Clostridioides difficile Revisited: What Clinicians Need to Know

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Interview Summary

The treatment options for *Clostridioides difficile* are changing, with two FDA-approved microbiota products, discontinued therapies, and changes in the FDA regulation of fecal microbiota transplantation. This article provides an update on the field, combining key recent data with perspectives from experts Cynthia Sears, Professor of Medicine and Oncology at the Johns Hopkins University School of Medicine and Professor of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; and Darrell Pardi, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, New York, USA, on how they are adapting their practice.

Sears' expertise focuses on gut infections, including diarrhea and *Clostridioides difficile* infection (CDI). Pardi is a physician specializing in gastroenterology and an expert in treating inflammatory bowel diseases and CDI.

With insights from Sears and Pardi, this article provides a timely update for physicians managing acute and recurrent CDI, with a particular focus on how approved, standardised microbiota-based treatments offer opportunities to break the cycle of CDI recurrence.

INTRODUCTION

CDI causes severe diarrhea and is now the leading cause of healthcare-associated infection.[1-3] Community-acquired CDI is also increasing, accounting for approximately 50% of all cases and making it an equally inpatient and outpatient disease.[4] Current standard of care antibiotic treatment often leaves patients with microbial dysbiosis, leading to a cycle of recurrence.[1] After a primary CDI, between 20–35% of patients will experience a recurrence and, of these, up to 60% will experience a subsequent infection.[5]

"The morbidity and long-term consequences of recurrent CDI (rCDI) are only just beginning to be uncovered," explains Sears. "A major outcome is that patients don't seem to routinely return to their life baseline," she says. "They have ongoing abdominal discomfort, continued bursts of irregularly formed stools, and many say they don't have energy, can't go back to work, and can't eat things they ate before. CDI appears to trigger a chronic gastrointestinal symptom-based morbidity that's poorly defined."

TREATMENT OF ACUTE CDI

"I think one word sums up the current treatment landscape for CDI, and that would be inadequate, in the sense that currently used treatments, mostly vancomycin here in the United States, are insufficient," says Sears.

Vancomycin has superior efficacy to previous standard of care antibiotics,[6-8] but the decision to treat with vancomycin comes with trade-offs, including the risk of causing further microbial dysbiosis.[1]

"Vancomycin is a very broad-spectrum antibiotic when taken orally and knocks out a lot of the protective flora in the colon,[1] and, as a result, our therapy fuels us forward into more recurrence, which is the burning problem in the field," says Sears.

There is also the risk of driving the emergence of antibiotic resistance. Current guidelines state that oral prophylactic vancomycin can be considered in patients at high-risk of recurrence, such as those taking systemic antibiotics for another indication, although the data to support this is uncertain.[9,10] A recent

study showed that using vancomycin for secondary prophylaxis in rCDI achieves no significant improvement in recurrence rates compared with placebo, but drives drug resistance, with 50% of vancomycin-treated patients colonized with vancomycin-resistant *Enterococci* after treatment, although the study was underpowered.[11]

Decreased susceptibility of *C. difficile* to vancomycin is associated with treatment failure, reducing the odds of a sustained clinical response.[12] Despite these risks, most physicians tend to opt for vancomycin because of its accessibility and lower cost.[12]

Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) 2021 guidelines recommend fidaxomicin as a first-line treatment option for CDI.[13] Fidaxomicin is a narrow-spectrum antibiotic approved solely for CDI that has more limited activity against commensal bacteria.[14] After additional clinical trial data confirmed lower recurrence rates in primary CDI with fidaxomicin,[15-18] IDSA/SHEA updated its guidance in 2021 to recommend fidaxomicin over vancomycin for initial and recurrent CDI,[11] while the American College of Gastroenterology (ACG) guideline recommends either option.[9]

Despite this shift in recommendations, uptake of fidaxomicin has been mixed. "Fidaxomicin has been around more than a decade (FDA-approved, 2011), but uptake remains marginal because of cost," says Sears. However, a recent analysis found that the updated IDSA guidance was associated with an immediate 4% reduction in the odds of 30-day CDI recurrence and a significant reduction in length of hospital stay, with no significant ongoing upward trend in costs.[19]

