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Clostridioides is Not so *Difficile* with New Agents: A Review of the 2021 Update to the IDSA *Clostridioides difficile* Guidelines

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Clostridioides difficile infections (CDI's) are one of the most common reasons for healthcare-associated infections and even death in the United States; accompanying these infections are increased healthcare costs totaling over $4 billion.[1-3] Defined by the Center of Disease Control as a "positive C. difficile toxin assay or a positive C. difficile molecular assay," over 15,000 cases were reported to the Emerging Infections Program. This program is a national resource for infectious disease surveillance and control.[4]

Although it is a common member of the human gut flora, *C. difficile* rapidly becomes pathogenic if given the opportunity. According to the 2017 guidelines from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), certain risk factors can increase the likelihood of a CDI in patients. Risk factors for initial infection include advanced age, severity of illness, length of antibiotic exposure, cancer chemotherapy, and possibly proton pump inhibitor (PPI) use.[5] Most of these factors share a common trend in that they are associated with longer hospital stay durations. In addition to these risk factors, there are also patient factors such as: one recurrent CDI episode in the previous 6 months, age of 65+ years, immunocompromised status, and severe CDI on presentation. Although these factors do contribute to an increased risk of infection, patients can also experience CDI's without any risk factors. For this reason, diagnostic tests are recommended for confirmation.[5] For confirmation, a variety of tests are available including glutamate dehydrogenase assays, nucleic acid amplification tests, and toxin assays with IDSA guidelines recommending stool toxin tests in combination with other testing methods as part of a multiple step algorithm.[5] Examples of testing may include an initial stool toxin test coupled with glutamate dehydrogenase assays with further arbitration by nucleic acid amplification tests.

As mentioned above, a common cause and risk factor for CDI is extended antibiotic exposure. This is especially true for fluoroquinolones, clindamycin, and later generation cephalosporins such as cefdinir and cefepime. As the normal gut flora of a patient is disrupted, *C. difficile* becomes pathogenic due to the lack of competition for resources in the large intestine. As the bacteria continue to divide and numbers grow, secretion of toxin A and toxin B into the environment is taken up by endothelial cells. Once the toxins have entered the endothelial cell, they interrupt the function of the Rho protein family; cytoskeleton structures, signal transduction pathways, and cellular tight junctions of the intestinal mucosa are all impacted.[6] As the mucosal cells are damaged, inflammation occurs and an influx of fluid secretion. The result of this toxin release is ulceration and diarrhea that can eventually lead to severe dehydration and even death if not properly treated.[6]

As a result of the pathogenicity and healthcare burden associated with CDI's, the IDSA and SHEA have worked together to publish guidelines on the management of CDI's since 2010. As epidemiological trends have changed and treatments have emerged, these two organizations have updated their guidance in accordance with evidence from the scientific community. In 2021, a focused update to the guidelines on management of *Clostridioides difficile* was published with updated recommendations for both initial episodes and recurrent episodes in adults.[7] It is important to note that this update did not change recommendations for testing, dosing schemes, or treatment preferences for children. Instead, the 2021 update focused specifically on the place in therapy of the two newest agents for use in CDI: fidaxomicin and bezlotoxumab.

In the 2017 guidelines, fidaxomicin was listed as a possible treatment option for both initial CDI and recurrent infections, although no preference over oral vancomycin. Additionally, bezlotoxumab was only briefly mentioned in the 2017 edition without a recommendation as it was too novel for sufficient data collection. In the 2021 update, these agents have advanced in the treatment algorithm with fidaxomicin now as the preferred treatment for initial and recurrent CDI while bezlotoxumab is considered viable for adjunctive therapy in patients at a high risk for recurrent infection.[7] An updated treatment algorithm from the new IDSA guidelines as well as pharmacologic comparisons of the agents referenced are depicted in **Figure 1** and **Table 1** respectively.

Clinical Trials

The purpose of this manuscript is to review the four new studies that support lower recurrence rates in patients receiving

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Table 1 | Pharmacologic Comparison[15-17]

Medication	Mechanism of Action	PK/PD Parameters	Adverse Events	Monitoring	Dosage & Administration
Vancomycin (oral)	Disruption of cell wall through inhibition of RNA[a] polymerase	Poor oral bioavailability Limited metabolism Excretion in feces	Nausea (17%) GI[b] upset (15%) Hypokalemia (13%) Diarrhea (9%) Nephrotoxicity (5%)	Symptom resolution & management	Primary CDI[c]: 125 mg PO[d] QID[e] x 10 days Recurrent CDI[c]: Tapered/pulsed extended regimen
Fidaxomicin	Disruption of cell wall through inhibition of RNA polymerase	Poor oral bioavailability P-glycoprotein substrate Excretion in feces	Fever (13%) Nausea (11%) Abdominal Pain (6%)		Primary CDI[c]: 200 mg PO[d] BID[f] x 10 days Recurrent CDI[c]: 200 mg PO[d] BID[f] x 10 days
Bezlotoxumab	Monoclonal antibody binding to Toxin B	Poor oral bioavailability Limited metabolism Elimination via catabolism	Heart failure exacerbation (12.7%) Infusion reactions (10%) Nausea (7%)		10 mg/kg IV[g] given 1 hour continuous infusion

