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Review

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Updates in Treatment of Recurrent *Clostridium difficile* Infection

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Abstract

Recurrent *Clostridium difficile* infection (CDI) is a perpetual problem that leads to increased economic burden, higher healthcare cost, and significant morbidity and mortality. Its treatment remains a challenge. While various treatment approaches have been attempted with different levels of success, robust data establishing the superiority of one approach over the others is lacking. In this article, we review the current evidence pertaining to conventional pharmacological treatment as well as fecal microbiota transplantation (FMT) as a novel, rapidly emerging treatment modality for recurrent CDI.

Keywords: Recurrent *Clostridium difficile*; Fecal microbiota transplantation; Tapering and pulsed vancomycin; Fidaxomicin

Introduction

Recurrence of *Clostridium difficile* infection (CDI) is very common leading to significant morbidity and increased healthcare costs. It is defined as a relapse of CDI symptoms within 2 - 8 weeks of successful treatment of the initial episode [1]. About 15-35% of CDI patients suffer from recurrent infections [2]. Frequently, CDI is a relapse of the same infection rather than a re-infection with a new strain [3, 4]. Second and subsequent recurrences are even more common after the first recurrence [5].

Risk Factors

The literature has identified various risk factors that predispose patients to recurrent CDI. Some of these factors are well-established, such as advanced age and antibiotic use. Controversy exists in regard to others, such as gastric acid suppression [6, 7]. Advanced age has been identified as a risk factor in multiple studies [7-9]. It has been speculated that gastric acid suppression may result in a more suitable environment for *Clostridium difficile* (*C. difficile*) to transition through the stomach and proliferate; however, the data in this regard are conflicting. A small retrospective study of 125 patients and a meta-analysis of 18 observational studies found that patients receiving gastric acid-suppressing medications were at a higher risk of suffering from recurrent CDI [8, 10]. However, a recent retrospective study that included 435 patients concluded that antisecretory medications do not increase the risk of recurrent CDI. In the same study, advanced age and partial colectomy were identified as independent risk factors [7]. Hypoalbuminemia (albumin < 2.5 g/dL) was also found to be a significant risk factor in a retrospective study [8]. A recent prospective study that evaluated ATLAS score and albumin as predictors for recurrent CDI showed that only serum albumin predicted 90-day disease recurrence [11].

Management Options

Tapering/Pulsed vancomycin

The underlying rationale for tapering and/or pulsed regimens is to target the spores that are otherwise resistant to antibiotics. Once they germinate, vegetative forms are targeted by the antibiotics being given as part of a prolonged course in a tapered and/or pulsed regimen. Even though a randomized controlled trial (RCT) comparing the standard with extended duration vancomycin is lacking, current literature supports the use of extended duration vancomycin therapy. The latest Infectious Disease Society of America (IDSA) guidelines recommend tapered and pulsed vancomycin therapy for the first recurrence [1]. A recent systematic review evaluated two randomized open-label clinical trials [12, 13] and three case series [14-16]. Two of these case series [14, 16] and one of these clinical trials [13] used tapered and pulsed regimen, whereas the other case series [15] and clinical trial [12] utilized pulsed only regimen. Authors concluded that the reviewed literature supports extended duration tapering and pulsed vancomycin therapy for recurrent CDI [17]. All of these studies were small, evaluating a total of only 174 patients. Optimal treatment for recur-

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rent CDI (OpTION trial) is a randomized clinical trial that is currently recruiting. It will compare standard fidaxomicin with standard vancomycin treatment and extended duration vancomycin (standard course followed by taper and pulse) with standard vancomycin treatment alone in patients with either a first or second CDI recurrence [18] (NCT 02667418).

