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[1]

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ABSTRACT

This clinical practice guideline is a focused update on management of *Clostridioides difficile* infection (CDI) in adults specifically addressing the use of fidaxomicin and bezlotoxumab for the treatment of CDI. This guideline was developed by a multidisciplinary panel representing the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). This guideline is intended for use by healthcare professionals who care for adults with CDI, including specialists in infectious diseases, gastroenterologists, hospitalists, pharmacists, and any clinicians and healthcare providers caring for these patients. The panel's recommendations for the management CDI are based upon evidence derived from topic-specific systematic literature reviews.

Summarized below are the recommendations for the management of CDI in adults. The panel followed a systematic process which included a standardized methodology for rating the certainty of the evidence and strength of recommendation using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) (see Figure 1). A detailed description of background, methods, evidence summary and rationale that support each recommendation, and knowledge gaps can be found online in the full text.

I. In patients with an initial CDI episode, should fidaxomicin be used rather than vancomycin?

Recommendation:

I. For patients with an initial CDI episode, we suggest using fidaxomicin rather than a standard course of vancomycin (conditional recommendation, moderate certainty of evidence). **Comment:** This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources. Vancomycin remains an acceptable alternative.

II. In patients with recurrent CDI episode(s), should fidaxomicin be used rather than vancomycin?

Recommendation:

I. In patients with recurrent CDI episodes, we suggest fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (conditional recommendation, low certainty evidence). **Comment**: Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first CDI recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin.

II.

III. In patients with a CDI episode, should bezlotoxumab be used as a co-intervention along with standard-of-care (SOC) antibiotics rather than SOC antibiotics alone?

***Recommendation*:**

I. For patients with a recurrent CDI episode within the last six months, we suggest using bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (conditional recommendation, very low certainty of evidence). **Comment:** This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations. In settings where logistics is not an issue, patients with a primary CDI episode and other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host [per history or use of immunosuppressive therapy], and severe CDI on presentation) may particularly benefit from receiving bezlotoxumab. Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited. The FDA warns that "in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk".

II.

INTRODUCTION

Since publication of the 2017 Clinical Practice Guidelines for *Clostridioides* (formerly *Clostridium*) *difficile* Infection (CDI) [1], new relevant evidence has emerged for treatment options in the management of CDI in adults. The previous guidelines included pediatric treatment recommendations, but the scope of this focused update is restricted to adults and includes new data for fidaxomicin and for bezlotoxumab, a monoclonal antibody targeting toxin B produced by *C. difficile*. Both of these agents have increased clinical efficacy and other advantages over older agents, but implementation may be challenging because of initial monetary cost and logistics. In addition, the shift towards more sensitive diagnostic strategies emphasizes the importance of selecting appropriate patient populations and establishing the correct diagnosis when considering the use of these agents. While additional data have been published for other treatment entities, the quality of the data was determined not sufficient to alter our current treatment recommendations. New estimates on the burden of CDI have also been reported by Centers for Disease Control and Prevention [2]. While the adjusted estimate for total CDI burden nationally decreased by 24% from the previous report, they still estimated 462,100 cases annually and the burden of first CDI recurrences was unchanged. Recurrent CDI remains one of the most important treatment challenges for clinicians with estimates of 31,300 and 38,500 recurrences for community-associated and health care-associated cases, respectively, in 2017 [2].

This focused update includes three new recommendations for the treatment of CDI in adults, two of which modify our previous recommendations on treatment of an initial CDI episode and treatment of a first recurrent CDI episode. The other recommendation is a new recommendation for use of an adjunctive treatment agent for CDI. These new recommendations are also included in an updated table from the previous guidelines (see Table 1, Recommendations for the Treatment of *C. difficile* Infection in Adults). While the previous recommendation for use of fecal

microbiota transplantation (FMT) has not been changed, it should be noted that three separate safety alerts have been published by the Federal Drug Administration (FDA) since June of 2019, which outline adverse events or potential adverse events among recipients of FMT. Two alerts document transmission of pathogenic *Escherichia coli* from donor to FMT recipients, some of whom became ill and some of whom died [3-5]. The other alert concerns the potential for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6]. As a reminder, FMT is recommended only for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments and where appropriate screening of donor and donor fecal specimens has been performed, in accordance with these newer FDA recommendations [4, 5].

The purpose of this guideline is to provide evidence-based guidance on the most effective management of CDI and recurrent CDI in adult patients. The target audience for these guidelines includes general physicians, infectious diseases specialists, gastroenterologists, pharmacists, and other healthcare providers managing this condition.

METHODOLOGY

Clinical Practice Guidelines

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [7]. The IDSA Handbook for Clinical Practice Guidelines Development provides more detailed information on the processes followed throughout the development of this guideline [8].

Guideline Panel Composition

The Chair of the guideline panel (S.J.) was selected by the IDSA Standards and Practice Guidelines Committee (SPGC). A total of seven panelists comprised the full panel. The panel included physicians and pharmacists with expertise in infectious diseases, gastroenterology, pharmacy, medical microbiology and epidemiology. Panelists also were diverse in gender, geographic distribution, and years of clinical experience. A guideline methodologist (V.L.) oversaw all methodological aspects of the guideline development and identified and summarized the scientific evidence using the "PICO" format (Patient/Population [P]; Intervention/Indicator [I]; Comparator/Control [C]; Outcome [O]) questions. IDSA staff (G.D., R.G.) oversaw all administrative and logistic issues related to the guideline panel.

Disclosure and Management of Potential Conflict of Interest

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guideline Committee (SPGC) Chair, the SPGC liaison to the Guideline panel and the Board of Directors liaison to the SPGC, and if necessary, the COI Ethics Committee. This assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of this guideline for the disclosures reported to IDSA.

Clinical Questions and Evidence Review

The last iteration of the clinical practice guideline for *Clostridium difficile* infection in adults and children was completed late 2017, and published in *Clinical Infectious Diseases* early 2018 [1]. By the time of its publication and dissemination, new relevant evidence had emerged which could either change the current recommendations presented in the 2017 guideline or require the development of new recommendations on topics not previously addressed. Consequently, a list of relevant clinical questions for this focused update was created, reviewed, and approved by the panel.

As per the GRADE approach, all outcomes are not considered equally important in the decision-making process. These need to be ranked by importance to permit weighing the balance of desirable and undesirable consequences and thus providing guidance on the optimal course of action as well as to determine the certainty of evidence for a specific recommendation**.** Outcomes of interest were identified *a priori* by the panel and their relative importance for decision-making (either "critical", 'important but not critical" or "of limited importance") was explicitly determined by voting for each PICO question. Critical and important outcomes (presented in their respective Summary of Findings Tables (Tables 2, 3, and 4) were those that ultimately provided guidance on the optimal course of action. Resource use (monetary cots and cost-effectiveness for example) was rated as "of limited importance" by the panel and was not included in the initial assessment. Nevertheless, resource use was considered as a key factor when developing the recommendations.

A Medical Librarian (S.K.) designed the literature searches and MeSH terms for Ovid Medline Ovid platform including Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, and Cochrane Central Register of Controlled Trials. Searches were limited to studies published in English. For clinical questions that needed updating from the 2017 guideline, the searches were restricted to studies published since the last systematic review of the literature performed (i.e., from October 2016 to May 2020); for new clinical questions, no search restriction

was applied based on year of publication. The initial formal literature search was performed in May 2019 and an update of the review of the literature was conducted again in May 2020. To supplement the electronic searches, the panelists had the option of manually searching journals, conference proceedings' reference lists, regulatory agency websites for relevant information, as well as communicating with study sponsors for post hoc analysis.

A subgroup of panelists (K.W.G., A.G.L., S.J., A.M.S.) screened titles and abstracts of all identified citations. All potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria that were tailored to meet the specific population, intervention, and comparator of each clinical question. Abstracts and conference proceedings, letters to the editor, editorials, review articles, and unpublished data were excluded. The results of the literature search were supervised and thoroughly reviewed by the guideline methodologist for the final selection of the relevant articles. For recommendations requiring an update, all prior articles identified from the 2017 clinical practice guideline and meeting the predefined inclusion and exclusion criteria were also considered for final selection. Once the articles were selected, the two panelists extracted the data independently in duplicate for all patient-important outcomes as pre-determined. Where applicable, the guideline methodologist pooled the data using random effects model (fixed effects model for pooling of rates) using RevMan 5.4 [9].

