Ther Adv Infectious Dis
2019, Vol. 6: 1–10
DOI: 10.1177/2049936119868548

Clostridioides difficile therapeutics: guidelines and beyond

Robert Orenstein and Roberto L. Patron

***Abstract*:** *Clostridioides difficile* infection (CDI) has become an increasingly common infection both within and outside of the hospital setting. The management of this infection has been evolving as we learn more about the role of the human microbiota in protecting us from this gastrointestinal opportunist. For many years the focus of treatment had been on eradication of the vegetative, toxin-producing form of the organism, with little regard for its collateral impact on the host's microbiota or risk of recurrence. With the marked increase in *C. difficile* disease, and, particularly, recurrent disease in the last decade, new guidelines are more focused on targeting and reducing collateral damage to the colonic microbiota. Immune-based strategies that manipulate the microbiota and provide a humoral response to toxins have now become mainstream. Newer strategies are needed to look beyond simply resolving the primary episode but are focused on delayed outcomes such as cure at 90 days, reduced morbidity and mortality, and patient quality of life. The purpose of this review is to familiarize readers with the most recent evidence-based guidelines for *C. difficile* management, and to describe the role of newer antimicrobials, immunological-, and microbiota-based therapeutics to prevent recurrence and improve the outcomes of people with CDI.

Keywords: *C. difficile*, FMT, guidelines, treatment

Received: 6 March 2019; accepted in revised form: 17 July 2019.

Correspondence to:
Robert Orenstein
Division of Infectious Diseases, Mayo Clinic Arizona, 5777 East Mayo Boulevard, Phoenix, AZ 85054, USA
Orenstein.robert@mayo.edu

Roberto L. Patron
Division of Infectious Diseases, Mayo Clinic Arizona, Phoenix, AZ, USA

Introduction

Clostridioides difficile infection (CDI) has become an increasingly common infection within communities, hospitals, and long-term care facilities.[1] Pseudomembranous colitis is not a new disease; it was described in 1893 by Finney, and later associated with antibiotic use in the 1950s, when thought to be due to *Staphylococcus aureus*.[2,3] Following outbreaks in the 1970s associated with clindamycin use, it became recognized that the disease was mediated by *Clostridium difficile* toxins.[4] Initial strategies for tackling this infection were focused on infection control, reducing antibiotic utilization, and, when necessary, treating with either oral vancomycin or metronidazole to eliminate the causative organism. In the mid-1990s, due to the spread of vancomycin-resistant enterococci, the primary treatment for *C. difficile* infection became oral metronidazole, which was inexpensive and equally effective compared with vancomycin. Unfortunately, the 21st century brought a new North-American Pulsefield type 1, Ribotype 027 (NAP1/027) strain of *C. difficile*, which, in the setting of widespread fluoroquinolone use, precipitated a global epidemic.[5,6] Metronidazole, which had seemed reliable for many years, appeared to be associated with increasing numbers of treatment failures.[7–10] Studies began to demonstrate it to be inferior to oral vancomycin in severe disease.[7,11]

Overall cases of CDI began to significantly increase in the 1990s.[12,13] Additionally, there seemed to be an emerging epidemic of recurrent disease despite treatment with either of the aforementioned agents, particularly amongst the elderly.[14] More patients were failing traditional, poorly studied regimens such as the vancomycin pulse-taper, leaving clinicians with few therapeutic options. The lack of evidence-based guidelines

led to poor practice standardization and outcomes for these persons. One ancient procedure, rarely used in the US before the 1990s, the instillation of healthy human feces into the dysbiotic gut of the *C. difficile* patient, became increasingly used for refractory disease, with anecdotal reports of high rates of cure. A procedure [fecal microbiota transplantation (FMT)], which most people previously found distasteful, became the gold standard for refractory and multiply recurrent disease.[15]

The management of this infection has evolved as we have begun to understand the role of the human microbiota in protecting us from this gastrointestinal opportunist. Initial therapeutics have evolved from a focus on eradication of the vegetative, toxin-producing form of the organism with little regard for its collateral impact on the host's microbiota or risk of recurrence. These developments stimulated a new era in research, and the development of therapeutics and guidance for both *C. difficile* treatment and prevention, which we will review in this paper. These new guidelines have become focused on targeting and reducing collateral damage to the colonic microbiota.

IDSA/SHEA 2018 guidelines

In 2018, the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology (SHEA) published updated guidelines for the diagnosis and management of CDI.[16] These guidelines address both a diagnostic as well as a management approach to CDI.