Fidaxomicin

Fidaxomicin (DIFICID) is a macrolide bactericidal antibiotic that is active against *C. difficile* and has been approved by the US Food and Drug Administration (FDA) for use in adults with CDI [19]. It has a narrower spectrum of activity compared to vancomycin and metronidazole, hence causes minimal disruption of the gut flora. An RCT comparing oral vancomycin and fidaxomicin that evaluated 548 patients showed similar cure rates but significantly fewer recurrence rates with fidaxomicin. However, this study only used patients with non-NAP1 (North American pulsed-field gel electrophoresis type 1) strains [20]. The NAP1 strain has a higher prevalence and reduced cure rates, and it tends to cause more severe disease [21, 22]. But, the data pertaining to this is conflicting, as some studies have shown no association between NAP1 and severe disease [23-25]. Another RCT not only confirmed the non-inferiority of fidaxomicin compared to vancomycin but also showed higher cure rates in a subgroup analysis of patients who were simultaneously receiving antibiotics for other conditions [26]. IDSA guidelines recommend a 10-day fidaxomicin course as an alternative first-line treatment for recurrent CDI [1]. A recent systematic review and meta-analysis analyzed 24 trials comparing 13 different treatment options. It concluded that amongst the available treatment options for non-multiply recurrent CDI, fidaxomicin results in a sustained symptomatic cure more frequently [27]. Another review worth mentioning is a multicenter retrospective review of CDI patients treated with fidaxomicin. Out of 97 patients who received fidaxomicin, 16 were excluded for < 8-week follow-up. Complete response was noted in 90% and 19% developed recurrent CDI. Recurrence rate was significantly higher in patients with prior episodes of CDI (0% with first episode versus 23% and 29% with one and two prior episodes respectively) [28]. In a RCT of 364 patients with age ≥ 60 years at 86 European hospitals, extended duration fidaxomicin administered in tapered and pulsed fashion was compared with a standard 10-day course of vancomycin. It revealed that extended duration fidaxomicin was superior in terms of sustained clinical cure at 30 days after the end of treatment. This benefit was seen even at 90 days follow-up. However, this trial does not specify whether the study participants were being treated for an initial or recurrent episode [29]. Fidaxomicin's premium price tag is prohibitive for its routine use. The data from studies on its overall cost-effectiveness are conflicting. For instance, a study conducted in the UK showed similar costs with fidaxomicin and vancomycin in severe CDI and first recurrence, but quality-adjusted life year (QALY) gains with fidaxomicin indicated that fidaxomicin was more cost-effective. Contrarily, a study conducted in US found vancomycin to be cost-effective as compared to fidaxomicin or bezlotoxumab plus vancomycin [30].

Ridinilazole

Ridinilazole is a non-absorbable antibiotic that has proven to be successful in treating CDI in Phase 2 trials [31]. It specifically targets clostridia while causing minimal damage to the normal gut microbiota, thus minimizing collateral damage to the normal gut flora [32, 33]. In Phase 2 trials, ridinilazole has exhibited superiority over vancomycin in sustained clinical responses [31]. Currently, a Phase 2 clinical trial comparing the safety and efficacy of ridinilazole with that of fidaxomicin is underway [34].

Nitazoxanide

Nitazoxanide, a broad-spectrum antiparasitic and antiviral drug has also been used in some cases of recurrent CDI with favorable results as evidenced by a case report from 2011 [35]. In a prospective, double-blinded study of hospitalized patients with *C. difficile* colitis, nitazoxanide was found to be just as effective as metronidazole in the treatment of *C. difficile* colitis. This study compared metronidazole for 10 days, nitazoxanide for 7 days and nitazoxanide for 10 days. There was no significant difference in the size of the symptom-free population at the end of 7 and 31 days between these groups. Even though the response rate at the end of 7 days and sustained response at 31 days was higher with nitazoxanide, the difference was not significant. Nonetheless, the sample size was not large enough to determine statistical significance [36]. In another double-blind RCT, nitazoxanide was found to be just as effective as vancomycin in treating CDI but the sample size was very small (50) to draw any definitive conclusions [37]. There is a dearth of recent and strong quality data in this realm deterring the routine use of this antibiotic.

Fecal microbiota transplantation (FMT)

FMT, or stool transplantation, has been used with a lot of success in patients with recurrent CDI. Altered colonic microbiota, primarily due to antibiotics, is the underlying cause of recurrent CDI and restoration of that normal microbiota is the principle of FMT. Multiple anecdotal reports and RCTs have demonstrated the success of FMT in treating recurrent CDI. Current practice involves the use of FMT in managing second recurrences of CDI [1], but FMT may also be attempted for refractory CDI. Current evidence does not support the use of FMT as a first-line of treatment for the first recurrence. Early RCTs that compared FMT with antibiotic therapy in patients with recurrent CDI exhibited improved outcomes in patients treated with FMT compared to vancomycin [12, 38]. For instance, in the RCT conducted by van Nood et al patients were randomly assigned to receive an initial vancomycin regimen for 4 days, followed by bowel lavage and then infusion of donor feces through a nasoduodenal tube; standard vancomycin regimen for 14 days; or standard vancomycin regimen followed just by bowel lavage. The study population had relapsed CDI after at least one previous course of adequate antibiotic

