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Updates on the Treatment of *C. difficile* Infection: Highlights from the New IDSA and ACG Guidelines

Introduction

Clostridioides difficile infection (CDI) places a significant burden on the US healthcare system. The Centers for Disease Control and Prevention estimate a national burden of 462,100 cases annually with an incidence of 143.6 per 100,000 population. Despite declining rates of health-care associated CDI, rates of community-acquired CDI and episodes of first recurrent CDI remain unchanged.[1]

In 2017, the IDSA published new diagnosis and treatment guidelines for the management of CDI.[2] These guidelines recommended a treatment paradigm shift away from metronidazole to oral vancomycin, with fidaxomicin recommended as an alternative first-line agent. The 2017 guideline resulted in noticeable prescribing changes, as treatment courses of oral vancomycin and fidaxomicin significantly increased, while courses of metronidazole markedly decreased.[3]

In the past few months, both IDSA/SHEA and the American College of Gastroenterology (ACG) published updated 2021 guidelines for the treatment of CDI.[4,5] This newsletter highlights the key similarities and differences between these recommendations and provides commentary and opinion regarding the guideline updates.

Updates to IDSA Guidelines

The 2021 IDSA focused updates address three specific treatment scenarios that we will address individually.

Initial Episode of CDI

Previously, the 2017 IDSA guidelines recommended either oral vancomycin or fidaxomicin, as an alternative, for treatment of a first CDI episode. In the 2021 guidelines, this recommendation has changed. Now, the panel *suggests* fidaxomicin over vancomycin for treatment of initial CDI. However, this *suggestion* is couched in conditional language, noting that vancomycin remains an acceptable alternative, especially when considering cost and access.

The basis for this change in recommendation is fundamentally based on data from two randomized trials[6,7] comparing fidaxomicin and oral vancomycin. Results from these two trials were pooled with prior data utilized in the 2018 guidelines to compare efficacy of vancomycin and fidaxomicin. In pooled analysis, fidaxomicin improved sustained response at four weeks from end of therapy (i.e. lower recurrence), when compared to a 10-day regimen of vancomycin (RR 1.16, 95% CI 1.09 – 1.24). There were no differences in cure rates, mortality, or adverse events. Based on this modest decrease in recurrence rates, the panel recommended fidaxomicin over vancomycin for initial CDI. It is important to note that oral vancomycin is preferred for fulminant CDI, as data for safety and efficacy for fidaxomicin are lacking in this situation.

Recurrent CDI Episodes

For recurrent episodes of CDI, the 2017 IDSA guidelines recommended tapered and pulsed vancomycin for treatment, with fidaxomicin as an acceptable alternative regimen. Now, in the 2021 guidelines, fidaxomicin (standard or extended-pulsed regimen) is *suggested* over standard oral vancomycin, with tapered and pulsed vancomycin as an acceptable alternative.

The evidence informing this recommendation results from subgroup analyses from three randomized trials. Again, pooled analysis of the subgroups demonstrated improved sustained response at 30 days following therapy, when compared to vancomycin (RR 1.27, 95% CI 1.05 – 1.54). However, this finding was lost at 90 days (RR 1.56, 95% CI 0.99 – 2.44). Cure rates, mortality, and adverse events were again comparable between fidaxomicin and vancomycin.

Bezlotoxumab for CDI

Finally, the 2021 IDSA guidelines address use of bezlotoxumab for treatment of CDI. This topic was not addressed in the previous 2017 guidelines. Bezlotoxumab is a humanized, monoclonal antibody targeting *C. difficile* toxin B. It was approved in 2016 for the prevention of CDI recurrence. It is given as a one-time infusion, over 60 minutes, concurrent with antibiotic therapy for CDI. The theory behind its ability to prevent CDI is that circulating antibody remains measurable for up to three months following infusion, and continues to neutralize toxin in the event of C. difficile regrowth after completion of antibiotic therapy.

The new guidelines *suggest* infusion of bezlotoxumab in combination with antibiotic therapy for treatment of CDI after recurrence within six months. If resources and logistics are not an issue, bezlotoxumab can be considered for initial CDI where recurrence risk is high (defined as the presence of one or more risk factors: age ≥ 65, immunocompromise, severe CDI on presentation). These recommendations result from pooled analysis of two randomized clinical trials, which demonstrated cotreatment with bezlotoxumab reduced CDI recurrence at 12 weeks (RR 0.62, 95% CI 0.51 – 0.75), and reduced CDI-associated 30-day hospital readmission (RR 0.46, 95% CI 0.29 – 0.71). Patients with initial CDI did not benefit from bezlotoxumab infusion, unless at least one risk factor noted above was present.[8]

Thoughts on the IDSA Guidelines

The available data suggest that fidaxomicin is modestly more effective than oral vancomycin in preventing CDI recurrence. The panelists note that recurrent CDI has a profound impact on patient quality of life, and that most patients with recurrent CDI are desperate to minimize chance of relapse. Furthermore, lower recurrence rates may lead to lower CDI-associated readmission rates, allowing hospitals to recoup some of the cost savings lost with fidaxomicin use. Indeed, several studies suggest the cost-effectiveness of fidaxomicin when compared with oral vancomycin. However, it should be noted that many cost-effectiveness studies are industry sponsored and rely heavily on assumptions imputed into the financial model. Regardless, taking all these statements into consideration, the authors recommend fidaxomicin over vancomycin, on the assumption that a majority of patients would prefer fidaxomicin to vancomycin treatment.