[a]Ribonucleic acid; [b]Gastrointestional; [c]*Clostrioides difficile* infection; [d]Taken by mouth; [e]Four times a day; [f]Twice a day; [g]Intravenous administration

these newer medications. Previously referenced studies pertaining to situations such as fulminant infections will not be addressed as these recommendations have not changed. Fidaxomicin, the new agent seeking to improve upon vancomycin's modus operandi, has evidence supporting its preferred treatment status from the EXTEND clinical trial and a second trial from Mikamo et al. Bezlotoxumab receives its position in the updated guidelines thanks to a series of clinical trials: MODIFY I & II. Together, these studies form the basis for the updated IDSA guidelines and, as will be shown, have varying levels of evidence behind them.

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EXTEND Trial[8]

The EXTEND trial was a randomized, controlled, open-label, parallel, superiority study assessing the efficacy of an extended regimen of fidaxomicin on sustained clinical cure of CDI in hospitalized patients throughout 86 hospitals in Europe.[8] A total of 356 hospitalized patients were randomized in a 1:1 ratio with subsequent administration of either standard dosing of vancomycin or extended-pulsed dosing of fidaxomicin. Patients were enrolled in the study if they were at least 60 years old with a confirmation of CDI within the 24 hours before randomization with the additional confirmation of toxin A or B within 48 hours of randomization. Initial confirmation was confirmed via either ≥3 unformed bowel movements or at least 200 milliliters of unformed stool in patients with rectal collection devices in addition to presence of toxin A or B within 48 hours of randomization confirmed by local laboratories. Patients were excluded from the study mainly based on antibiotic treatment for the episode of CDI lasting over 24 hours in the last 2 days and if they had a history of >2 previous CDI's within the previous 3 months. Patients eligible for inclusion were further stratified into groups based on infection severity, albumin levels, diagnosis of cancer, age, and number of previous CDI occurrences within three months before study entry.[8]

At the time of recruitment to the study, hospitalized patients with confirmed CDI were randomly assigned in a 1:1 ratio to either arm: oral vancomycin 125mg capsules four times a day for 10 days (n=166) or fidaxomicin 200mg tablets twice daily for 5 days then once daily every other day on days 7-25 of treatment (n=143). It should be noted that data on length of hospitalization is not currently available from the study; if patients had been discharged from the hospital, these assessments would be completed by telephone and patients would be self-reporting.[8] Patients were seen for a test of cure visit two days after completion of the antibiotic course where severity score and clinical response were assessed; day 12 for the vancomycin arm or day 27 of the extended fidaxomicin arm. At 30 days after the completion of treatment, day 40 for the vancomycin arm and day 55 for the fidaxomicin group, sustained clinical cure was also assessed. Infection course, severity score, and clinical response were all assessed at this visit and patients were followed at least every two weeks for 90 days total with recurrence was assessed at days 40, 55, and 90 of the study. These follow up assessments included screening for adverse events, infection recurrence, and changes in medication profiles. If patients were suspected to have a recurrence of CDI, defined as diarrhea after test of cure visit at a greater frequency than recorded at the end of antibiotic treatment, infection was confirmed by a CDI test that was positive for toxin A or B.

After the study had concluded the researchers divided the study population into two groups: the modified full analysis set and the per-protocol set. For inclusion in the modified full analysis (MFA) set, patients had to be randomized to a treatment arm, received at least one dose of study medication, and met the inclusion criteria. This group may be interpreted as the intention to treat group as well. Patients in the per-protocol (PP) set were all those in the MFA set without protocol deviations prior to initial primary outcome assessment and received at least 70% of the treatment assigned.

The primary outcome was the sustained clinical cure of CDI at 30 days after the end of treatment with the results summarized in **Table 2**. At 30 days after completion of therapy, 85% of the extended pulse fidaxomicin group experienced sustained clinical cure compared to 66% of the standard vancomycin group in the per-protocol data set (OR 2.99 [95% CI 1.52-5. 90]; p=0.0011). In the modified full analysis set, sustained clinical cure 30 days was also significantly in favor of fidaxomicin group (70%) versus 59% of the vancomycin group (OR 1.62 [95% CI 1.04-2.54]; p=0.030). When stratified by risk factors for reinfection, severity of infection decreased the chances of a patient experiencing sustained clinical

cure at 30 days in the modified intention to treat group only. In other words, there was no difference between patients with severe or non-severe infection in cure rate at 30 days. Other risk factors such as cancer and age had no effect on sustained clinical cure at 30 days (**Table 3**);however, patients with at least one prior episode of CDI did have an increased chance of experiencing sustained clinical cure at 30 days when treated with fidaxomicin (1 vs 0 CDI episodes: OR 0.43 [95% CI 0.20-0.92]; p=0.03) in the per protocol set.[8] Regarding patients with at least one prior episode of CDI, it was not clearly stated in the study what previous treatment was used in the patients.