Table 1. RCTs Comparing FMT With Pharmacotherapy

Author	Sample (n)	Intervention	Comparison	Outcome in the FMT group	Follow-up period
Van Nood et al 2013 [38]	42	FMT via ND tube preceded by V for 4 days and bowel lavage	V for 14 days and V for 14 days followed by bowel lavage	Resolution of symptoms in 15/16 (94%) patients	5 weeks
G Cammarota et al 2015 [12]	39	V for 3 days followed by FMT via C	V for 10 days followed by every 2-3 days for 3 weeks	Resolution of symptoms in 18/20 (90%) patients	10 weeks
Susy S. Hota et al 2017 [13]	30	V for 14 days followed by FMT via E	6-week taper of V	Resolution of symptoms in 7/16 (43.8%) patients	120 days
Hvas et al 2019 [39]	64	V for 4 - 10 days followed by FMT via C or NJ tube	V for 10 days, F for 10 days	Clinical resolution and negative CD test in 17/24 (71%)	8 weeks

RCT: randomized controlled trial; FMT: fecal microbiota transplantation; V: vancomycin; F: fidaxomicin; C: colonoscopy; E: enema; NJ: nasojejunal; ND: nasoduodenal.

treatment. In the fecal infusion group 81% patients had a resolution of diarrhea after the first infusion as compared to 31% in the vancomycin-only group and 23% in vancomycin followed by lavage ($P < 0.001$ for both). The study was cut short after an interim analysis [38]. Similarly, another RCT from Italy demonstrated encouraging results of this novel therapy. Patients were randomized to receive either short 3-day regimen of vancomycin followed by one or more infusion of feces via colonoscopy, or vancomycin (125 mg four times a day for 10 days followed by 125 - 500 mg/day every 2 - 3 days for 3 weeks at the minimum). 90% of patients in the fecal transplantation group had a resolution of diarrhea as compared to 26% in the vancomycin group ($P < 0.0001$). The study was terminated after a 1-year interim analysis [12]. However, an RCT by Hota et al failed to show any significant benefits resulting from FMT. Hota et al randomized patients with recurrent CDI to receive 14 days of oral vancomycin followed by a single FMT by enema or vancomycin taper over 6 weeks [13]. This study was terminated with an interim analysis of 30 patients. In the FMT group, 43% of patients experienced resolution of their symptoms and 56% experienced recurrence of CDI. In the vancomycin group, it was 58% and 42%, respectively. Contrarily a very recent single-center trial of 64 patients with recurrent CDI randomly assigned to receive FMT after 4 - 10 days of vancomycin 125 mg four times a day, 10 days of fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day. In the FMT group 71% of patients achieved the primary outcome of combined clinical resolution and negative *C. difficile* toxin testing 8 weeks after the treatment; 33% and 19% of patients had the above outcome in fidaxomicin and vancomycin group respectively. Clinical resolution without a documented negative test was seen in 92%, 42% and 19% patients in FMT, fidaxomicin and vancomycin groups respectively [39]. The outcomes of these randomized trials are summarized in Table 1 [12, 13, 38, 39]. A meta-analysis of seven studies by Khan et al recognized fecal transplantation as a promising modality. Their analysis found a nonsignificant trend favoring the FMT group as compared to the medical treatment group. Additionally, in a subgroup analysis, there was no significant difference between the frozen or fresh FMT in terms of resolution of diarrhea [40]. Appropriate patient selection prior to initiating FMT is critical as a multitude of host and donor-related factors determine the success of FMT. The safety and efficacy of FMT in solid organ transplant (SOT) patients was evaluated in a retrospective, multicenter study. The authors utilized the institutional FMT databases to identify eligible patients in 10 academic centers across the United States and Canada. The primary cure was defined as complete resolution of diarrhea and/or negative *C. difficile* testing after a single FMT, and the overall cure was defined achieving those outcomes with more than one FMT with or without anti-CDI antibiotics. A total of 94 study participants received FMT for recurrent (73/94), severe (14/94) or fulminant (7/94) CDI. The primary cure was achieved in 63.8% (60/94) at 1-month follow-up and 58.7% (54/92) at 3-month follow-up. The overall cure rate at 3-month was at 91.3% (84/92) [41].