Beginning in the early 2000s, it was recognized that the enzyme immunoassays used to detect *C. difficile* toxins lacked sensitivity. Clinicians would often order multiple stool tests, or would empirically treat those they suspected of disease in the absence of a positive test. The introduction of molecular testing by polymerase chain reaction (PCR) for the *C. difficile* toxin genes (tcdA and tcdB) greatly enhanced the sensitivity. An emerging challenge in the era of *C. difficile* molecular diagnostics has been the overdiagnoses of patients with diarrheal illness. Some studies have suggested PCR-based toxin assays may be falsely positive in up to 45% cases.[17–19] To limit falsely positive samples, the IDSA/SHEA guidelines suggest testing only those with three unformed (Bristol 6, 7) stools per 24 h in the absence of confounders that might cause diarrhea. The recommended test is the two-step, glutamate dehydrogenase antigen followed by a toxin A and B EIA (GDH/Toxin) test, which can be confirmed by PCR if the toxin EIA is negative. Repeat testing within 7 days is discouraged. Newer diagnostic tests include a single molecule assay.[20] This assay has been found to be 97.7% sensitive and 100% specific.[20] However, one recent study found it was not possible to differentiate those with symptomatic disease *versus* asymptomatic carriers based upon the single molecule or quantitative Gene EXPERT (Cepheid Corp) PCR.[21] Thus, the first step in managing CDI is appropriate diagnostic stewardship.

Once the diagnosis is appropriately made, one needs to decide the initial therapy of CDI as it may impact the long-term outcome of the disease. Prior to the 2018 guidelines, either oral metronidazole or vancomycin was recommended for a first episode of mild-to-moderate disease. However, more recent studies showing lower responses in metronidazole-treated patients, have led the guidelines to no longer recommend metronidazole as first line therapy.[16] Prior to 2000, four trials of metronidazole in mild-to-moderate disease showed only a 2.5% failure rate.[16] However, post-2000, five trials indicated an 18.2% primary failure rate with metronidazole therapy *versus* only 2.8% for oral vancomycin.[7,8,10] However, there remain some studies that have continued to show comparable success with metronidazole in mild disease.[11] The updated guidelines recommend either oral vancomycin or fidaxomicin over metronidazole for the initial episode of CDI regardless of its severity.

What is new in these guidelines is the addition of fidaxomicin as first line therapy based upon several well conducted trials.[16,22–24] In a trial conducted by Louie and colleagues, clinical success at the end of treatment with fidaxomicin 200 mg twice daily for 10 days was 92% *versus* 90% for oral vancomycin.[22] However, the recurrence rate at 28 days post-treatment with fidaxomicin was significantly lower (15 *versus* 25%) in those uninfected with a NAP 1 strain. Thus, fidaxomicin offers the advantage of equal effectiveness to vancomycin in the short term, but better long-term results. Unfortunately, 20–30% of patients still have recurrent symptoms after completion of therapy.

Recurrent CDI

Recurrent CDI (rCDI) is a major problem. There was a 189% increase in incidence between 2001

and 2012.[14] The predictors for recurrence include: age >65 years, prior CDI, recent or current antibiotic exposure, lack of antibody to toxins A or B, and exposure to acid suppressive medications.[14,25]

For patients who experience a recurrence, defined as absence of symptoms on treatment followed by recurrent symptoms off treatment, the IDSA/SHEA guidelines have been updated from previous work. If patients received vancomycin for the initial episode and then recur, they should either receive oral fidaxomicin for 10 days or a vancomycin taper-pulse regimen for their initial recurrence. Though not included in the guidelines, data from two randomized trials of bezlotuxumab,[26] suggests those with risk factors for recurrence could consider an intravenous infusion of bezlotuxumab to prevent recurrence.[27] Bezlotuxumab is a monoclonal antibody against *C. difficile* toxin B, which is given concurrently with oral antibiotic therapy directed against CDI. Its half-life is 19 days, so it may carry infected people through the window of vulnerability of 21 days where they are at greatest risk for recurrence.[28] A subgroup analysis of two large trials suggests that those with prior CDI within 6 months, clinically severe CDI, >65 years of age, or immune suppressed receive the greatest benefit, close to a 50% reduction in rCDI.[27] One could consider this approach in the high risk rCDI patient who needs to complete a concurrent course of systemic antibiotics.