Secondary endpoints of note include recurrence of CDI at day 40, 55, and 90 as well as sustained clinical cure at the same time points. As summarized in **Table 3**, the extended pulsed fidaxomicin group had an increased chance of experiencing sustained clinical cure at all three time points as well as decreased chances of CDI at day 40 and day 55. Adverse event occurrences between the two treatment arms were fairly similar, namely the fidaxomicin group had eight patients discontinue the drug due to adverse events compared to five in the vancomycin group. Common adverse reactions included constipation, diarrhea, heart failure, urinary tract infections, and some instances of subsequent *Clostridium* infection.

Mikamo H et al. 2018 Trial[9]

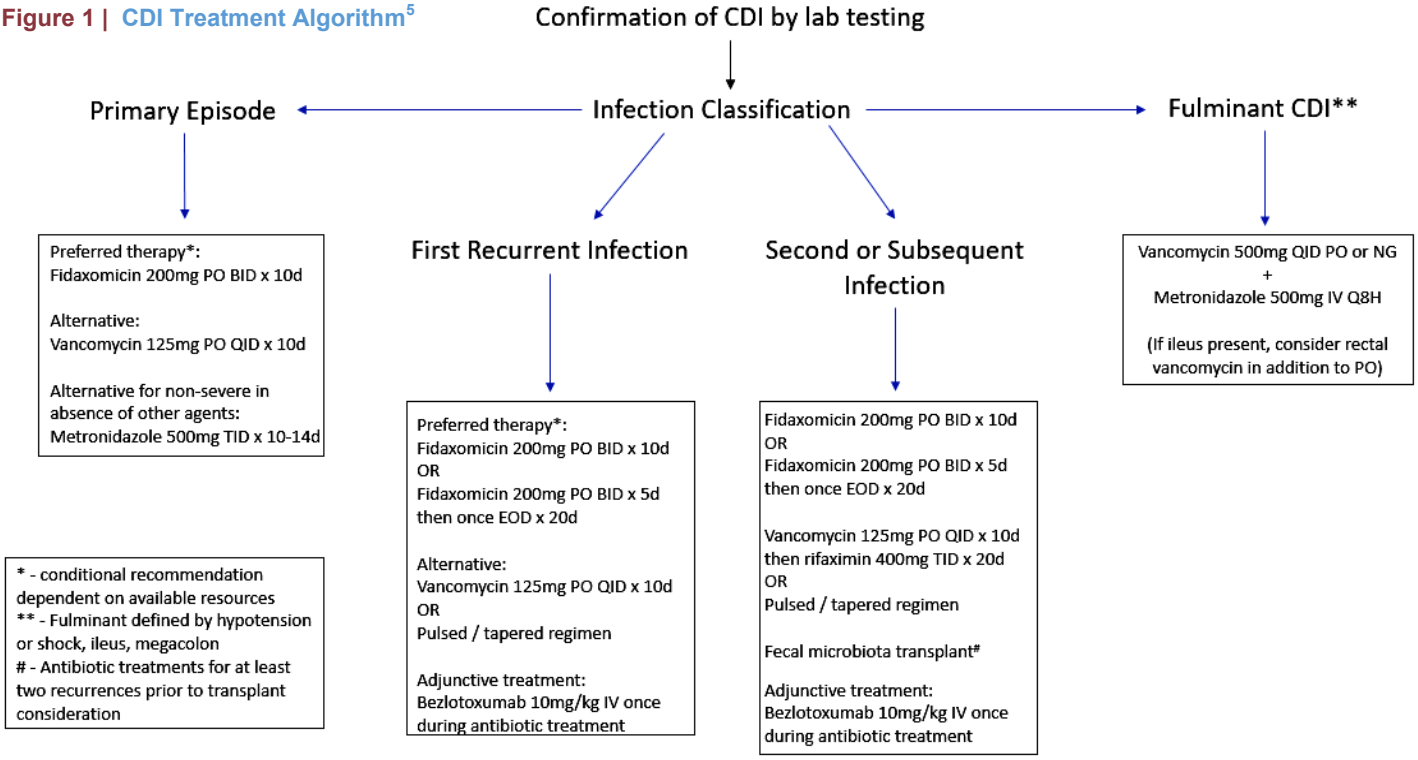
The trial conducted by Mikamo et al. in 2018 was a prospective, double blind, randomized, parallel study focused on the efficacy and safety of fidaxomicin in Japanese hospitals. A total of 82 centers in Japan participated in the study with a total of 215 patients being included in the study initially. Inclusion criteria consisted of symptomatic CDI, which the researchers defined as ≥4 episodes of unformed bowel movements within 24 hours of randomization and had not received antibiotic treatment for CDI; patients who had treatment failure after at least three days of metronidazole therapy were also eligible. Relevant exclusion criteria included fulminant CDI, toxic megacolon, prior fidaxomicin use, concomitant use of antibiotics for the treatment of CDI, antidiarrheal drugs administered, or ≥2 prior episodes of CDI in the last 3 months before study entry.[9]