FMT can be delivered in the upper gastrointestinal (GI) tract or lower GI tract. Various modalities, including nasogastric tubes, nasoduodenal tubes, nasojejunal tube, esophagogastroduodenoscopies, or capsules (containing fecal microbiota), can be used to deliver FMT in the upper GI tract. Retention enemas or colonoscopies can be used for the lower GI tract. The benefits of one versus the other routes of administration have been compared in multiple case series, meta-analyses, and systematic reviews. Primarily, the route of instillation depends on the institutional expertise, patient preference, severity of illness, and the safest approach. Four systematic reviews and meta-analyses [42-45] showed a trend towards better results in the lower GI route compared to the upper GI route. This may have occurred because the amount of stool instillation achieved through the lower GI route was higher. A recent retrospective analysis of Israeli hospitals involving 111 patients [46] did not demonstrate any differences in the success rates of the following three study arms: upper GI route (gastroscopy, nasogastric tube, or percutaneous endoscopic gastrostomy), oral capsule, and lower GI route (colonoscopy). This study along with a systematic review by Iqbal et al [47] revealed encapsulated FMT to be promising and a safe approach for recurrent CDI provided standard protocols are followed. Further research is needed to establish optimal capsule dosing regimens and duration of treatment.

No significant adverse effects related to FMT have been

reported. There is a risk of procedure-related complications when FMT is given through the upper or lower GI tract; however, the rate of complications should mirror the rate of complications when these procedures are performed for other reasons. Two cases of norovirus transmission have been reported in patients after receiving FMT from asymptomatic donors who did not have any sick contacts [48]. There have also been reports of inflammatory bowel disease flare-ups [49, 50] following FMT, with the most serious adverse effect being the necessity of a colectomy. In a retrospective analysis by Cheng et al [49] a patient who needed a colectomy had cytomegalovirus colitis following FMT, which points to the importance of donor screening prior to FMT.

In conclusion, while FMT is a safe and effective therapy for recurrent CDI, further research is necessary to establish the guidelines for FMT that include but not limited to appropriate donor screening, the timing of therapy, route of instillation, and formulation. One RCT currently being conducted in Norway is comparing metronidazole with FMT in primary CDI [51]. Future studies comparing FMT with current mainstream treatments like vancomycin and fidaxomicin would help us navigate through the treatment of recurrent CDI.

Prophylaxis

The effectiveness of oral vancomycin prophylaxis (OVP) has been examined in retrospective studies. A recently published review of three studies found a reduced risk of recurrent CDI with OVP however the data is not convincing as all of them were retrospective and lack randomization [52]. In one of these studies, OVP did not affect recurrence in patients with a single previous episode of CDI ($P = 0.69$). But in patients with recurrent CDI 54.4% in OVP group experienced a recurrence compared to 69.5% in those who did not receive OVP resulting in a number needed to treat (NNT) of 6.6 ($P < 0.0001$) [53]. The second reviewed study was a single-center retrospective study of 71 patients who had previous CDI and subsequently initiated on systemic antibiotics. OVP dose of 125 or 250 mg twice daily continued along with systemic antimicrobial regimen. Recurrent CDI occurred in 4% of the vancomycin group compared to 27% in the control group with an NNT of 5 ($P < 0.001$) [54]. Another recent retrospective single-center study from a community hospital demonstrated that administration of OVP to subjects with a history of CDI in 12 months prior to subsequent antibiotic exposure benefits in terms of risk reduction of recurrent CDI for up to 12 months [55]. The evidence currently supporting OVP is lacking in terms of long-term outcomes, adverse effects, and randomized trials. Ongoing prospective studies in this regard seek to fill this void [56-58].

Discussion

Treatment of recurrent CDI is rapidly evolving and the latest IDSA guidelines reflect that. Gupta et al in their clinical synopsis summarized the present IDSA guidelines. For the first recurrence tapered and pulsed vancomycin or fidaxomicin should be considered if the initial episode was treated with standard vancomycin. Alternatively, fidaxomicin or standard 10-day course of vancomycin can be used for those previously treated with metronidazole [59]. The evidence behind these recommendations is not strong and an ongoing RCT will likely address this [18] (NCT 02667418). Johnson et al in their letter to the editor highlighted other alternative therapies which have shown promising results in RCTs [60]. For example, in two RCTs, infusion of bezlotoxumab, a monoclonal antibody directed against toxin B in addition to standard antibiotic treatment was shown to reduce the rate of recurrence [61]. Ridinilazole has also shown positive results in initial studies and as additional data become available, we may see it become a part of a conventional regimen [31, 34]. Vancomycin in a tapered and pulsed manner, vancomycin followed by rifaximin, a standard course of fidaxomicin or FMT can be used for second or subsequent recurrences per the latest IDSA guidelines. The quality of evidence for these treatment options is low except for FMT where it is moderate. The panel recommended trying appropriate antibiotics for treating at least two recurrences before resorting to FMT [1]. Treatment of recurrent CDI is a work in progress. Newly emerging antibiotics, treatment regimens and novel therapies like FMT are a testament to that.

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None to declare.

Author Contributions

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