Management beyond the first recurrence is problematic for CDI-focused antimicrobials. Each successive course of vancomycin worsens the microbiota diversity index and may predispose to future recurrences.[29] Recurrent disease has significant impact on both the patient and healthcare facilities. Recurrent disease is associated with increased morbidity, delays in chemotherapy, more frequent hospital admission, greater likelihood of ending up in a skilled nursing facility, and higher costs.[30] Additionally, recurrence contributes to the reservoir for healthcare-acquired infection.

For patients who have multiply recurrent disease, traditional antimicrobial-therapy-based approaches are only modestly effective. Options recommended in the guidelines include the vancomycin pulse and taper (VPT) regimen. In one trial, this resulted in a 62% cure rate in those with greater than two preceding CDI episodes.[31] However, recurrence of diarrhea still occurred in 28% of patients, requiring retreatment. This is debilitating and frustrating for patients, as, at this point, most have already received in excess of 4 months of antibiotic therapies.

One suggested alternative antimicrobial approach for recurrent disease, cited in the guidelines, has been to use a 20-day course of oral rifaximin 400 mg three times daily after completing initial retreatment with oral vancomycin. This regimen, called the 'rifaximin chaser,' has been effective in 50% of patients with multiply recurrent disease.[32,33] Unfortunately, rifaximin remains expensive, and insurers are often reluctant to cover its cost for this unapproved use.

Recent studies have suggested that this is the place where fecal microbiota therapies have great value.[15,34,35] Most trials of FMT have shown a single administration of product by nasoenteric route, enema, capsule or endoscopic administration *via* the upper or lower GI tract has between a 65% and 95% success rate of cure.[15,34] Administration of FMT restores the stable and diverse colonic microbiota. The IDSA/SHEA and ACG Guidelines all endorse the use of microbiota therapeutics for multiply recurrent disease; however, FMT remains an unapproved, investigational procedure that requires either an investigational new drug application (IND) or performance under the enforcement discretion rules of the United States Food and Drug Administration (FDA).[35] Because FMT is investigational, and its short- and long-term risks are not yet known, informed consent and comprehensive screening of stool donors is essential. On June 13, 2019, the FDA issued a statement describing a new safety concern due to inadequately screened fecal microbiota used for transplant. Two individuals became colonized with a multiply resistant *Escherichia coli* from the donor, and one immune-compromised subject died due to an infection with this organism. The FDA advised all centers operating under enforcement discretion and INDs that donor screening must include screening for risk of multiply resistant organisms colonization as well as testing of the donor stool for these.[36] Due to these requirements, access to centers performing FMT may be limited compared with

accessibility of medications, leading to some patients being treated for months, or indefinitely, with oral vancomycin.

The role of the microbiota in protection against enteric infections is complex. It includes colonization resistance, altered immune signaling, production of bacteriocins, and alterations of the gut metabolome. Several studies suggest that one mechanism by which FMT may prevent CDI is by restoration of secondary bile acids that inhibit CD sporulation,[37,38] which are depleted following antimicrobial therapies.

Ursodeoxycholic acid (UDCA), a secondary bile acid used for treatment of biliary diseases, may be of value as a surrogate secondary bile acid to prevent rCDI in those who cannot get FMT. UDCA is being used as a replacement for deoxycholic acid. A recent uncontrolled study of 16 subjects with rCDI, who received prolonged adjunctive UDCA 300 mg three times daily, was promising, with a reduction of CDI recurrence.[39]

Clearly, improved strategies are needed to treat and prevent recurrent CDI. One such strategy was tested in the Extend trial.[40] This was a randomized, open label, controlled trial conducted in Europe amongst persons with less than 3 previous CDI episodes. Subjects were randomized to either vancomycin 125 mg four times daily for 10 days or fidaxomicin 200 mg twice daily for 5 days, followed by every other day from day 7 to 25. The primary efficacy outcome was clinical cure at 30 days after the end of treatment, but subjects were also analyzed at 90 days post treatment. The recurrence rate at day 30, with the extended pulsed fidaxomicin (EPF) regimen, was 4% (*versus* 19% for vancomycin) and 6% (19% for vancomycin) at 90 days. The hazard ratio of CDI recurrence at any time after day 10 for a vancomycin treated patient was 3.8-fold higher than the EPF group. The number needed to treat with EPF was 6.6. From this and the other comparative studies of fidaxomicin and vancomycin, it appears that sustained clinical cure is achieved in around 15% more patients treated with fidaxomicin based regimens.[41] The weaknesses of this study were a lack of comparison with standard or pulsed tapered vancomycin regimens and worse outcomes with severe disease.