There are two important caveats to note with regard to bezlotoxumab infusion. First, less than 5% of the analyzed patient cohort received fidaxomicin for treatment of CDI. Thus, it is unclear if the benefits of bezlotoxumab remain for those treated with fidaxomicin. Second, post hoc analysis demonstrated that patients with a history of heart failure that received bezlotoxumab were ate increased risk of heart failure exacerbation (RR 2.64, 95% CI 1.0 – 7.03) and 12-week mortality (1.56, 95% CI 0.83 – 2.92).

The 2021 ACG Clinical Guidelines

Comparison to IDSA Guidelines

There are several notable differences in the American College of Gastroenterology (ACG) Clinical Guidelines: Prevention, Diagnosis, and Treatment of *C. difficile* infections when compared with the IDSA guidelines. ACG specifies their guidelines are meant to be complementary to the 2017 IDSA Guidelines, expanding on areas of particular interest to gastroenterologists. There is more emphasis around the topic of colonization vs infection, CDI in inflammatory bowel disease, and best practices regarding fecal microbiota transplantation (FMT).

The first notable difference with respect to treatment recommendations is the equal preference for oral vancomycin and fidaxomicin for treatment of initial episodes of non-severe and severe CDI in the ACG guideline. The authors note, “although vancomycin is less expensive, lower recurrence rates of fidaxomicin imply overall similar cost-effectiveness for both agents.” While both the ACG and IDSA guidelines cite most of the same references, the ACG guidelines differ in their conclusions by weighing the fact that the cost-effective analyses were industry-led or sponsored.

The second notable difference surrounds treatment for recurrent CDI episodes. The ACG does not preferentially recommend either fidaxomicin or vancomycin. Rather, they suggest tapered and pulse dosed vancomycin for patients experiencing a first recurrence after an initial course of any antibiotic therapy, but also recommend fidaxomicin for those who experience a first recurrence following an initial course of vancomycin or metronidazole.

CDI Guideline Comparison	ACG 2021	IDSA 2021
Initial Episode	Vancomycin 125 mg PO QID x 10 days OR Fidaxomicin 200 mg BID x 10 days	Fidaxomicin 200 mg PO BID x 10 days OR extended-pulse regimen (BID x 5 days, QOD for next 20 days) Standard oral vancomycin acceptable alternative
Quality of Opinion	Strong recommendation, low quality	Conditional recommendation, moderate quality
First Recurrence of CDI	Tapered and pulsed oral vancomycin (regardless of initial regimen) OR Fidaxomicin if initial regimen of vancomycin or metronidazole	Fidaxomicin in standard or extended-pulsed regimen Oral vancomycin in standard or tapered and pulsed regimen acceptable alternatives
Role of Bezlotoxumab	Prevention of recurrent CDI in patients with high risk: - 65 years+ - Prior episode within 6 months - Immune compromise - Severe CDI	For patients with recurrence within 6 months Primary CDI with risk factors for recurrence

The panel specifically emphasizes there are no head-to-head trials of fidaxomicin vs tapered or pulsed vancomycin for the prevention of recurrent CDI. They also note the fidaxomicin studies have excluded patients with fulminant or life-threatening CDI.

Finally, the ACG guideline provides a general statement about the use of bezlotoxumab for prevention of recurrent CDI, suggesting its use for those over age 65 with high risk for recurrent disease. The IDSA guidelines provide a similar recommendation for bezlotoxumab, but extend this suggestion to all patients with a recurrent CDI episode within the prior six months, irrespective of age. Additionally, the IDSA guidelines suggest use of bezlotoxumab in patients with an initial episode of CDI with at least one risk factor for recurrence, when logistics are optimal.

Probiotics for the Prevention of CDI

ACG recommends against the use of probiotics for both primary and secondary prevention of CDI. The basis of this recommendation stems from the PLACIDE trial, a large double-blind, primary prevention trial with almost 3,000 patients at high risk of CDI who were receiving antibiotics.[9] Antibiotic-associated diarrhea occurred in 10.8% of the patients who received the probiotic preparation compared to 10.4% of those who did not (RR 1.04; 95% CI0.84-1.28; P=0.71). CDI occurred in only 12 individuals (0.8%) in the probiotic group and 17 persons (1.2%) in the placebo group, leading authors to conclude there was no benefit. The results of this trial were combined with four other RCTs in a meta-analysis evaluating primary prevention of CDI in older hospitalized patients on antibiotics. Similarly, no benefit was seen in this population.[10] Furthermore, recent microbiome analyses demonstrate that probiotics may impede normal recolonization of the colon after an antibiotic course.[11]

Oral Vancomycin Prophylaxis (OVP) for the Prevention of Recurrent CDI

The ACG also provides guidance for the use of oral vancomycin prophylaxis for the prevention of recurrent CDI. For a more thorough discussion of the data behind OVP, readers are referred to the November 2020 DASON Newsletter.

Conclusion

In conclusion, we have two recent clinical practice guidelines for treatment of CDI—one from IDSA/SHEA and one from ACG. Both have slightly different purposes but comment on some of the same clinical questions. The IDSA guideline endorses fidaxomicin over vancomycin in treatment of initial episode of CDI while the ACG guideline recommends both equally. Both guidelines note there is no difference in cure rates between the two drugs, but that fidaxomicin provides a modestly lower risk of recurrence. This sustained clinical response and easier dosing (twice daily vs. four times daily) may make fidaxomicin a more desirable drug for your patients. However, before your hospital can justify using fidaxomicin over vancomycin based on cost-effectiveness, we recommend you consider your own CDI patient population, recurrent CDI readmission rates, and other logistical barriers. There may be ways to use this drug more optimally in patients with higher risk of readmission from a recurrence of CDI. We also need to consider the significant barriers to patients obtaining fidaxomicin, including insurance coverage and pharmacy supply in the outpatient setting. Therefore, we highly recommend you discussing any local CDI standard practice or treatment guideline changes with your DICON or DASON liaison.

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