The guideline methodologist prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. The risk of bias was assessed by using the Cochrane risk of bias tool for randomized controlled trials (RCTs) [10]. The certainty in the evidence was determined for each critical and important outcome, and then for each recommendation using the GRADE approach for rating the certainty of the evidence (see Figure 1) [11, 12]. The Evidence Profile tables (presenting the balance between important desirable and undesirable outcomes and the certainty in the evidence) and the Evidence to Decision frameworks (summarizing the other key factors considered when developing the recommendations such as values and preferences, resource

use, equity, acceptability and feasibility) were developed in GRADEpro Guideline Development Tool [13] and reviewed by the Chair and edited as appropriate. The final evidence summaries were presented to the whole panel for deliberation and drafting of recommendations. Literature search strategies, Evidence Profile tables, Evidence to Decision frameworks and additional data, such as forest plots and characteristics of included studies when appropriate, can be found in the Supplementary Materials.

Development of Clinical Recommendations

All recommendations were labeled as either "strong" or "conditional" according to the GRADE approach [8]. The words "we recommend" indicate strong recommendations and "we suggest" indicate conditional recommendations. **Figure 1** provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. In summary, a "strong" recommendation implies that most individuals in this situation would want the recommended course of action and only a small proportion would not, while a "conditional" recommendation means that the majority of individuals in this situation would want the suggested course of action, but many would not. The latter recognizes that different choices will be appropriate for different patients and that clinicians must help each patient to arrive at a management decision consistent with their own values and preferences. For recommendations where the comparators are not formally stated, the comparison of interest is implicitly referred to as "not using the intervention". "Research Needs" were noted for recommendations as deemed appropriate by the panel.

Final presentation of evidence summaries and the development of the recommendations was performed by two conference calls with the whole expert panel on June 22 and 26, 2020. All members of the panel participated in the preparation of the draft guideline and approved the recommendations.

Revision process

Feedback was obtained from three external peer reviewers. The IDSA Standards and Practice Guidelines Committee and Board of Directors and the Society for Healthcare Epidemiology of America (SHEA) Board of Directors reviewed and approved the guideline prior to dissemination. The Society of Infectious Diseases Pharmacists (SIDP) and American Society of Health-System Pharmacists (ASHP) Guideline Committees reviewed and endorsed the guideline prior to publication.

Revision Dates

Approximately every two years and more frequently if needed, IDSA and SHEA will determine the need for revisions to the guideline by an examination of the current literature and the likelihood that any new data will have an impact on the recommendations. Any revision to the guideline will be submitted for review and approval to the appropriate Committees and Boards of IDSA and SHEA.

RECOMMENDATIONS

I. In patients with an initial CDI episode, should fidaxomicin be used rather than vancomycin?

Recommendation:

I. For patients with an initial CDI episode, we suggest using fidaxomicin rather than a standard course of vancomycin (conditional recommendation, moderate certainty of evidence).

Comment: This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources. Vancomycin remains an acceptable alternative.

Background

Fidaxomicin, approved by the FDA in May 2011, was the first new drug approved for CDI treatment in 31 years [14, 15]. This drug has several characteristics that make it an attractive therapy for CDI. Like vancomycin, it is orally delivered with minimal systemic absorption and it is highly active against *C. difficile in vitro*. In addition, resistance to fidaxomicin has rarely been reported in *C. difficile* [16]. Unlike vancomycin, there are no other treatment indications and it is a "narrow spectrum" agent with more limited activity against other enteric commensal bacteria [17]. These pharmacologic characteristics have translated into clinical studies showing improved sustained clinical response (initial clinical response without subsequent recurrent symptoms) for patients with CDI. Initial clinical responses are similar for both agents, whereas CDI recurrences are fewer following fidaxomicin. The evidence is more robust for patients with an initial episode of CDI, but recent additional studies support its use in recurrent CDI.

Summary of evidence

The 2017 guideline included two non-inferiority RCTs evaluating the efficacy of fidaxomicin compared with vancomycin in patients with confirmed CDI on sustained response, on initial clinical cure, on drug-related adverse events, and on all-cause mortality [14, 15]. Our update of the literature identified two more recently published RCTs [18, 19] addressing similar clinical questions (see Figure 2). All studies reported a similar rate of patients presenting with an initial episode of CDI (ranging from 79 to 86%) and with a comparable clinical severity on presentation (although definitions of severity differed between studies); the latter two studies restricted inclusion only to inpatients in contrast with earlier studies where only 59 to 68% were hospitalized. All studies compared fidaxomicin to a standard regimen of vancomycin (125 mg orally four times daily for 10 days). Patients included in the Guery 2018 study received an extended fidaxomicin regimen (200 mg orally twice daily for five days, followed by once daily on alternate days on day 7-25) rather than a

standard regimen (200 mg orally twice daily for 10 days), although both regimens amounted to the same total dose of fidaxomicin (see Supplementary Materials).

The pooled analysis of the four included studies demonstrates that fidaxomicin increased sustained response of CDI four weeks after end of therapy as compared with standard vancomycin (risk ratio [RR]: 1.16; 95% confidence interval [CI]: 1.09 to 1.24; moderate certainty of evidence), while its use resulted in comparable CDI initial clinical cure (RR: 1.00; 95% CI: 0.96 to 1.04; moderate certainty of evidence) and failed to show a reduction in mortality (RR: 0.90; 95% CI 0.66 to 1.23; moderate certainty of evidence). The evidence also suggests that fidaxomicin did not result in an increase in drug-related adverse events (RR: 1.02; 95% CI: 0.76 to 1.36; low certainty of evidence). The overall certainty in the evidence was rated as moderate due to the unblinded design of the Guery 2018 study, especially for self-reported outcomes, and to imprecision issues due to small number of events for some outcomes (see Table 2).

The higher sustained clinical response associated with fidaxomicin may be especially beneficial in patients at greater risk for recurrence of CDI [20, 21]. Risk factors for recurrence may include age ≥65 years, compromised immunity, severe CDI, and ribotype 027/078/244 infections [22, 23]. However, the potential added benefits of fidaxomicin in these higher risk groups has not been studied in prospective randomized controlled trials. A history of prior CDI is a prominent risk factor for further recurrences and is addressed separately below.

The previous iteration of the treatment guidelines recommended either vancomycin or fidaxomicin for treatment of an initial CDI episode for both non-severe and severe (but not fulminant) disease [1]. Either drug was preferred over metronidazole, and this was a strong recommendation. With the additional RCT data confirming the lower recurrence rate with fidaxomicin seen in the original non-inferiority RCTs, the preference is now fidaxomicin over vancomycin for an initial CDI episode, but this is a conditional recommendation. The previous iteration of the guidelines also recommends vancomycin (500 mg four times daily orally or by

nasogastric tube) rather than fidaxomicin for treatment of fulminant (previously known as severe, complicated) CDI. This recommendation remains unchanged. Fulminant CDI is not common. Furthermore, the studies demonstrating equivalent efficacy for fidaxomicin and vancomycin in initial clinical response to therapy for CDI generally excluded patients with fulminant disease. Hence, there are no available data supporting the use of fidaxomicin for treatment of fulminant CDI.

Rationale for recommendation

The panel agrees that the overall balance of benefits and harms favors using fidaxomicin over vancomycin for an initial episode of CDI and that the certainty of evidence was moderate (see Supplementary Materials). Although the panel recognizes potential variability exists on how patients value the avoidance of a subsequent CDI episode, the moderate costs and possible reduction in equity, the panel judges that the use of fidaxomicin is likely cost-effective, acceptable to patients and their providers, and feasible to implement when considering the dosing and duration of fidaxomicin treatment.