Cases of emerging fidaxomicin resistance or reduced susceptibility among circulating *C. difficile* strains have been reported,[20-22] with a recent study reporting reduced fidaxomicin susceptibility in six of 108 CDI cases over 3 years, including three patients who initially responded to fidaxomicin but progressed to clinical failure.[21]

Owing to metronidazole's inferior efficacy relative to vancomycin and fidaxomicin[6,23] and the prevalence of *C. difficile* isolates with reduced metronidazole susceptibility,[24,25] it is now only recommended for low-risk patients if fidaxomicin or vancomycin are unavailable[13] or together with vancomycin for fulminant CDI.[9]

"The transition away from metronidazole is good news," says Pardi. "But after first infection, even with good antibiotics, there's still a high chance of *C. difficile* coming back. It would be good to prevent that first recurrence in the first place."

CURRENT MANAGEMENT OF RECURRENT CDI

The IDSA/SHEA (2017 and 2021) and ACG (2021) guideline recommendations for first and subsequent recurrence focus on second-line antibiotics, dependent on the drug used for the primary episode.[9,10,13] Both IDSA/SHEA and ACG recommend a tapered and pulsed vancomycin regimen as an option for a first recurrence. Recent data suggest that a taper/pulse regimen may be superior to standard vancomycin for achieving a sustained clinical response (58.6% versus 44.1% at Day 59).[26]

For high-risk patients, add-on agents included the monoclonal antibody bezlotoxumab, which is no longer commercially available, and fecal microbiota-based therapies for second and subsequent recurrences.[9,13]

The prevention of subsequent recurrence is an important consideration in the management of CDI. "Many patients with a prior CDI are under the constant threat of recurrence," says Sears. "We've really got to get ahead of recurrence upfront and break the cycle, otherwise it becomes increasingly difficult to prevent."

A key driver of CDI recurrence is dysbiosis of the microbiome,[1] and IDSA/SHEA 2017 and 2021 and ACG 2021 guidelines were developed before the availability of FDA-approved fecal microbiota-based therapies.[9,10,13]

The American Gastroenterological Association (AGA) 2024 guideline for fecal microbiota-based therapies in select

gastrointestinal diseases[27] is the first to include new, FDA-approved, standardized live biotherapeutic products (LBP), VOWST® (VOS; Nestlé, Vevey, Switzerland; fecal microbiota spores live-brpk)[28] and REBYOTA® (RBL; Ferring Pharmaceuticals Inc., Saint-Prex, Switzerland; fecal microbiota live-jslm),[29] recommending their use in recurrent CDI, and their earlier use in severe, fulminant, or refractory CDI.[27]

Following approval of VOS and RBL, the FDA revised its position on conventional fecal microbiota transfer (FMT), citing safety concerns and requiring an investigational new drug application for its use,[30] leading OpenBiome (Cambridge, Massachusetts, USA), the major stool bank of FMT material in the US, to cease distribution.[31]

The efficacy of FMT has been inconsistent, with reported efficacy lower in most randomized trials than in non-randomized reports,[10] and there have been safety concerns related to the number of patients exposed to a particular donor and transmission of infectious agents.[30] Recently, a trial comparing oral FMT capsules with placebo was stopped early for futility after FMT showed no superiority in reducing CDI recurrence or death at Day 56.[32]

"From my perspective, the FDA revised Discretionary Enforcement Policy on FMT was a good thing," says Sears, "because it is time for us to turn away from the unregulated, uncontrolled process of transplanting stool from one person into another, towards stable products that have been well tested for patients."

At the Mayo Clinic, Pardi's team had their own FMT program, so the closure of OpenBiome has not impacted treatment options, but they're still moving to close this facility down.

"Having the approved microbiota-based products has affected our practice," says Pardi. "We try to stratify patients in terms of their risk of recurrence. If I have someone with a fulminant infection, either primary or first recurrence, I'm going to try to get a microbiome replacement product approved to prevent rCDI, rather than waiting for the next recurrence, which might put them back in the ICU."