Eligible patients were randomly assigned in a 1:1 ratio to either the fidaxomicin treatment group or the vancomycin control group. Patients in the fidaxomicin group received both a 200 mg oral tablet twice a day and a vancomycin placebo pill for 10 days. Likewise, the patients assigned to the vancomycin group received a total daily dose of 500 mg vancomycin divided into four doses in addition to fidaxomicin placebo tablet for 10 days. After randomization, 106 patients were allocated to the fidaxomicin group and 109 went to the vancomycin group.[9]

Once all the data had been collected for the study and final completion rates were established for patients, the researchers divided the study population into different groups for further secondary analysis. Groups included the full analysis set (FAS), or intention to treat group, per-protocol set (PPS), modified full analysis set (mFAS), and per-protocol set for recurrence among others. Of note, the mFAS consisted of patients in the FAS who received at least three days of treatment and the per-protocol set for recurrence (PPS-R) consisted only of those patients in the PPS who achieved clinical cure and had no recurrence 31 days after the end of treatment without any other medications for CDI.[9]

The primary outcome of this trial sought to determine if fidaxomicin was non-inferior to vancomycin in global cure rate of infection as defined by patients with clinical cure at the end of therapy with no recurrence during the 28 day follow up period. The researchers pre-defined a non-inferiority margin of 10% for determination; this margin was not achieved by the confidence interval from the FAS (fidaxomicin vs vancomycin: 1.2% [95% CI -11.3%-13.7%]; p<0.05). As a result, the full data set fails to show non-inferiority of fidaxomicin compared to vancomycin with respect to global cure rate based on a pre-defined margin set by the researchers. When post hoc analysis for global cure at the end of

Figure 1 | CDI Treatment Algorithm[5]



treatment was conducted on either the mFAS (4.6% [95% CI -7.9%-16.8%]; p<0.05) or the PPS-G (3.9% [95% CI -9.1%-16.8%]; p<0.05), fidaxomicin was shown to be non-inferior to vancomycin. Secondary endpoints of the study included cure rates at the end of treatment, microbiological eradication, and others as described in **Table 3**. Notably, recurrence rates during the follow-up period were lower in the fidaxomicin group (19.5%) than in the vancomycin group (25.3%) in the full analysis set for remission as well as the per-protocol and modified full analysis sets as described in **Table 2.**[9]

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MODIFY I & II Trials[10-11]

MODIFY I and MODIFY II were both part of a series of randomized, double-blind, placebo-controlled trials to assess the efficacy of bezlotoxumab as add-on therapy for the prevention of recurrent CDI in over 30 different countries around the world. Bezlotoxumab was administered as a single 10 mg/kg IV infusion over 60 minutes in combination with one of three standard-of-care antibiotics: metronidazole, vancomycin, or fidaxomicin. The studies did not report standardized dosing for these agents though it was mentioned that some patients may have received both vancomycin and metronidazole. It should be noted that the trials were conducted prior to the release of the 2017 IDSA guidelines and metronidazole was used in over 40% of the patient population of the study. Both trials were designed to mimic to each other to allow for pooling of results for further secondary analysis. Across the two studies and between the treatment and placebo groups, patient demographics were similar. Adults with confirmed initial or recurrent CDI receiving standard-of-care antibiotics for 10-14 days were recruited to the study; both ≥3 unformed bowel movements in 24 hours and a positive stool test for toxigenic *C. difficile* were the criteria for confirmed CDI.[10]

Patients were randomly assigned in a 1:1:1:1 ratio to a single infusion dose of bezlotoxumab at 10 mg/kg (n=781), actoxumab with bezlotoxumab at 10 mg/kg each (n=773), placebo infusion of normal saline (n=773), or actoxumab only in MODIFY I (n=232); actoxumab was not evaluated alone in the MODIFY II study due to a lack of efficacy and increases in serious adverse events including death. Further stratification occurred based on which antibiotic the patient was using and hospitalization status; approximately 70% of patients in each treatment arm were inpatient at the time of bezlotoxumab administration.[10] Of note, when the patients were stratified by SOC antibiotic, 48% received vancomycin, 47% received metronidazole, and 4% received fidaxomicin. After randomization, patients received the assigned infusion in conjunction with their antibiotic. Upon discharge, patients were tasked with monitoring new onset of unformed bowel movements in a journal and with check-ins via telephone contact until day 80 to 90 of the study.