Achieving both initial and sustained clinical responses are key goals of CDI therapy. The observed lower recurrence rates following fidaxomicin therapy as compared with vancomycin are an important advantage. Quality-of-life scores decrease in patients with CDI recurrence compared with patients with an initial episode of CDI based on the health-related Cdiff32 questionnaire study [21]. CDI recurrence also leads to additional diagnostic and treatment costs and, in some instances, to hospital admission or fulminant disease. Hence, the use of fidaxomicin substantially improves desirable consequences (including a moderate increase in sustained resolution of CDI at four weeks, with comparable CDI initial clinical cure at end of therapy), while not increasing undesirable consequences (no increase in drug-related adverse events and mortality). Fidaxomicin also has an advantage of twice daily dosing whereas vancomycin is administered four times daily. Considering the moderate improvement in desirable effects in the absence of increased undesirable effects, the balance favors the use of fidaxomicin rather than vancomycin in patients with an initial CDI episode.

A limited number of cost effectiveness models have compared oral fidaxomicin 200 mg two times daily to oral vancomycin 125 mg four times daily for treatment of an initial CDI episode [24-28]. For example, a study based on data from the registration trials [14, 15] used a "willingness to pay" threshold of $50,000 per quality-adjusted life-year (QALY) gained and found that fidaxomicin had incremental cost-effectiveness ratios ranging from €26,900 (~USD 32,000) to €44,500 (~USD 52,000) per QALY gained versus vancomycin [24]. Another study comparing fidaxomicin and vancomycin use as initial therapy for CDI in the general population reported similar total treatment costs of $14,442 for fidaxomicin and $14,179 for vancomycin [25]. Cost-effectiveness studies of fidaxomicin use in recurrent CDI are discussed below (see Supplementary Materials, Table s5), but the panel acknowledged the uncertainty of the estimates and conclusions reported in these studies due to several limitations (cost-effectiveness studies are highly influenced by the assumptions made and data input in the model (e.g., type of population, prevalence of disease, rate of recurrence and rate of hospital readmission for CDI), and prone to publication bias since often funded by industry).

The panel agrees that the cost-effectiveness analysis probably favors the use of fidaxomicin over vancomycin in patients with an initial episode of CDI, due to its greater effectiveness with respect to sustained clinical response, but acknowledge that implementing this recommendation probably reduces equity due to variation in medical insurance coverage.

Implementation considerations

Fidaxomicin is orally administered and is generally well-tolerated. However, its cost may be prohibitive without adequate insurance coverage. The average wholesale price of $4,871 per 20-tablet package [29] has not changed appreciably since launch of the drug in 2011; however, patient assistance mechanisms are available.

Conclusion and research needs

The panel suggests the use of fidaxomicin as the preferred therapy of an initial CDI episode to improve sustained response after therapy but recognizes that vancomycin remains an acceptable alternative if fidaxomicin is not available. Additional, well-designed, independent, cost-effectiveness studies for patients with CDI are needed to improve the strength of this recommendation given that cost is a substantial barrier to fidaxomicin use. In particular, studies that utilize the total (patient and insurance) cost savings from reduced CDI recurrences to determine to what extent the greater initial acquisition cost is offset are needed. These studies must also consider the non-financial benefits of reducing CDI recurrences. Comparative trials of extended-pulsed dosing of fidaxomicin to standard fidaxomicin dosing and potentially to extended-dosing of vancomycin are needed to understand where best to implement this regimen. The efficacy of fidaxomicin for treatment of fulminant CDI also warrants study.

II. In patients with recurrent CDI episode(s), should fidaxomicin be used rather than vancomycin?

Recommendation:

I. In patients with recurrent CDI episodes, we suggest fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (conditional recommendation, low certainty evidence). **Comment**: Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first CDI recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin.

II.

Background

As noted above, there is robust evidence supporting fidaxomicin treatment for patients with an initial episode of CDI. Recent additional studies have been identified which also support its use in recurrent CDI. Although optimal dosing regimens are still yet to be defined, fidaxomicin has pharmacologic characteristics which may favor use of this agent in the management of patients with recurrent CDI. With the understanding that risk of a subsequent recurrence increases with each episode of CDI, we continue to make a distinction between patients with a first CDI recurrence and those with multiple recurrences (two or more recurrences) [30].

Summary of evidence

The best available evidence identified to inform this recommendation consisted of subgroup analyses originating from three different randomized controlled trials [14, 15, 18]. The 2017 guideline discussed one study [31] reporting a pooled analysis of patient subgroups with a first CDI recurrence from two different RCTs comparing the efficacy of fidaxomicin with vancomycin [14, 15]. Our literature update identified a third RCT where information on patients experiencing recurrent CDI (one or more recurrences) was available [18] (see Figure 2). Randomization was stratified for the number of previous episode(s) of CDI in all three RCTs. Patients included in the Guery 2018 study (EXTEND trial) received an extended fidaxomicin regimen albeit amounting to the same total dose of fidaxomicin as a standard course [18] (see Supplementary Materials).

The pooled analysis of the three included subgroups demonstrates that fidaxomicin increased sustained response of CDI 30 days after end of therapy compared with vancomycin (RR: 1.27; 95% CI: 1.05 to 1.54; low certainty evidence), while the evidence failed to show a beneficial effect of fidaxomicin on sustained response at 90 days (RR: 1.56; 95% CI: 0.99 to 2.44; very low certainty evidence). The use of fidaxomicin resulted in comparable CDI initial clinical cure (RR: 1.03;

95% CI: 0.94 to 1.14; low certainty evidence) but failed to show a reduction in all-cause mortality (RR: 0.81; 95% CI: 0.20 to 3.38; low certainty evidence). The evidence is very uncertain regarding the reduction in serious adverse events at 90 days with the use of fidaxomicin compared with vancomycin (RR: 0.68; 95% CI: 0.35 to 1.29; very low certainty evidence). The overall certainty in the evidence was rated as low due to serious concerns regarding imprecision (small number of events and small sample size of these subgroups) as well as risk of bias due to the unblinded design in the EXTEND trial (for self-reported outcomes) (see Table 3).

The previous iteration of the treatment guidelines included fidaxomicin as an option for treating recurrent CDI, although the preference for choosing fidaxomicin or vancomycin as treatment for patients with a first CDI recurrence was based solely on the treatment regimen given for the initial episode [1]. With the addition of a new RCT comparing fidaxomicin and vancomycin, which also included patients with recurrent CDI [18], evidence now suggests fidaxomicin should be preferred over vancomycin in this setting. It should be noted that vancomycin also predictably results in a successful initial clinical cure, even for patients with recurrent CDI, and vancomycin in an extended, tapered and pulsed regimen has been used successfully in managing patients with multiple CDI recurrences [32]. We completed an additional ad-hoc subgroup analysis of the RCT data for fidaxomicin and vancomycin, separating patients with one prior CDI recurrence and two or more recurrences; the relative risk for sustained response to fidaxomicin at 30 days following end of therapy in patients with one prior recurrence was 1.23 (95% CI: 1.01 to 1.49) and 2.0 (95% CI: 0.88 to 4.54) for patients with two or more prior recurrences. Both subgroups showed an increased in sustained response, despite the effect of fidaxomicin failing to achieve a statistical difference in patients with two or more prior recurrences. The certainty for the effect in the latter group was very low as data were only available from one study judged at high risk of bias (potential unblinding for a self-reported outcome) and imprecise due to the very small number of patients randomized (n=20) [18] (see Supplementary Materials).