Because of the lack of effective regimens for these multiply recurrent cases, other novel antimicrobial approaches have been explored, with some anecdotal reports of success. These include novel uses of fidaxomicin, including pulse taper regimens.[42]

Lee and colleagues recently reported a small open label trial of a prolonged fidaxomicin course: 200 mg twice daily for 10 days followed by once daily for 20 days in subjects with multiply recurrent CDI.[42] Of the 29 enrollees, 11 had multiple prior FMTs. The primary endpoint of this study was the clinical response at day 30 post treatment: 83% (24/29) had a complete response at day 30; 76% (22/29) at week 8 and 73% (8/11) who had multiple previous FMTs had a complete response (CR) at week 8.[43] The more selective impact of fidaxomicin on the recovering microbiota may be responsible for these improved outcomes.

Development of new therapeutics for CDI has thus focused on less disruptive antimicrobials to the colonic microbiota. Recently studied agents include surotomycin, cadazalid, and ridinilazole.

Unfortunately, both cadazolid and surotomycin development have been halted due to lack of efficacy in clinical trials.[44] Ridinilazole was found to be superior to vancomycin in phase II clinical trials, with a sustained clinical response of 67% *versus* 42% for vancomycin.[45]

Ridinilazole has moved into phase III trials. Several other antimicrobial agents are in early stages of development.[46]

Because concurrent antibiotic use is commonly a risk factor for recurrent CDI, agents that block their impact on the intestinal microbiota are being explored. One strategy is the administration of a beta-lactamase, SYN-004 (ribaximase) given concomitantly with ceftriaxone, which degrades the beta-lactam before it can impact the intestinal microbiota.[47] Unfortunately, these agents would only be useful with beta-lactam antibiotics.

Fecal microbiota transplantation

The simplest way to restore the colonic microbiota is by reinstilling it from a healthy donor. FMT, the instillation of processed stool from a healthy human donor into an ill person has become the therapy of choice for multiply recurrent CDI.[15,48–53] Prevention of recurrence of CDI following FMT has ranged from 70% to 90% in both observational and randomized clinical

trials.[49–53] FMT has also been valuable in severe disease and has been associated with improved quality of life.[50]

The challenges of FMT include availability, heterogeneity of the donors and their samples, dosing and pharmacology, modes of administration, and safety monitoring. However, demand for FMT products exceeds supply and has led to the creation of several repositories or stool banks. The largest of these in the USA, Open Biome, has provided processed stool samples for oral, endoscopic, and enema-based delivery throughout the USA for both clinical trials and direct patient management.

Studies evaluating the role of FMT have been heterogeneous. After many uncontrolled observational studies appeared to show this to be beneficial, with success rates in the 90% range, Dutch investigators performed the first randomized trial demonstrating the superiority of nasoduodenal FMT *versus* vancomycin.[50] Since that time, several randomized controlled trials have demonstrated similar efficacy.[50–54] European investigators have used FMT for first recurrence, and, more recently, looked at FMT for treating a first CDI episode.[55]

A recent Danish open label, randomized study[56] compared oral vancomycin or fidaxomicin to FMT performed *via* colonoscopy or nasojejunal following a short therapeutic course of CD antibiotics. Clinical resolution and a negative PCR test for CD toxin at 8 weeks post treatment was seen in 71% of the FMT group *versus* only 33% with fidaxomicin and 19% for vancomycin. Though impressive, the success rates with oral vancomycin and fidaxomicin seem low compared with other studies. Because of the hurdles of FMT, and the opportunities to develop new microbiota therapies, several companies embarked on the development of FDA-approved microbiota replacement therapeutics *via* the traditional clinical trials pathway. Both Seres Therapeutics and Rebiotix have conducted advanced phase clinical trials to address the safety and effectiveness of their microbiome therapeutics.[53,57]

Seres 109, is a stool-based ecobiotic composed of the Firmicute spore fraction of stool from healthy donors. In an early trial of Seres 109, 86.7% (26/30) subjects with rCDI were *C. difficile* free at 8 weeks post treatment.[57] The Rebiotix product, RBX 4660, a standardized whole microbiota product from healthy stool donors, which is administered as an enema, was demonstrated to be safe and effective in its phase II, phase IIb, and open label historical control trials.[53,54] Ongoing late stage placebo controlled trials of these microbiota therapeutics are being conducted by Rebiotix, Seres, and Finch Therapeutics in the USA.