A recently published analysis of the impact of VOS on the gut microbiome showed that, at baseline, gut dysbiosis was similar in those with first and multiple recurrent CDI.[33] This underscores that recurrence happens in the context of dysbiosis and highlights the importance of addressing dysbiosis in rCDI regardless of the number of recurrent episodes.[33]

Recent data are providing further insights on the routine use of LBPs. The REBYOTA™ Prospective Registry,[34] and a study of 128 adult patients with CDI treated with RBL in an outpatient setting,[35] are reporting treatment outcomes comparable to RBL clinical trials[36] in older populations with a high level of comorbidities, and significant improvements in health-related quality of life.[35] A network meta-analysis of 18 studies involving 4,347 patients comparing several microbiota-based treatments found that RBL, VOS, and an investigational drug, VE303, all reduced the risk of rCDI.[37] After a Bayesian analysis, only VOS demonstrated a statistically significant reduction in rCDI relative risk (RR: 0.26; 95% CI: 0.09–0.81).[37]

"I think one of the key studies this year was the CDI-SCOPE findings, demonstrating the efficacy and safety of RBL given by colonoscopy," says Pardi. In this off-label, multicenter, single-arm study, 92.7% (38/41) of participants experienced no further CDI episodes within 6 months.[38,39] Most physicians (90.2%) regarded the procedure 'positively' or 'very positively',[40] and all participants reported that their diarrhea symptoms were less severe than at baseline.[41]

MODERNIZING CDI TREATMENT APPROACHES

"I don't think the current guidelines emphasize using microbiome replacement products after first recurrence in selected populations, even though the field is moving towards this," says Pardi. "I would expect that when the guidelines are next updated, we'll see more of that discussed, even if it's not explicitly recommended, as something for people to think about for given patient populations."

Despite data supporting the effectiveness of LBPs in preventing rCDI, the costs of these treatments can be a barrier. However, a recent cost-effectiveness analysis found that early use of VOS or RBL after first recurrence consistently outperformed delayed use in terms of incremental cost effectiveness and quality-adjusted life years gained.[42]

Pardi suggests microbiota LBPs might even be moved earlier in treatment, to replace front-line antibiotics altogether, and highlights a recent small study in Europe that directly compared FMT to vancomycin for primary CDI.[43] In this multi-center study of 104 adults with primary CDI, FMT was found to be non-inferior to vancomycin for clinical cure at 14 days without recurrence at 60 days without additional treatment.[43]

"This study is initial proof of concept of what many people thought would be the case," said Pardi. "That addressing the problem, which is the dysbiosis, is going to ultimately be at least equal to, if not better than, antibiotics."

Sears' projection for the field:
"We hypothesize that use of LBPs after primary CDI, at least for some patients, will reduce rCDI," agrees Sears. "We now have two FDA-approved microbiota therapies, but these have not yet been studied for use following antibiotics in primary CDI. We need formal RCTs evaluating these products after primary CDI."

FUTURE RESEARCH IN MANAGING CDI

Several new therapeutics are in the pipeline for CDI, including a narrow-spectrum antibiotic, ibezapolstat,[44] and omadacycline, an approved tetracycline analog reported to have a low propensity to cause CDI.[45] An alternative anti-toxin B neutralizing antibody (AZD5148) is also being explored in preclinical studies[46] and a standardized microbiota-based therapy, VE303, is in clinical trials.[47,48] Several vaccines have also been tested in clinical trials, but none have met the primary endpoint of preventing CDI.[49]

"Preventing CDI with a vaccine is probably a long way off, but I hope we are close to what I call 'one and done', where a patient with primary CDI receives a treatment combination that treats the active infection and prevents recurrence," says Pardi. "*C. difficile* comes back because of two things: spores and microbiome dysbiosis. In addition to better treatments for dysbiosis, it would be good if we could prevent the activation of spores to infection."

"I'm hopeful that we'll end up with highly engineered products of microbial communities and specific strains, allowing us to move to more refined, effective microbiota therapy for rCDI" says Sears. "We're probably not going to get rid of CDI, but my goal would be for patients to feel well afterwards and not under the constant threat of recurrence."

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