Evidence supporting an extended-pulsed regimen of fidaxomicin comes from an *in vitro* human gut model study, which showed persistence of fidaxomicin at above inhibitory concentrations which might prolong suppression of *C difficile* and facilitate recovery of a protective microbiota [33]. Indeed, this study provided the rationale for the extended-pulsed fidaxomicin regimen that was used by Guery et al [16]. Because fidaxomicin, like vancomycin, is minimally absorbed and achieves high fecal concentrations, fidaxomicin in a tapered and pulsed regimen following suppressive treatment has been used successfully in patients with multiple CDI recurrences [34]. Appropriate comparative data for these patients, however, are lacking. The RCT comparing extended-pulsed fidaxomicin with vancomycin (EXTEND trial) showed improved sustained responses and one of the lowest rates of recurrence ever reported (2% compared to 17% with vancomycin at day 40) [18]. The comparison in this study, however, was a standard course of vancomycin and the sustained response achieved was similar to that achieved in the phase III trials comparing a standard course of fidaxomicin with vancomycin [35]. In addition, the treatment phase of this regimen (200 mg of fidaxomicin) was only given for five days which was barely sufficient to resolve CDI in the *in vitro* model [33] and the time to diarrhea resolution in the EXTEND trial was 34.0 hours (95% CI: 25.0 to 49.0) compared with 22.0 hours (95% CI: 10.0 to 30.0) for vancomycin [18].

Rationale for recommendation

The panel agrees that the overall balance of benefits and harms favors using fidaxomicin rather than vancomycin for patients with CDI recurrence and that the certainty of evidence was low (see Supplementary Materials). Despite the moderate costs and possible reduction in equity, the panel judges that patients' values and preferences, cost-effectiveness, acceptability, and feasibility further support the preferential use of fidaxomicin over vancomycin.

The panel recognizes potential variability on how patients value the avoidance of a subsequent CDI episode. Quality-of-life scores decrease in patients with recurrent CDI compared

with patients with an initial episode of CDI, and further consistently decrease with increasing number of CDI episodes [21]. Panel's expert experience also suggests that patients with multiple recurrent CDI episodes become increasingly desperate with each subsequent CDI episode and are willing to consider non-standard or non-approved therapies. Consequently, the panel judges that patients experiencing recurrent CDI will invariably put a high value on avoidance of a subsequent CDI episode. Furthermore, the use of fidaxomicin is considered likely acceptable to patients and their providers and feasible to implement when considering the dosage and duration of fidaxomicin.

Two industry sponsored cost-effectiveness models using the EXTEND trial data reported that despite higher acquisition costs than vancomycin, extended-pulsed fidaxomicin was cost-effective [26, 27]. The probability of cost-effectiveness for extended-pulsed fidaxomicin at a willingness-to-pay threshold of £30,000 (~USD 38,000) per QALY gained was 76% [26] and 99.9% at a threshold of €30,000 (~USD 35,000) per QALY gained [27]. Two non-industry sponsored decision analyses for recurrent CDI found fidaxomicin was more cost-effective than vancomycin for multiple CDI recurrences if FMT was not an option [36] and vancomycin was most cost-effective for first CDI recurrence in outpatients [37]. These results are highly influenced by the assumptions made and data input in the model. The panel agrees that the cost-effectiveness analysis probably favors the use of extended-pulsed fidaxomicin over vancomycin in patients with recurrent CDI but acknowledges that implementing this recommendation also probably reduces equity due to variation in medical insurance coverage.

Implementation considerations

Although fidaxomicin is orally administered and is generally well-tolerated, the cost is prohibitive without adequate insurance coverage. The average wholesale price of $4,871 per 20-tablet package [29] has not dropped appreciably since launch of the drug in 2011, although patient assistance mechanisms are available.

Conclusion and research needs

The panel suggests the use of fidaxomicin as the preferred therapy for patients with recurrent CDI episode(s) to improve sustained response after therapy. More well-designed RCTs for patients with recurrent CDI, particularly multiply recurrent CDI, are needed to improve the strength of recommendations. In particular, studies with more appropriate controls for extended-pulsed fidaxomicin should help clarify the role of this dosing strategy for patients with recurrent CDI both in terms of efficacy and quality of life.

III. In patients with a CDI episode, should bezlotoxumab be used as a co-intervention along with standard-of-care (SOC) antibiotics rather than SOC antibiotics alone?

***Recommendation*:**

I. For patients with a recurrent CDI episode within the last six months, we suggest using bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (conditional recommendation, very low certainty of evidence). **Comment:** This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations. In settings where logistics is not an issue, patients with a primary CDI episode and other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host [per history or use of immunosuppressive therapy], and severe CDI on presentation) may particularly benefit from receiving bezlotoxumab. Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited. The FDA warns that "in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk".

Background

Bezlotoxumab was approved by the FDA in October 2016 and was the first humanized monoclonal antibody against *C. difficile* toxin B approved for the prevention of recurrent CDI in high-risk adults in conjunction with SOC antibiotics. Bezlotoxumab is given as a one-time infusion at a recommended dose of 10 mg/kg over 60 minutes. Bezlotoxumab has an elimination half-life of approximately 18 days, translating to measurable antibody concentrations up to three months after the one time infusion [38]. These pharmacologic characteristics translated into two phase III clinical studies (MODIFY I/II) showing reduced rates of CDI recurrence in patients with CDI given bezlotoxumab compared with placebo.

Summary of evidence

Our review of the literature identified one study reporting a pooled analysis of two phase III RCTs evaluating bezlotoxumab as an adjunctive therapy to SOC antibiotics in patients with primary or recurrent CDI [22]. The efficacy of adding bezlotoxumab to SOC antibiotics was measured on different patient-important outcomes such as CDI recurrence after initial clinical cure, CDI-associated hospital readmission, drug-related adverse events and all-cause mortality. Patient-important outcomes were all reported in the study published by Wilcox and al. [22], except for CDI-associated hospital readmission which was only reported in a subgroup analysis of patients hospitalized at the time of randomization [22, 23] (see Figure 3). Efficacy was also measured in prespecified subgroups at risk for recurrent CDI including age >65 years, history of CDI, compromised immunity, severe CDI, and infection with certain virulent strains (ribotypes 027/078/244). Of note, the determination of 'immunocompromise' in the phase III trials was made by study investigators based on medical history or use of immunosuppressive therapy without further clarifications. CDI represented a primary episode for 73% of participants and severe CDI accounted for 16% of cases; however, the assessment of severity was performed at the point of randomization to study drug rather than when SOC antibiotic treatment was initiated. Thus, it is likely that the true proportion of CDI cases with

severe disease was greater than 16%. Approximately 68% of patients were hospitalized at the time of recruitment. SOC antibiotics consisted of vancomycin (48%), metronidazole (47%), and fidaxomicin (4%). Participants received one 60-minute intravenous infusion of bezlotoxumab (10 mg/kg body weight) in addition to SOC antibiotics (see Supplementary Materials).

The pooled analysis of these two RCTs demonstrates that the addition of bezlotoxumab reduced CDI recurrence after initial clinical cure at 12 weeks (RR: 0.62; 95% CI: 0.51 to 0.75; moderate certainty evidence) and reduced CDI-associated hospital readmission at 30 days (RR: 0.46; 95% CI: 0.29 to 0.71; very low certainty evidence), but failed to show a reduction in mortality (RR: 0.94; 95% CI: 0.66 to 1.34; low certainty evidence). The certainty in the evidence for benefits was initially rated as moderate, mainly due to indirectness of the evidence when fidaxomicin is used as the SOC antibiotics (see Table 4).

These two phase III trials enrolled patients between November 2011 and May 2015 [22]. During this time period, the IDSA-SHEA 2010 Clinical Practice Guidelines for *C. difficile* infection suggested metronidazole be used for mild-moderate CDI and oral vancomycin be given for more severe disease [39]. Following these guideline recommendations, most patients received either metronidazole (47%) or oral vancomycin (48%) in the phase III bezlotoxumab clinical trials. However, based on decreasing efficacy of metronidazole, SOC antibiotics now includes vancomycin and fidaxomicin in the updated 2017 IDSA-SHEA CDI guidelines [1]. Despite planned sub-analyses of the bezlotoxumab phase III trials demonstrating that the choice of SOC antibiotics did not influence the effect on clinical outcomes, uncertainty remains regarding the generalizability of this evidence when fidaxomicin is used as the SOC antibiotic (fidaxomicin being administered as the SOC antibiotic in less than 5% of the studied cohort [n=60 patients]) [23].