Two additional strategies for managing recurrent *C. difficile* have received less attention. These include a nontoxigenic *C. difficile* strain, which colonizes the GI tract and may prevent infection,[58] and several *C. difficile* vaccines which thus far have had limited value.

Newer studies are evaluating combinations of specifically cultivated microbial mixes from stored microbial libraries based upon data implying the role of specific microbes in protection against CDI.[59]

Once patients have had CDI, they remain at risk of recurrence.[16] Current strategies have focused on preventing disruption of the microbiota when antimicrobials are required for other infections. Often, patients with rCDI acquired this due to antibiotic treatments for frequent urinary tract or respiratory infections. In the licensing trials of fidaxomicin, 28% of subjects received concomitant antibiotic therapy during, or within, 4 weeks of treatment of their CDI, which increased their risk of recurrence by 50%.[60] A strategic approach to antimicrobial choices with lower risk of triggering CDI is needed. Though virtually all antibiotics can trigger recurrent CDI, those that achieve low colonic concentrations, or are active *versus* *C. difficile* may be less likely to cause recurrence.

Doxycycline appears to have a low risk of precipitation of CDI.[61] This agent could be used in respiratory and skin and soft tissue infections to minimize CDI risk. For UTIs, avoidance of antimicrobials in asymptomatic bacteriuria, and the use of ibuprofen or D-mannose for symptomatic cystitis may be a strategy worth exploring. When antibiotics are needed for cystitis, oral fosfomycin or nitrofurantoin would be preferred over beta-lactams and fluoroquinolones for susceptible organisms.

When broad spectrum antibiotics cannot be avoided, one strategy has been the use of low dose oral vancomycin prophylaxis (OVP).[8,62] In the latter, retrospective, study, subjects received oral

vancomycin during concomitant antibiotics and for up to 1 week after. The majority received 125 or 250 mg of oral vancomycin twice daily along with their systemic antibiotics. Those receiving OVP had an 88% reduction in recurrent CDI (4.2% *versus* 26.6%). Similarly, in high-risk allogeneic stem-cell transplant recipients given 125 mg oral vancomycin twice daily from the time of inpatient admission through post-transplant discharge, the sustained clinical cure rate amongst these persons was 95.6% (86/90) at 90 days *versus* 80% in the controls.[63]

In a cohort of renal transplant recipients, vancomycin 125 mg twice daily was given along with broad spectrum antibiotics and compared with controls who did not receive OVP. None of the OVP subjects developed CDI *versus* 8% of the controls.[64,65]

Tariq and colleagues recently performed a meta-analysis of all available OVP studies, and reported no significant decrease in risk of CDI in patients who received OVP for primary prevention but a 67% reduced risk for secondary prevention, particularly in those at highest risk.[66] Thus, this strategy may be useful in those with a high risk of recurrence. Another question that arises is the role of preventive vancomycin or fidaxomicin for individuals with a history of rCDI who have undergone a prior FMT. A recent study in 404 such subjects found that 8.1% of the entire cohort developed rCDI. Those receiving non-CDI antibiotics had an 8.44 relative risk of developing CDI. However, there was no difference in those who received concomitant CDI prophylaxis *versus* those who did not.[67] In this latter study, those who received preventive probiotics actually had a higher risk for rCDI. Similar data looking at the primary role of oral probiotics (Bio-K+ - *Lactobacillus acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2) failed to reduce hospital-onset CDI in a practical study of over 1500 patients.[68] In a critical review of the role of probiotics for CDI by the CADTH, the authors concluded that there remains inadequate evidence to support the use of various probiotics for the prevention of CDI.[69]

Future perspectives

A more strategic approach to the management of CDI is emerging. This involves a three-pronged attack: appropriate antibiotic stewardship, enhanced diagnostic stewardship, and a focus on improving long-term outcomes.

Starting with the best initial treatment regimen may reduce this risk of recurrence of CDI. A more individualized approach that focuses on those at greatest risk for both short- and long-term complications may improve outcomes. Though previous studies focused on short-term outcomes, newer trials like the EXTEND trial need to focus on what happens to these patients over a much longer window of time. These patients will often require further systemic antimicrobials. The use of targeted antimicrobials, selective use of bezlotuxumab, and microbiota replacement therapies may not only reduce the individual risk for recurrence, but also have the potential to reduce the reservoir of infection.

