxon, Octapharma, Pardes, Pfizer, Pharmaceutical Security Institute, Scynexis, and Seres Therapeutics; has accepted speaker honoraria from Abbot, AbbVie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Noscendo, Pfizer, and Shionogi; has served as an expert witness for Cidara; has participated on advisory boards for Actelion, Allegra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Pulmocide, Shionogi, and the Prime Meridian Group; has filed for a patent with the German Patent and Trade Mark Office (Geschlossene Inkubationssysteme mit

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#### References

- 1 Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. *Lancet* 1983; **2**: 1043–46.
- 2 Zar FA, Bakkanagari SR, Moorthi KMLST, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007; **45**: 302–07.
- 3 Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; **364**: 422–31.
- 4 Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis* 2012; **12**: 281–89.
- 5 Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis* 2014; **59**: 345–54.
- 6 Daley P, Louie T, Lutz JE, et al. Surotomycin versus vancomycin in adults with *Clostridium difficile* infection: primary clinical outcomes from the second pivotal, randomized, double-blind, phase 3 trial. *J Antimicrob Chemother* 2017; **72**: 3462–70.
- 7 Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis* 2018; **18**: 296–307.
- 8 Gerding DN, Cornely OA, Grill S, et al. Cadazolid for the treatment of *Clostridium difficile* infection: results of two double-blind, placebo-controlled, non-inferiority, randomised phase 3 trials. *Lancet Infect Dis* 2019; **19**: 265–74.
- 9 Wolf J, Kalocsai K, Fortuny C, et al. Safety and efficacy of fidaxomicin and vancomycin in children and adolescents with *Clostridioides (Clostridium) difficile* infection: a phase 3, multicenter, randomized, single-blind clinical trial (SUNSHINE). *Clin Infect Dis* 2020; **71**: 2581–88.
- 10 Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of *Clostridioides (Clostridium) difficile* infection in a randomized, double-blind, comparative phase III study in Japan. *J Infect Chemother* 2018; **24**: 744–52.
- 11 McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; **66**: e1–48.
- 12 Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis* 2021; **73**: 755–57.
- 13 Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. *Am J Gastroenterol* 2021; **116**: 1124–47.
- 14 Gerding DN, Meyer T, Lee C, et al. Administration of spores of nontoxicogenic *Clostridium difficile* strain M3 for prevention of recurrent *C. difficile* infection: a randomized clinical trial. *JAMA* 2015; **313**: 1719–27.
- 15 Sailhamer EA, Carson K, Chang Y, et al. Fulminant *Clostridium difficile* colitis: patterns of care and predictors of mortality. *Arch Surg* 2009; **144**: 433–39.
- 16 Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. *Clin Infect Dis* 2008; **46** (suppl 1): S12–18.
- 17 Dallal RM, Harbrecht BG, Boujoukas AJ, et al. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. *Ann Surg* 2002; **235**: 363–72.
- 18 Boix V, Fedorak RN, Mullane KM, et al. Primary outcomes from a phase 3, randomized, double-blind, active-controlled trial of surotomycin in subjects with *Clostridium difficile* infection. *Open Forum Infect Dis* 2017; **4**: ofw275.
- 19 Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of *Clostridium difficile* colitis. *Clin Infect Dis* 2006; **43**: 421–27.
- 20 van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. *Clin Microbiol Infect* 2021; **27** (suppl 2): S1–21.
- 21 Krutova M, de Meij TGJ, Fitzpatrick F, Drew RJ, Wilcox MH, Kuijper EJ. How to: *Clostridioides difficile* infection in children. *Clin Microbiol Infect* 2022; **28**: 1085–90.
- 22 Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med* 2017; **376**: 305–17.

- 23 Daley P, Louie T, Lutz JE, et al. Surotomycin versus vancomycin in adults with *Clostridium difficile* infection: primary clinical outcomes from the second pivotal, randomized, double-blind, phase 3 trial. *J Antimicrob Chemother* 2017; **72**: 3462–70.
- 24 Boix V, Fedorak RN, Mullane KM, et al. Primary outcomes from a phase 3, randomized, double-blind, active-controlled trial of surotomycin in subjects with *Clostridium difficile* infection. *Open Forum Infect Dis* 2017; **4**: ofw275.
- 25 Gerding DN, Cornely OA, Grill S, et al. Cadazolid for the treatment of *Clostridium difficile* infection: results of two double-blind, placebo-controlled, non-inferiority, randomised phase 3 trials. *Lancet Infect Dis* 2019; **19**: 265–74.
- 26 Guery B. *Clostridium difficile* infection trials: what is the primary endpoint? *Lancet Infect Dis* 2019; **19**: 219–20.
- 27 Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med* 2017; **376**: 305–17.
- 28 Dubberke ER, Gerding DN, Kelly CP, et al. Efficacy of bezlotoxumab in participants receiving metronidazole, vancomycin, or fidaxomicin for treatment of *Clostridioides (Clostridium) difficile* infection. *Open Forum Infect Dis* 2020; **7**: ofaa157.
- 29 El Feghaly RE, Stauber JL, Deych E, Gonzalez C, Tarr PI, Haslam DB. Markers of intestinal inflammation, not bacterial burden, correlate with clinical outcomes in *Clostridium difficile* infection. *Clin Infect Dis* 2013; **56**: 1713–21.
- 30 Binder HJ. Role of colonic short-chain fatty acid transport in diarrhea. *Annu Rev Physiol* 2010; **72**: 297–313.
- 31 Vandeputte D, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. *Gut* 2016; **65**: 57–62.
- 32 Tirelle P, Breton J, Riou G, Déchelotte P, Coëffier M, Ribet D. Comparison of different modes of antibiotic delivery on gut microbiota depletion efficiency and body composition in mouse. *BMC Microbiol* 2020; **20**: 340.
- 33 Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997; **32**: 920–24.
- 34 Figueroa I, Johnson S, Sambol SP, Goldstein EJ, Citron DM, Gerding DN. Relapse versus reinfection: recurrent *Clostridium difficile* infection following treatment with fidaxomicin or vancomycin. *Clin Infect Dis* 2012; **55** (suppl 2): S104–09.
- 35 Zeng Z, Zhao H, Dorr MB, et al. Bezlotoxumab for prevention of *Clostridium difficile* infection recurrence: distinguishing relapse from reinfection with whole genome sequencing. *Anaerobe* 2020; **61**: 102137.
- 36 Abujamel T, Cadnum JL, Jury LA, et al. Defining the vulnerable period for re-establishment of *Clostridium difficile* colonization after treatment of *C. difficile* infection with oral vancomycin or metronidazole. *PLoS One* 2013; **8**: e76269.
- 37 Tamma PD, Sandora TJ. *Clostridium difficile* infection in children: current state and unanswered questions. *J Pediatric Infect Dis Soc* 2012; **1**: 230–43.
- 38 Faust SN, Wilcox MH, Banaszekiewicz A, Bouza E, Raymond J, Gerding DN. Lack of evidence for an unmet need to treat *Clostridium difficile* infection in infants aged <2 years: expert recommendations on how to address this issue. *Clin Infect Dis* 2015; **60**: 912–18.

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