The primary endpoint examined in the trials was the proportion of patients that experienced a recurrent CDI episode within 12 weeks after clinical cure of baseline episode during the follow-up period in a modified intention to treat (mITT) population with a summary found in **Table 2**. The mITT set excluded randomized patients that did not receive the study drug, did not have a positive toxin assay, or did not receive one of the standard-of-care antibiotics before or within one day of study infusion. In MODIFY I, the proportion of patients in the bezlotoxumab group that had recurrent infection was significantly lower than the placebo group (bezlotoxumab vs. placebo: -10.1%; 95% CI [-15.9% to -4.3%]; p<0.001). The MODIFY I study also showed that combination treatment with bezlotoxumab and actoxumab concurrently with standard of care antibiotics decreased recurrence of infection (bezlotoxumab + actoxumab vs. placebo: -11.6%; 95% CI [-17.4% to -5.9%]; p<0.001).[10]

As in MODIFY I, MODIFY II examined recurrent CDI episodes within 12 weeks of clinical cure of baseline CDI episode. To allow subsequent pooling and analysis of data from both trials, the same inclusion criteria were used for initial randomization and inclusion in the mITT. MODIFY II showed that administration of bezlotoxumab with standard of care antibiotics significantly decreased the percentage of patients who had recurrent CDI (bezlotoxumab vs. placebo: -9.9%; 95% CI [-15.5% to -4.3%]; p<0.001).[10] Significance was also shown when the combination of bezlotoxumab and actoxumab was administered in conjunction with standard of care antibiotics (bezlotoxumab + actoxumab vs. placebo: -10.7%; 95% CI [-16.4% to -5.1%]; p<0.001). Taken together in pooled analysis, both MODIFY I & MODIFY II show that bezlotoxumab is effective at decreasing recurrence of CDI for up to 12 weeks after the initial infection has been eradicated (Risk Ratio: 0.62; 95% CI [0.51-0.75]). The number needed to treat to prevent one recurrence was found to be 10. The secondary end point stated in the studies was rate of sustained cure with significance being reached in MODIFY II but not in the MODIFY I trial.

To look at the role risk factors for recurrent CDI play in the effectiveness of bezlotoxumab, a separate post hoc analysis of the

Table 2 | Primary Outcomes[8-10]

Trial	Outcome	Intervention	Result (95% CI)	P-Value
EXTEND	Cure at 30 days after end of treatment	Fidaxomicin 200 mg BID[a] x 5 days then once every other day on days 7-25	70% v 59% (mFAS[c])	0.03
		Vancomycin 125 mg QID[b] x 10 days	85.5% v 66.4% (PPS[d])	0.0011
Mikamo et al.	Recurrence at 28 days after end of treatment	Fidaxomicin 200 mg BID[a] x 10 days	18.6% v 25.3% (mFAS-R[f])	<0.05
		Vancomycin 500 mg TDD[e] x 10 days	16.0% v 24.1% (PPS-R[g])	
MODIFY I / II	CDI recurrence within 12 weeks of cure	Bezlotoxumab 10 mg/kg IV[h] plus antibiotic	17% v 27% (mFAS[c])	<0.001
		Antibiotic alone		

[a]Twice a day; [b]Four times a day; [c]Modified full analysis set; [d]Per-protocol set; [e]Total daily dose; [f]Modified full analysis set for recurrence, [g]Per-protocol set for recurrence; [h]Intravenous administration

Table 3 | Secondary Endpoints[8-10]

Trial	Intervention	Endpoint	Protocol	P-Value
EXTEND	Fidaxomicin 200 mg BID[a] x 5 days then once every other day on days 7-25	Recurrence at 40 days	PPS[c]	<0.0001
			mFAS[d]	<0.0001
		Recurrence at 55 days	PPS	0.0032
			mFAS	<0.0001
		Recurrence at 90 days	PPS	0.048
			mFAS	<0.00073
	Vancomycin 125 mg QID[b] x 10 days	Infection severity	PPS	0.273
			mFAS	0.025
		Age	PPS	0.059
			mFAS	0.825
		Previous CDI	PPS	0.03
			mFAS	0.642
Mikamo et al.	Fidaxomicin 200 mg BID[a] x 10 days	Clinical cure	PPS	<0.05
			mFAS	
	Vancomycin 500 mg TDD[e] x 10 days	Global cure	PPS	
			mFAS	
MODIFY I / II	Bezlotoxumab 10 mg/kg IV[f] plus antibiotic	Rate of sustained cure	n/a[g]	0.0001
	Antibiotic alone			

[a]Twice a day; [b]Four times a day; [c]Per-protocol set; [d]Modified full analysis set; [e]Total daily dose; [f]Intravenous administration; [g]Not applicable

pooled MODIFY I & II data was conducted by Gerding DN et al.[11] Risk factors were specified as age ≥65 years, previous history of CDI, immunocompromised status, severe CDI, and ribotype 027/078/244. Of note, the researchers did not include concomitant systemic antibiotic treatment in their analysis due to risk factors at the time of randomization being the only ones included. Bezlotoxumab was successful in reducing the rate of recurrent CDI compared to placebo in patients with one or more risk factor with absolute reduction of -14.2% (95% CI: -21.9% to -6.4%), -14.2% (95% CI: -24% to -4.1%), and -24.8% (95% CI: -39.1% to -9.3%) in patients with 1, 2, and 3 or more risk factors, respectively. Separate analysis looked at patients with no reported risk factors and found the percentage of patients who experienced recurrence was similar between the bezlotoxumab group and placebo.