Rather than subject our patients to suboptimal regimens and risk for recurrence, proactive strategies that reduce risk to those receiving concomitant antimicrobials should be further studied. Currently available targeted antimicrobials and microbiota replacement therapies may benefit those patients who require systemic antimicrobials.

For years, our approach to HIV prevention was to provide education and implement infection prevention measures (i.e. condoms and safe sex). In spite of these efforts, new infections continued at the same rate. We have used the same approach for CDI; education and infection prevention have not limited the burden of the epidemic. New therapeutic approaches, more effective treatment as prevention, may be a new strategic approach to controlling this disease.

Funding

The author(s) received no financial support for the research, authorship, and publication of this article.

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Robert Orenstein https://orcid.org/0000-0001-5210-1258

References

1. Lessa FC, Mu Y, Bamberg WM, *et al*. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015; 372: 825–834.

2. Finney JMT. Gastroenterology for cicatrizing ulcer of the pylorus. *Bull Johns Hopkins Hosp* 1893, 4: 53–55.
3. Khan MY and Hall WH. Staphylococcal enterocolitis–treatment with oral vancomycin. *An Intern Med* 1966; 65: 1–8.
4. Tedesco FJ, Bartoni RW and Alpers DH. Clindamycin-associated colitis: a prospective study. *Ann Intern Med* 1974; 81: 429–433.
5. McDonald LC, Kilgore GE, Thompson A, *et al*. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med* 2015; 353: 2433–2441.
6. Loo VG, Poirier L, Miller MA, *et al*. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2015; 353: 2442–2449.
7. Zar FA, Bakkanagari SR, Moorthi KM, *et al*. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile* associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007; 45: 302–307.
8. Kelly CP and Lamont JT. *Clostridium difficile*-more difficult than ever. *N Engl J Med* 2008; 359: 1932–1940.
9. Musher DM, Aslam S, Logan N, *et al*. Relatively poor outcome after treatment of *Clostridium difficile* with metronidazole. *Clin Infect Dis* 2005; 40: 1586–1590.
10. Johnson S, Louie TK, Gerding DN, *et al*. Vancomycin, metronidazole or tolevamer for *Clostridium difficile* infection: results from two multinational randomized controlled trials. *Clin Infect Dis* 2014; 59: 345–354.
11. Stevens VW, Nelson RE, Schwab-Daugherty EM, *et al*. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with *Clostridium difficile* infection. *JAMA Intern Med* 2017; 177: 546–553.
12. Ricciardi R, Rothenberger DA, Madoff RD, *et al*. Increasing prevalence and severity of *Clostridium difficile* colitis in hospitalized patients in the United States. *Arch Surg* 2007; 142: 624–631.
13. Leffler DA and Lamont JT. *Clostridium difficile* infection. *N Engl J Med* 2015; 372: 1539–1548.
14. Ma GK, Brensinger CM, Wu Q, *et al*. Increasing incidence of multiply recurrent *Clostridium difficile* infection in the United States: a cohort study. *Ann Intern Med* 2017; 167: 152–158.
15. Gough E, Shaikh J and Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2011; 53: 994–1002.
16. McDonald LC, Gerding DN, Johnson S, *et al*. Clinical practice guidelines *for Clostridium difficile* infection in adults and children: 2017 update by the infectious disease society of America (IDSA) and society for healthcare epidemiology of America (SHEA). *Clin Infect Dis* 2018; 66: 987–994.
17. Polage CR, Gyorke CE, Kennedy MA, *et al*. Over diagnosis of *Clostridium difficile* infection in the molecular test era. *JAMA Intern Med* 2015; 175: 1792–1801.
18. Fang F, Polage CR and Wilcox MH. Point-counterpoint: what is the optimal approach for detection of *Clostridium difficile* infection? *J Clin Microbiol* 2017; 55: 670–680.
19. Bagdasarian N, Rao K and Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. *JAMA* 2015; 313: 398–404.
20. Sandlund J, Bartolome A, Almazan A, *et al*. Ultrasensitive detection of *Clostridioides difficile* toxins A and B by use of automated single-molecule counting technology. *J Clin Microbiol* 2018; 56: e00908–e00918.
21. Pollock NR, Banz A, Chen X, *et al*. Comparison of *Clostridioides difficile* stool toxin concentration in adults with symptomatic infection and asymptomatic carriage using an ultrasensitive quantitative immunoassay. *Clin Infect Dis* 2019; 68: 78–86.
22. Louie TJ, Miller MA, Mullane KM, *et al*. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; 364: 422–431.
23. 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, randomized controlled trial. *Lancet Infect Dis* 2012; 12: 281–289.
24. Beinortas T, Burr NE, Wilcox MH, *et al*. Comparative efficacy of treatments for *Clostridium difficile* infection: a systematic review and network meta-analysis. *Lancet Infect Dis* 2018; 18: 1035–1044.
25. Kyne L, Warny M, Qamar A, *et al*. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000; 10: 390–397.