One study reanalyzed the modified intent-to-treat population of those who received bezlotoxumab or placebo in the phase III trial (n = 1554) by risk factors for recurrent CDI that were prespecified in the statistical analysis plan: age ≥65 years, history of CDI, compromised immunity,

severe CDI, and certain virulent ribotypes (ribotypes 027/078/244) [23]. Placebo participants with any risk factor in the phase III trials experienced a recurrent CDI rate of 37.2% compared with 20.9% amongst those without a risk factor. Risk of CDI recurrence also increased with the number of risk factors; patients with one risk factor experienced a 31.3% likelihood of CDI recurrence compared with a 46.1% likelihood in patients with three or more risk factors. Absolute rate reduction for bezlotoxumab recipients was highest in patients with greater than or equal to three risk factors (-24.8%; 95% CI: -39.1 to -9.3), two risk factors (-14.2%; 95% CI: -24.0 to -4.1), or patients with one (-14.2%; 95% CI: -21.9 to -6.4) compared with patients with no risk factors (-2.1%; 95% CI: -11.1 to 6.9). Patients with primary CDI and no risk factors likewise did not benefit from bezlotoxumab. However, there was an effect seen in primary CDI patients who also had risk factors for recurrence. The risk difference for patients with primary CDI and with at least one risk factor who received bezlotoxumab was -15.1% (95% CI:-22.0 to -8.1) and -1.5% (95% CI:-10.7 to 7.7) for primary CDI patients without any risk factor (see Figure 5).

To assess whom might benefit the most from receiving bezlotoxumab in addition to SOC, we completed an additional post-hoc subgroup analysis using data supplied by the sponsor of the MODIFY trials to estimate the effect of using bezlotoxumab on CDI recurrence after initial clinical cure at 12 weeks in patients with recurrent CDI . The risk difference for patients with one episode of CDI in the previous six months who received bezlotoxumab was -16.8% (95% CI: -29.2 to -4.5) and -15.9% (95% CI: -33.1 to 1.4) for patients with two or more episodes in the past six months. This effect was judged very uncertain due to the lack of stratification for these risk groups during randomization and the number of patients included in the subgroups. However, there was no heterogeneity (I-square 0%) between these subgroups and the pooled effect for patients with a recurrent CDI within the last 6 months was -17.4% (95% CI: -27.5 to -7.3) (see Figure 4).

The evidence also suggests that drug-related adverse events did not differ among patients receiving bezlotoxumab from those not receiving bezlotoxumab (RR: 1.27; 95% CI: 0.88, 1.85; low

certainty evidence). Nevertheless, a post hoc analysis showed that patients with a history of congestive heart failure who received bezlotoxumab may be at increased risk of heart failure and mortality in the 12 weeks following the infusion (RR: 2.64; 95% CI: 1.00 to 7.03 and RR: 1.56; 95% CI: 0.83 to 2.92, respectively) [40].

The pivotal clinical trials have further been supported by two real-world studies that demonstrated similar reductions in CDI recurrence after initial clinical cure (ICC) among patients at high-risk for recurrent CDI who received bezlotoxumab [41, 42]. One of these studies, a retrospective multicentered cohort study, evaluated 200 patients receiving bezlotoxumab in addition to SOC antibiotics (vancomycin in 130 patients [68.5%], fidaxomicin in 60 patients [30.0%], and metronidazole in three patients [1.5%]) from United States outpatient infusion centers from 2017 to 2018 [41]. Most patients had prior CDI episodes (86.5%) and had at least two risk factors for recurrent CDI (79.0%). The rate of recurrent CDI at 90 days was 15.9% (31 of 195 patients), which did not differ when stratifying by SOC antibiotics received (vancomycin fixed dose in 10 out of 73 patients [13.7%], vancomycin tapered regimen 11 out of 60 patients [18.3%], fidaxomicin in 9 out of 59 patients [15.2%], and $P = 0.76$). This finding further supports the sub-analyses of the bezlotoxumab phase III trials demonstrating that the choice of SOC antibiotics did not influence the effect of bezlotoxumab on clinical outcomes, but the combined effect of bezlotoxumab to fidaxomicin will need to be studied further.

Rationale for recommendation

The panel agrees that the overall balance of benefits and harms favors adding bezlotoxumab to SOC antibiotics for patients with a CDI episode and at least one risk factor for recurrence (recurrent CDI episode within the last six months, age $\geq$ 65 years, immunocompromised host, and severe CDI on presentation), but seems more favorable in patients with multiple risk factors of recurrent CDI and especially in patient with a prior CDI in the last 6 months (See Figure 4 and Table s12, Supplementary Materials). The certainty of evidence is moderate overall, but very low in

subpopulations at high risk of CDI recurrence. Despite limited feasibility due to logistical considerations in certain settings (particularly for patients with primary CDI, see "implementation considerations" below), the moderate costs, and possible reduction in equity, the panel judges that patients' values and preferences (especially for those experiencing recurrent CDI), cost-effectiveness, and acceptability for patients and providers further support the addition of bezlotoxumab to SOC antibiotics. Consequently, the panel suggests the addition of bezlotoxumab to SOC antibiotics in patients with a recurrent CDI within the last six months but also acknowledges that in settings where logistics are not an issue, patients with a primary CDI episode and with at least one other risk factors for CDI recurrence may also benefit from receiving bezlotoxumab.

Two industry sponsored cost effectiveness studies using data from the MODIFY I and II clinical trials evaluated the addition of bezlotoxumab compared with SOC antibiotics alone using European and USA cost estimates, respectively [43, 44]. Both models focused on cost effectiveness of the addition of bezlotoxumab based on the same risk factors for recurrence studied in the MODIFY I/II studies and sub-analyses. Using European cost estimates, the probability of cost-effectiveness for bezlotoxumab at a willingness to pay threshold of €21,000 (~USD 25,000) per QALY was highest for patients aged ≥65 years with at least one CDI recurrence in the previous six months (99.6%), followed by those with at least one CDI recurrence in the previous six months of any age (94.5%), or age ≥65 years (85.5%). All high-risk variables had at least a 50% probability of being cost-effective at that set threshold. Using U.S. cost estimates demonstrated similar results. Bezlotoxumab was associated with 0.12 QALYs gained and was cost effective in preventing CDI in the entire trial population, with an incremental cost-effectiveness ratio of $19,824/QALY gained. Sub-populations that were shown to be most cost effective, especially if the subgroups had one or more episodes of CDI in the previous six months, were immunocompromised patients, patients aged ≥65 years, and patients with severe CDI on presentation. A non-industry sponsored decision tree analysis found

that bezlotoxumab plus vancomycin was less cost-effective than vancomycin for first recurrence in outpatients [37]. These results are highly influenced by the assumptions made and data input in the model.

The panel agrees that the cost-effectiveness analysis favors the addition of bezlotoxumab to SOC antibiotics in patients with a recurrent CDI episode within the last six months but acknowledge that implementing this recommendation also probably reduces equity due to variation in medical insurance coverage.

Implementation considerations

The infusion of bezlotoxumab should be performed while a patient is receiving SOC antibiotics and has been shown to be effective in preventing CDI if administered at any time before ending antibacterial treatment [45]. Implementation, however, is often limited by logistical and feasibility considerations, particularly for patients with primary CDI. The population currently targeted for receipt of bezlotoxumab is quite different from the population included in the phase III RCTs. In the phase III RCT studies, the majority of participants had primary CDI episodes (73%) and were hospitalized at the time of recruitment (68%) [22]. In contrast, real-world experience indicates the majority of patients receiving bezlotoxumab have had prior CDI episodes (87%) and receive the infusion in outpatient infusion centers [41]. Identifying patients with primary CDI who might benefit from bezlotoxumab and establishing a referral to an infusion center is complicated by fact that they are typically not seen by Infectious Disease or Gastroenterology specialists, but are initially managed by primary care or other physicians often without experience managing CDI. Panel's expert experience has shown that many patients have difficulty receiving bezlotoxumab even after referral, most commonly due to insurance denials. Despite these considerations, the use of bezlotoxumab is considered likely acceptable to patients and their providers and feasible to implement.