Updated Recommendations

As a clinical organization producing guidelines on disease states, the IDSA and SHEA have to be able to adjust their recommendations based on new data.[5,7] As presented, there is a case to be made for better outcomes regarding recurrent CDI in patients receiving fidaxomicin compared to vancomycin and bezlotoxumab as adjunct therapy. From these results, the review panel has produced new recommendations that coincide with this data.

Treatment of Initial CDI

The 2021 focused IDSA update lists fidaxomicin 200mg twice daily for 10 days as the preferred treatment for an initial episode of CDI over a standard vancomycin regimen.[7]

When pooled, the four clinical trials show a statistically significant increase in sustained response of CDI four weeks after the end of therapy when compared to a standard 10 day vancomycin regimen (risk ratio [RR] – 1.16; 95% CI – 1.09-1.24). Additionally, it should be noted that fidaxomicin has a narrow spectrum of action; highly targeted against *C. difficile* with limited activity against other microbes that make up the normal flora. This may contribute to the increased protection from recurrent CDI. It should also be noted that while fidaxomicin is effective at increasing sustained response after the completion of therapy, its effectiveness at achieving initial clinical cure is comparable to the standard vancomycin regimen when the study results are pooled (RR – 1.00; 95% CI: 0.96-1.04). Likewise, comparable risk of mortality and drug-related adverse events with treatment of an initial episode of CDI explains a conditional recommendation for fidaxomicin treatment from IDSA.[7]

Treatment of Recurrent CDI

Fidaxomicin has also become the preferred therapy to vancomycin in the setting of recurrent CDI with the 2021 guideline update.[7]

Guery et al showed a significantly lower rate of recurrence in patients receiving fidaxomicin versus vancomycin 30 days after the end of therapy (RR: 1.27; 95% CI: 1.05-1.54) for CDI.[8] This effect was diminished when recurrence rates were examined at 90 days and showed no difference in initial cure rate, adverse event frequency, and all-cause mortality in the setting of recurrent CDI.[6] Of note, patients with more than two episodes of CDI in the last three months were excluded from the study essentially eliminating any patients who may be afflicted with resistant CDI.[8]

These recommendations come with a very low certainty rating from the expert panel. This is in part due to the small number of events that were used for the analysis where across three studies that were pooled, only 253 participants were analyzed. The guideline committee performed an additional ad hoc subgroup analysis of data for fidaxomicin and vancomycin where they separated patients with recurrent CDI by number of episodes (1 or ≥2). Patients with history of one prior CDI had a significant in-

crease in the chance of sustained response at 30 days when given fidaxomicin (1.23; 95% CI: 1.01 – 1.49) while those with two or more episodes did not.[7]

Use of Bezlotoxumab

For patients with a recurrent CDI episode within the last 6 months, the IDSA suggests using bezlotoxumab in conjunction with standard antibiotic regimens.[7]

Bezlotoxumab was approved by the FDA in October of 2016 as an adjunct treatment to standard antibiotic therapy and is the first drug in its class, utilizing humanized monoclonal antibodies to bind and inactivate toxin B released by *C. difficile*. While standard antibiotic regimens recommended by the IDSA now consist of 10 day regimens of either vancomycin or fidaxomicin, the studies were conducted before the 2017 IDSA guideline update. For this reason, most of the patients examined in the MODIFY series were receiving either metronidazole for mild-moderate infections and vancomycin for more severe infections with only 4% receiving fidaxomicin. This results in limited generalizability of the findings in the MODIFY series that clinical outcome was independent of antibiotic choice

Additionally, IDSA and SHEA conducted their own post hoc analysis of the MODIFY trial data to discern whether multiple episodes of recurrent CDI would have an impact on the effectiveness of bezlotoxumab. To do this patients were grouped as either having one episode of CDI in the last 6 months or having two or more episodes within 6 months; similar risk differences were found between the two groups respectively (-16.8% [95% CI: -29.2% to -4.5%] vs -15.9% [95%CI: -33.1% to 1.4%]). When pooled together, the effect of bezlotoxumab on patients with a recurrent CDI in the previous 6 months was -17.4% (95% CI: -27.5% to -7.3%). These findings in addition to those published in MODIFY I & II lend themselves to the addition of bezlotoxumab to antibiotic regimens at high risk for recurrence and especially those who have a history of a recurrent CDI infection within the previous 6 months of treatment.