26. Wilcox MJ, Gerding DN, Poxton IR, *et al*. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med* 2017; 376: 305–317.

27. 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: 649–656.

28. Abujamel T, Cadnum JL, Jury LA, *et al*. Defining the vulnerable period for reestablishment of *Clostridium difficile* colonization after treatment of *C. difficile* infection with oral vancomycin or metronidazole. *PLoS One* 2013; 8: e76269.

29. Isaac S, Scher JU, Djukovic A, *et al*. Short and long-term effect of oral vancomycin on the human intestinal microbiota. *J Antimicrob Chemother* 2017; 72: 128–136.

30. Reveles KR, Dotson KM, Gonzales-Luna A, *et al*. *Clostridioides* (formerly Clostridium) *difficile* infection during hospitalization increase the likelihood of non-home patient discharge. *Clin Infect Dis* 2019; 68: 1887–1893.

31. Sirbu BD, Soriano MM, Manzo C, *et al*. Vancomycin taper and pulse regimen with careful follow-up for patients with recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2017; 65: 1396–1399.

32. Johnson S, Schriever C, Patel T, *et al*. Rifaximin redux: treatment of recurrent *Clostridium difficile* infections with rifaximin immediately post-vancomycin treatment. *Anaerobe* 2009; 15: 290–291.

33. Garey KW, Ghantoji SS, Shah DN, *et al*. A randomized, double blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhea in patients with *Clostridium difficile* infection. *J Antimicrob Chemother* 2011; 66: 2850–2855.

34. Mamo Y, Woodworth MH, Wang T, *et al*. Durability and long-term clinical outcomes of fecal microbiota transplant treatment in patients with recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2018; 66: 1705–1711.

35. Kelly BJ and Tebas P. Clinical practice and infrastructure review of fecal microbiota transplantation for *Clostridium difficile* infection. *Chest* 2018; 153: 266–277.

36. U.S. Food and Drug Administration. Information pertaining to additional safety protections regarding use of fecal microbiota for transplantation–screening and testing of stool donors for multi-drug resistant organisms, https://www.fda.gov/vaccines-blood-biologics/safety-availabilty-biologics/information-pe (2019, 18 June 2019).

37. Weingarden AR, Chen C, Zhang N, *et al*. Ursodeoxycholic acid inhibits *Clostridium difficile* spore germination and vegetative growth and prevents the recurrence of ileal pouchitis associated with the infection. *J Clin Gastroenterol* 2016; 50: 624–630.

38. Weingarden AR, Chen C, Bobr A, *et al*. Microbiota transplantation restores normal fecal bile acid composition in recurrent *Clostridium difficile* infection. *Am J Physiolo Gastrointest Liver Physiol* 2014; 306: G310–G319.

39. Webb BJ, Brunner A, Lewis J, *et al*. Repurposing an old drug for a new epidemic: ursodeoxycholic acid to prevent recurrent *Clostridioides difficile* infection. *Clin Infect Dis* 2019; 68: 498–500.

40. 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 randomized, controlled, open-label phase 3b/4 trial. *Lancet Infect Dis* 2018; 18: 296–307.

41. Gerding DN. Is pulsed dosing the answer to treatment of *Clostridium difficile* infection? *Lancet Infect Dis* 2018; 18: 231–233.

42. Soriano MM, Danziger LH, Gerding DN, *et al*. Novel fidaxomicin treatment regimens for patients with multiple *Clostridium difficile* infection recurrences that are refractory to standard therapies. *Open Forum Infect Dis* 2014; 1: ofu069.

43. Lee C, Habib M, Kim C, *et al*. 500. Efficacy of 30-day fidaxomicin for treatment of acute *Clostridium difficile* infection with history of multiple recurrences. *Open Forum Infect Dis* 2018; 5(Suppl. 1): S185–S186.