Conclusion and research needs

The panel suggests using bezlotoxumab as a co-intervention along with SOC antibiotics for patients with a recurrent CDI with the last six months to reduce the risk of a subsequent CDI recurrence after initial clinical cure. In patients with a history of CHF, the FDA warns that bezlotoxumab should be reserved for use when the benefit outweighs the risk. Head-to-head trials of differing anti-CDI recurrence strategies using narrow-spectrum antibiotics that target *C. difficile*, restoration of the microbiome using biotherapeutics or FMT, or augmentation of the host immune response with agents such as bezlotoxumab given alone or in combination (e.g., in combination with fidaxomicin) are needed.

NOTES

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***Potential Conflicts of Interest*.** The following list is a reflection of what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Standard and Practice Guidelines Committee (SPGC) Chair, the SPGC liaison to the development panel and the Board of Directors liaison to the SPGC and, if necessary, the Conflict of Interest (COI) Ethics Committee. The assessment of disclosed relationships for possible COIs is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. **K.W.G.** has served as a consultant/advisor to Merck and Synthetic Biologics; receives research grants from Summit Therapeutics, Paratek Pharmaceuticals, Acurx Pharmaceuticals, Tetraphase Pharmaceuticals, and the National Institutes of Health (NIH); and has received research grants from Tetraphase Pharmaceuticals. **S.J** serves as an Advisory Board member for Bio-K+ and Acurx Pharmaceuticals; receives numeration from Pfizer as a member of the Data Monitoring Committee, and Ferring Pharmaceutical in developing an education monograph for

transition of care for *C. difficile*; has served as an Advisory Board member for Cutis Pharma and Summit Therapeutics; and served on the Steering Committee for Synthetic Biologics. **C.P.K.** serves as an advisor for Matrivax, Vedanta, Merck, Cour, Acurx Pharmaceuticals, Finch, Microbiota, and Milky Way Life Science; has served as an advisor for Artugen, Glutenostix, Innovate, and Sanofi; receives honoraria from Merck for serving as a symposium speaker; has received honoraria from Biocodex for serving as a symposium speaker; has held stock in Glutenostix; receives research funding from the NIH and the National Institute of Allergy and Infectious Diseases; has received research funding from Instit Merieux, Merck, and Allergan; currently serves as the President of the Society for the Study of Celiac Disease and as the Secretary for the Foundation for Celiac Disease Outcome Measures; and his organization, Beth Israel Deaconess Medical Center, has received organizational benefits from the Sydney Frank Foundation and Milky Way Life Sciences. **V.L.** has received past research funding from the Fonds de recherche du Québec Research (FRQ-S) **A.S.** has received honoraria from the American Society of Health-System Pharmacists. **M.H.W.** serves as an advisor for Summit and Seres; has served as an advisor for Merck and Astellas; receives research grants from Summit, Seres, the Centers for Disease Control and Prevention, the NIH, the United Kingdom Medical Research Council, and the European Union Innovative Medicines Initiative; and has received research grants from Merck and Astellas. All other no disclosures reported.

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Figure Legends:

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (Unrestricted use of the figure granted by the U.S. GRADE Network)

Figure 2. PRISMA Flow Diagram, PICOs 1 and 2 on the use of fidaxomicin vs vancomycin for initial or recurrent episode of CDI

Figure 3. PRISMA Flow Diagram, PICO 3 on the use of bezlotoxumab as a cointervention along with standard of care

Figure 4. Forest plot, PICO 3: Post-hoc subgroup analysis of CDI recurrence after ICC (follow up 12 weeks) *

*Data provided by company through personal communication with the guideline panel (post hoc analysis of Wilcox 2017)

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Figure 5. Forest plot, PICO 3: Post-hoc subgroup analysis of CDI recurrence after ICC (follow up 12 weeks) *

*Data published in Gerding 2018 (post hoc analysis of Wilcox 2017)

Table 1. Recommendations for the Treatment of *Clostridioides difficile* Infection (CDI) in Adults*

Clinical presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources.
	Alternative: Vancomycin 125 mg given four times daily by mouth for 10 days	Vancomycin remains an acceptable alternative.
	Alternative for non-severe CDI, if above agents are unavailable: Metronidazole, 500 mg three times daily by mouth for 10 – 14 days	Definition of non-severe CDI is supported by the following laboratory parameters: White blood cell count of 15,000 cells/mL or lower and a serum creatinine level less than 1.5 mg/dL
First CDI recurrence	Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for five days followed by once every other day for 20 days	
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg four times daily for 10–14 days, two times daily for seven days, once daily for seven days, and then every two to three days for two to eight weeks
	Alternative: Vancomycin 125 mg given four times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics**	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure***
Second or subsequent CDI recurrence	Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for five days followed by once every other day for 20 days	
	Vancomycin by mouth in a tapered and pulsed regimen	
	Vancomycin 125 mg four times daily by mouth for 10 days followed by rifaximin 400 mg three times daily for 20 days	
	Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatments for at least two recurrences (i.e., three CDI episodes) should be tried prior to offering fecal microbiota transplantation.
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given	Data when combined with fidaxomicin

	intravenously once during administration of SOC antibiotics**	are limited. Caution for use in patients with congestive heart failure**
Fulminant CDI	Vancomycin 500 mg four times daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every eight hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present.	Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon

*The recommendations are based the 2017 guidelines and these current focused guidelines

** Bezlotoxumab may also be considered for patients with other risks for CDI recurrence but implementation depends upon available resources and logistics for IV administration particularly for those with an initial CDI episode. Additional risk factors for CDI recurrence include age >65 years, immunocompromised host (per history or use of immunosuppressive therapy), and severe CDI on presentation. SOC: Standard of care.

***The FDA warns that "in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk".

Table 2. Summary of findings table, PICO 1: "In patients with an initial CDI episode, should fidaxomicin be used rather than vancomycin?"

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with vancomycin	Risk difference with fidaxomicin (95% CI)
Sustained response of CDI (follow up: 4 weeks after EOT)	1,673 (4 RCT)	⊕⊕⊕◯ MODERATE [a,b]	RR 1.16 (1.09 to 1.24)	631 per 1,000	101 more per 1,000 (57 more to 151 more)
CDI initial clinical cure * (follow up: 2 days after EOT)	1,673 (4 RCT)	⊕⊕⊕◯ MODERATE [a,b,c]	RR 1.00 (0.96 to 1.04)	856 per 1,000	0 fewer per 1,000 (34 fewer to 34 more)
Drug-related adverse events (follow up: 4 to 12 weeks)	1,721 (4 RCT)	⊕⊕◯◯ LOW [a,b,d]	RR 1.02 (0.76 to 1.36)	95 per 1,000	2 more per 1,000 (23 fewer to 34 more)
All-cause mortality (follow up: 4 to 12 weeks)	1,721 (4 RCT)	⊕⊕⊕◯ MODERATE [a,b,d]	RR 0.90 (0.66 to 1.23)	87 per 1,000	9 fewer per 1,000 (30 fewer to 20 more)

CI: Confidence interval; **RR:** Risk ratio, **EOT**: End of therapy, **SOC**: Standard of care.

* **Initial clinical cure** was defined as no diarrhea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for ≤16 days.

References

1. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med **2011**; 364(5): 422-31.
2. 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(4): 281-9.
3. 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(3): 296-307.
4. 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(9): 744-52

Explanations

a. Despite many subgroup analyses without prior stratification of the randomization reported in the study, Cornely 2012 and Louie 2011 were not considered at high risk of bias since the complete modified intention-to-treat population was used in our analysis. Guery 2018 study was at high risk of bias for self-reported outcomes due to potentially inadequate blinding. Guery 2018 and Mikamo 2018 were considered at unclear risk of bias for possible attrition bias (significant loss to follow-up for the primary endpoint with imputation of missing data with failure for sustained clinical response).
b. Not rated down for indirectness since patients with an initial CDI episode represented most patients included in the 4 reported (between 80 and 85%).
c. Outcome determined as the primary endpoint in Cornely 2012 and Louie 2011 (while Mikamo 2018 used global cure rate). Not rated down for imprecision, based on their pre-specified margin of non-inferiority of -10% (one-sided lower 97.5% CI).
d. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm (i.e., cross the null value) and few events reported do not meet the optimal information size.