A significant portion of the patients studied are hospitalized which does pose an issue to generalizability with the outpatient population. With the exception of the MODIFY I/II studies, none of the trials referenced treatment in an outpatient setting. Further research is needed on the topic of treatment location to obtain a clear clinical picture.

Clinical Implications

As with any therapy in an outpatient setting, patients should be involved in the management of their CDI. With this now comes a discussion focused around the possibility of increased remission in exchange for a drug that might be cost prohibitive. Depending on what insurance a patient has and what their financial situation is, they may not know which option would be right for them. Some patients may find the increased chance for extended remission worth the extra cost of this new therapy. Additionally, while the addition of bezlotoxumab may yield better results regarding recurrence of infection, the logistics of receiving the infusion may be a barrier to access for some patients. As described in the 2021 IDSA guidelines, the clinical trials of bezlotoxumab were all conducted in an inpatient population where infusions are commonplace. Among the issues with administering the infusion in an outpatient setting is referral to an outpatient infusion center and insurance complications.

When focus is shifted to the inpatient setting, the issue of patient agency becomes less of an issue while pricing concerns remain. Considerations about cost should be made when hospital formularies are being produced. In 2016, Zhang et al estimated that the average management of hospital onset CDI was about $34,000 dollars and community acquired being about $20,000.[12] These estimates were obtained before fidaxomicin and bezlotoxumab had the presented evidence behind them; the addition of these medications may contribute more to these costs. The average wholesale cost for a 20-tablet package of fidaxomicin, in 2012, currently costs about $4,000.[13] Although some payment assistance programs are offered by the manufacturer, not all patients will be eligible for such assistance if using government insurance benefits. In contrast, vancomycin for oral administration may have some cost barriers associated with it at $5-$25 per capsule, but may be more affordable than the now preferred agent of fidaxomicin. In addition to fidaxomicin, bezlotoxumab also comes with significant cost burden of >$4,000 per treatment.[14]

Conclusion

The field of medicine is constantly changing with new therapies being developed to assist healthcare workers in providing the best care for patients. In the case of CDI, the same medication has been in use for decades. As new therapies come forward and are put through the rigor of scientific analysis, providers must be cognizant of how data was obtained and what informs certain societal guidelines. For fidaxomicin and bezlotoxumab, there is still much work to be done for them to be regarded as therapies of choice in CDI. When patient factors allow, the data suggest that these newer agents may provide some additional protection and efficacy in preventing recurrent CDI infections and may be quite desirable to providers and patients; however, until barriers to utilization such as cost and insurance issues are further deconstructed, treatment of initial and recurrent CDI with the standard 10 day vancomycin regimen as recommended by the IDSA should not be overlooked as an option.

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Personalized Medicine Corner

Venlafaxine and CYP2D6 Pharmacogenetics

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Patient Case Presentation

A.A. is a 40-year-old female known case of hypertension and depression that failed multiple antidepressant medications in the past (e.g., sertraline, escitalopram, and duloxetine). Her current medications are lisinopril 40 mg daily and venlafaxine 225 mg daily.

Venlafaxine (VEN) is an antidepressant that belongs to the serotonin norepinephrine reuptake inhibitors (SNRI) class, it exerts its effects through dual inhibition of serotonin (SLC6A4), norepinephrine (SLC6A2) transporters and to a lesser extent the reuptake of dopamine (SLC6A3). It has FDA approved indications for generalized anxiety, major depressive, and social anxiety disorders. [1,2]

A.A. follows up with her PCP with a chief complaint of uncontrolled home BP readings, excessive sweating, dry mouth and decreased libido. Other than that, she reported that her mood has improved since venlafaxine was started 2 months ago.

After administration, VEN undergoes an extensive first pass metabolism via cytochrome P 450 enzyme CYP2D6 to form its major metabolite O-demethylvenlafaxine (ODV), also known as Desvenlafaxine; an FDA approved prodrug of VEN, which has a similar potency compared to the parent compound. The receptor affinity differs between VEN and ODV, while they both have higher affinity for the serotonin receptors compared to norepinephrine receptors in general, ODV's affinity for norepinephrine receptors is higher when compared to VEN. At doses up to 75 mg daily, VEN has almost exclusive work as selective serotonin reuptake inhibitor (SSRI), however, this selectivity is lost at higher doses (150-225 mg and above), when it is more of an SNRI and this is evident by the pronounced adrenergic side effects at such doses. Therefore, it's expected to see a higher ODV:VEN ratio in CYP2D6 normal metabolizer (NM) and ultrarapid metabolizers (UM) and a lower ODV:VEN ratio in CYP2D6 intermediate (IM) and poor metabolizers (PM). In other words, UM and NM are exposed more to ODV than VEN, which in theory would predispose the patient to more adrenergic side effects and the opposite is true in IM and PM, where serotonergic side effects are more noticeable. Although their role is minor, CYP2C9 and CYP2C19 contribute to the formation of ODV, which explains its presence in plasma in individuals who are CYP2D6 poor metabolizers. N-demethylvenlafaxine is a less potent metabolite that is formed by N-demethylation of VEN, catalyzed by CYP3A5 and CYP2C19. [2-7]

Common side effects (≥ 5%) reported with VEN are nausea, somnolence, dry mouth, sweating, abnormal ejaculation, anorexia, constipation, erectile dysfunction, and decreased libido. The adrenergic side effects, hypertension and tachycardia are dose dependent and are clinically significant at doses 15-225 mg/day. Overall, caution is advised when using VEN in patients with heart failure, uncontrolled blood pressure, recent myocardial infarction, angle closure glaucoma, or hyperthyroidism.[2,8]

Pharmacogenetic tests were ordered to guide A.A.'s depression and returned as CYP2D6 *3/*4 PM (no enzyme activity) and CYP2C19 *1/*1 NM (normal enzyme activity).

Table 4 | Summary of Higher Level Evidence Recommendations for CYP2D6-Venlafaxine

Resource	Recommendation
FDA Label[8]	**PM** had increased levels of VEN and reduced levels of ODV vs NM. No dose adjustment recommended
FDA Table of PGx Associations[18]	**PM** alters systemic parent drug and metabolite concentrations. Consider dosage reductions
Clinical Pharmacogenetics Implementation Consortium (CPIC)[19]	Level A/B – Provisional
The Pharmacogenomics Knowledge Base (PharmGKB)[1]	Level 1A—Actionable PGx for the CYP2D6 variants: *1, *3, *4, *5, *6, *10, *81
Dutch Pharmagenetics Working Group (DPWG)[20]	**UM:** if necessary, increase the dose to 150% of the standard dose. **IM/PM:** It is not possible to offer adequately substantiated advice for dose. Reduction based on literature as follows: 1- Avoid and use alternatives that are not metabolized by CYP2D6 (e.g. duloxetine, mirtazapine, citalopram and sertraline). 2- If it is not possible to avoid and side effects occur: Reduce the dose OR monitor the effect/side effects or check the plasma level of VEN and ODV.

PGx: Pharmacogenomics, PM: Poor Metabolizer, UM: Ultrarapid metabolizer, IM: Intermediate Metabolizer

The current high-level evidence highlights the increased systemic exposure to VEN and its metabolite, ODV, in CYP2D6 IM/PM. Yet, no consensus on recommendations for the therapeutic management. The *FDA Table of Pharmacogenomics (PGx) associations* recommends considering dose reduction if CYP2D6 PM. Instead, the *Dutch Pharmacogenetics Working Group* (DPWG) 2019 guidelines has more conservative approach for CYP2D6 IM/PM by recommending switching to an alternative agent, and if this is not possible, to decrease the dose, as highlighted in **Table 4**.

There are numerous pharmacokinetics studies that has shown a positive association between CYP2D6 activity score and ODV level, and illustrating that CYP2D6 IM/PM has an increased exposure to VEN.[3-7]

On the other hand, several studies investigated the link between the CYP2D6 phenotypes with the clinical outcomes of VEN, which were all inconclusive. As such, the test is not recommended as a standard of practice in current time.[12-15] Conversely, a secondary analysis of four double-blind placebo-controlled trials, showed that VEN was more effective than placebo in CYP2D6 NM but not with CYP2D6 PM. With the knowledge that PM have lower ODV:VEN ratio, this may link the lack of response with lower ODV level in CYP2D6 PM, which consequently suggests that ODV might have a greater antidepressant effect compared to VEN.[16] Safety wise, few case studies of patients who were CYP2D6 PMs reported severe side effects of tachycardia and agitation. [9-11] Conversely, on a larger scale clinical studies that assessed the association between CYP2D6 phenotypes and adverse effects or discontinuation rate; there was no significant difference between NM and PM phenotypes.[12-16]

Despite the various literature describing the association between CYP2D6 phenotypes with the plasma level of active compounds (VEN and VEN + ODV); there is less evidence assessing the effect of CYP2D6 phenotypes on the clinical outcomes. Practitioners are advised to use caution when prescribing VEN in patients who are CYP2D6 PM utilizing the current knowledge of VEN pharmacologic and pharmacokinetic profile, coupled with patient's specific risk factors that increase the likelihood of adverse effects such as age and comorbid conditions.

Clinical Outcome

The physician decided to reduce venlafaxine dose to 150 mg since the patient's mood is controlled with this agent and to reassess in 6 weeks for continued depression and hypertension control. An alternative approach if depression control is affected or intolerable persisted is stop venlafaxine and start fluoxetine at 40 mg daily and monitor for efficacy and tolerability.

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