Table 3. Summary of findings table, PICO 2: "In patients with a recurrent CDI episode, should fidaxomicin be used rather than vancomycin?"

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with vancomycin	Risk difference with fidaxomicin (95% CI)
Sustained response of CDI (follow up: 30 days after EOT)	253 (3 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.27** (1.05 to 1.54)	558 per 1,000	**151 more per 1,000** (from 34 more to 269 more)
Sustained response of CDI (follow up: 90 days after EOT)	75 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	**RR 1.56** (0.99 to 2.44)	410 per 1,000	**229 more per 1,000** (9 more to 449 more)
CDI initial clinical cure * (follow up: 2 days after EOT)	253 (3 RCT)	⨁⨁◯◯ LOW [a,d]	**RR 1.03** (0.94 to1.14)	853 per 1,000	**26 more per 1,000** (58 fewer to 110 more)
Serious adverse events (follow up: 90 days)	75 (1 RCT)	⨁◯◯◯ VERY LOW [a,e]	**RR 0.68** (0.35 to 1.29)	410 per 1,000	**132 fewer per 1,000** (from 345 fewer to 80 more
All-cause mortality (follow up: 90 days)	75 (1 RCT)	⨁⨁◯◯ LOW [e]	**RR 0.81** (0.20 to 3.38)	103 per 1,000	**19 fewer per 1,000** (from 150 fewer to 112 more)

CI: Confidence interval; **RR:** Risk ratio, **EOT**: End of therapy, **SOC**: Standard of care.

* **Initial clinical cure** was defined as no diarrhea for 2 consecutive days after completion of standard-of-care antibiotic therapy administered for ≤16 days

References

1. 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(3): 296-307.
2. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med **2011**; 364(5): 422-31.
3. 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(4): 281-9.

Explanations

a. Rated down for risk of bias for self-reported outcomes due to potentially inadequate blinding in Guery 2018. Despite subgroup analyses performed with prior stratification of the randomization in both Cornely 2012 and Louie 2011studies, unclear risk of bias regarding the random sequence generation in two very small sample size subgroups (some concerns were expressed by the authors regarding non-significant variability of patients (baseline characteristics in the pooled per protocol analysis, but the pooled full dataset is not presented).
b. Small sample size not meeting the optimal information size which suggests fragility of the estimate.
c. Few events reported and small sample size not meeting the optimal information size which suggests fragility of the estimate.
d. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm (i.e., cross the null value) and small sample size which does not meet the optimal information size.
e. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm (i.e., cross the null value), very few events reported and small sample size which do not meet the optimal information size.

Table 4. Summary of findings table, PICO 3: "In patients with a CDI episode, should bezlotoxumab be used as a co-intervention along with standard-of-care (SOC) antibiotics rather than SOC antibiotics alone?"

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with SOC antibiotics	Risk difference with bezlotoxumab + SOC antibiotics (95% CI)
CDI recurrence after ICC * (follow up: 12 weeks)	1,246 (1 RCT)	⊕⊕⊕◯ MODERATE [a,b]	RR 0.62 (0.51 to 0.75)	326 per 1,000	125 fewer per 1,000 (174 fewer to 77 fewer)
CDI-associated hospital readmission (follow up: 30 days)	1,050 (1 RCT)	⊕◯◯◯ VERY LOW [b,c,d]	RR 0.46 (0.29 to 0.71)	112 per 1,000	61 fewer per 1,000 (93 fewer to 28 fewer)
Drug-related adverse events (follow up: 4 weeks)	1,567 (1 RCT)	⊕⊕◯◯ LOW [a,b,e]	RR 1.27 (0.88 to 1.85)	59 per 1,000	16 more per 1,000 (9 fewer to 41 more)
All-cause mortality (follow up: 12 weeks)	1,567 (1 RCT)	⊕⊕◯◯ LOW [a,b,e]	RR 0.94 (0.66 to 1.34)	76 per 1,000	4 fewer per 1,000 (30 fewer to 22 more)

CI: Confidence interval; **RR:** Risk ratio, **EOT**: End of therapy, **SOC**: Standard of care.

* **Recurrent *C. difficile* infection after ICC** was defined as a new episode of *C. difficile* infection after initial clinical cure of the baseline episode.

References

1. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. N Engl J Med **2017**; 376(4): 305-17.
2. Gerding DN, Kelly CP, Rahav G, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection in Patients at Increased Risk for Recurrence. Clin Infect Dis **2018**; 67(5): 649-56.

Explanations

a. Despite many subgroup analyses without prior stratification of the randomization reported in the study, it was not considered at high risk of bias for this outcome since the complete modified intention-to-treat population was included in our analysis.
b. Rated down for indirectness due to concerns on the generalizability of the evidence to current practice: SoC antibiotics received in Wilcox 2017 study were: 46.7% of patients received metronidazole, 47.7% received vancomycin and only 3.6% received fidaxomicin; SoC antibiotics in current practice now includes fidaxomicin and vancomycin, but not metronidazole.
c. Rated down for risk of bias due to subgroup analysis addressing patients who were inpatients at the time of the randomization (post hoc analysis for pre-specified risk factors without stratified randomization).
d. Few events reported do not meet the optimal information size and suggest fragility of the estimate.
e. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm (i.e., cross the null value) and few events reported do not meet the optimal information size.

Figure 1

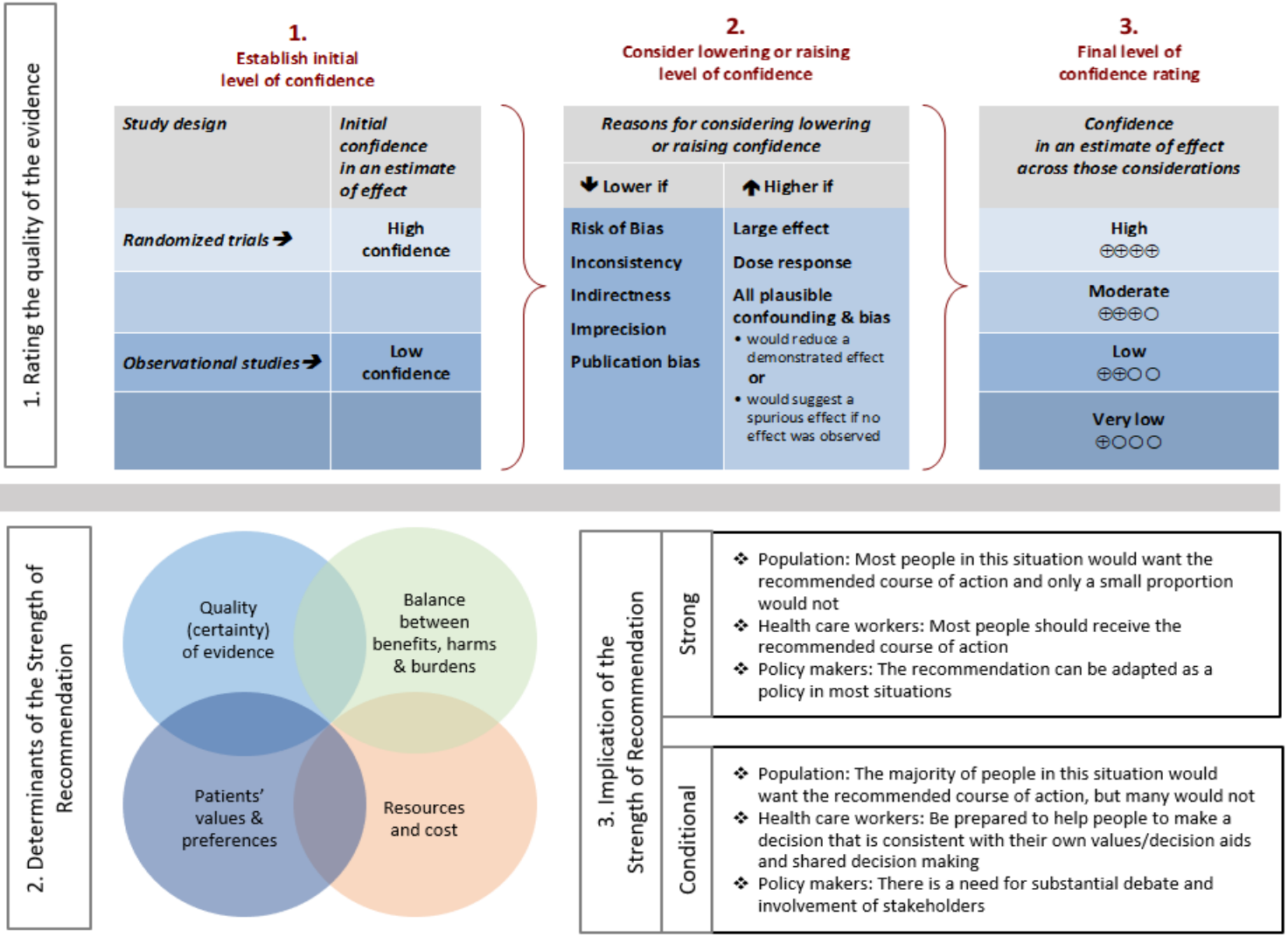

Figure 2

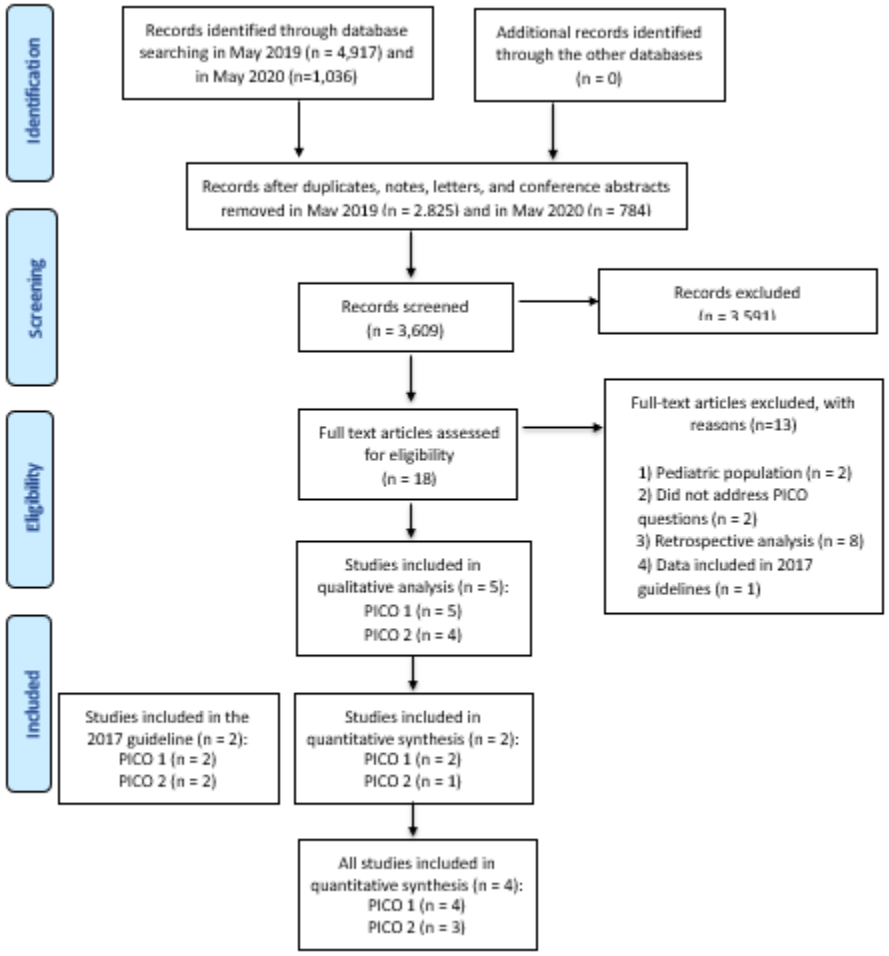

Figure 3

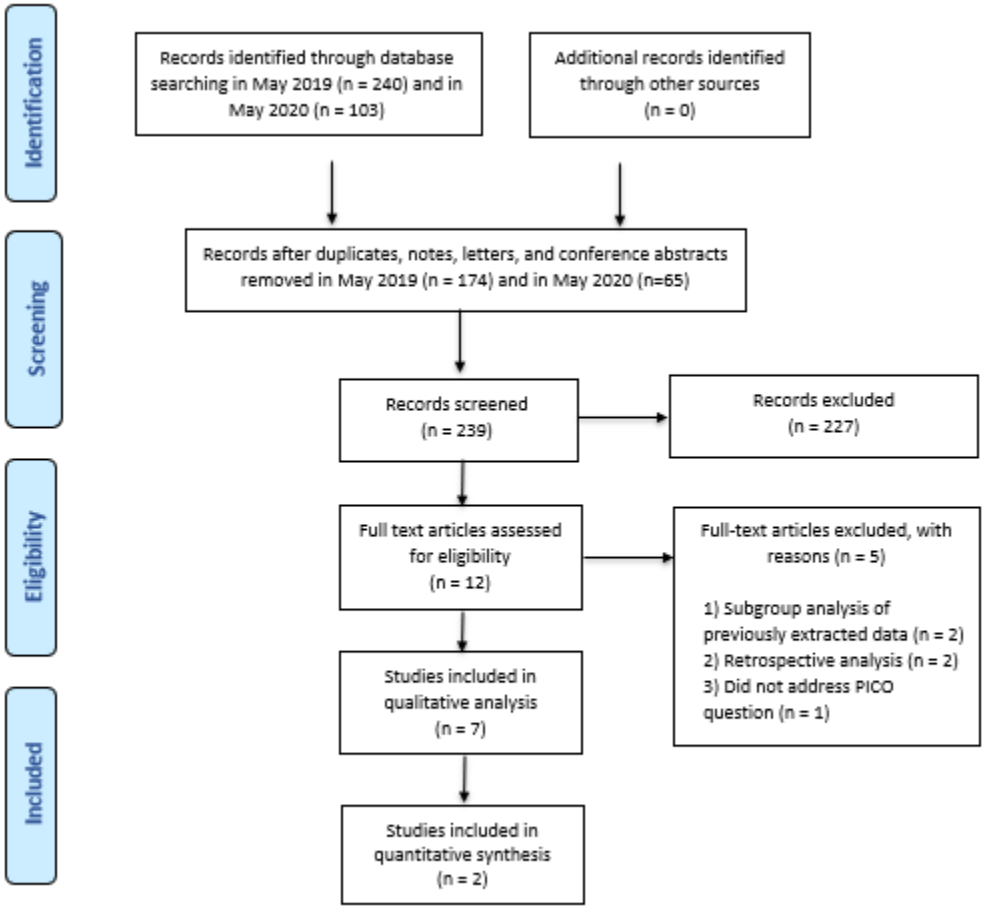

Figure 4

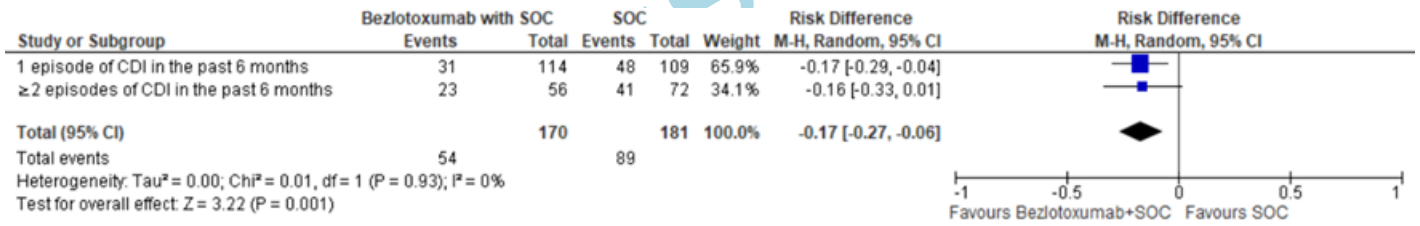

Figure 5