44. Gerding DN, Cornely OA, Grill S, *et al*. Cadazolid for the treatment of *Clostridum difficile* infection: results of two double-blind placebo-controlled, non-inferiority, randomized phase 3 trials. *Lancet Infect Dis* 2019; 19: 265–274.

45. Vickers RJ, Tillotson GS, Nathan R, *et al*. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of *Clostridium difficile* infection: a phase 2, randomized, double-blind, active-controlled, non-inferiority study. *Lancet Infect Dis* 2017; 17: 735–744.

46. Petrsillo N, Granat G and Catald MA. Novel antimicrobials for the treatment of *Clostridium diffcile* infection. *Front Med* 2018; 5: 96.

47. Kokai-Kun F, Roberts T, Coughlin O, *et al*. The oral beta-lactamase SYN-004 (Ribaxamase) degrades ceftriaxone excreted into the intestine in phase 2a clinical studies. *Antimicrob Agents Chemother* 2017; 61: e02197–e02216.

48. Hui W, Li T, Liu W, *et al*. Fecal microbiota transplantation for treatment of recurrent *C. difficile* infection: an updated randomized controlled trial met-analysis. *PLoS One* 2019; 14: e0210016.

49. Van Nood E, Vrieze A, Nieuwdorp M, *et al*. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; 368: 407–415.

50. Cammarota G, Masucci L, Ianiro G, *et al*. Randomized clinical trial: faecal microbiota transplantation by colonoscopy vs vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2015; 41: 835–843.

51. Youngster I, Russel GH, Pindar C, *et al*. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA* 2014; 312: 1772–1778.

52. Kelly CR, Khoruts A, Staley C, *et al*. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* infection: a randomized trial. *Ann Intern Med* 2016; 165: 609–616.

53. Orenstein R, Dubberke ER, Hardi R, *et al*. Safety and durability of RBX2660 (microbiota suspension) for recurrent *Clostridium difficile* infection: results of the PUNCH CD study. *Clin Infect Dis* 2016; 62: 596–602.

54. Dubberke ER, Lee CH, Orenstein R, *et al*. Results from a randomized placebo-controlled clinical trial of RBX-2660–a microbiota based drug for the prevention of recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2018; 67: 1198–1204.

55. Juul FE, Garborg K, Bretthauer M, *et al*. Fecal microbiota transplantation for primary *Clostridium difficile* infection. *N Engl J Med* 2018; 378: 2535–2536.

56. Hvas CL, Jorgensen SMD, Jorgensen SP, *et al*. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent *Clostridium difficile* infection. *Gastroenterology* 2019; 156: 1324– 1332.e3.

57. Khanna S, Pardi DS, Kelly CR, *et al*. A novel microbiome therapeutic increases gut microbial diversity and prevents recurrent *Clostridium difficile* infection. *J Infect Dis* 2016; 214: 173–181.

58. Gerding DN, Meyer T, Lee C, *et al*. Administration of spores of non-toxigenic *Clostridium difficile* strain M3 for prevention of recurrent *C. difficile* infection: a randomized clinical trial. *JAMA* 2015; 313: 1719–1727.

59. Bobilev D, Vaickus L, DePetrillo P, *et al*. VE 303, a live biotherapeutic product for prevention of recurrent *Clostridiodes difficile* infection. Preliminary results of a phase 1, open-label healthy volunteer study of oral VE303 after vancomycin. *Gastroenterology* 2019; 156(6): S899–S900.

60. Mullane KM, Miller MA, Weiss K, *et al*. Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. *Clin Infect Dis* 2011; 53: 440–447.

61. Tariq R, Cho J, Kapoor S, *et al*. Low risk of primary *Clostridium difficile* infection with tetracyclines: a systematic review and metaanalysis. *Clin Infect Dis* 2018; 66: 514–522.

62. Van Hise NW, Bryant AM, Hennessey EK, *et al*. Efficacy of oral vancomycin in preventing recurrent *Clostridium difficile* infection in patients treated with systemic antimicrobial agents. *Clin Infect Dis* 2016; 63: 651–653.

63. Ganetsky A, Han JH, Hughes ME, *et al*. Oral vancomycin prophylaxis is highly effective in preventing *Clostridium difficile* infection in allogeneic hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2018; 68: 2003–2009.

64. Splinter LE, Kerstenetzky L, Jorgenon MR, *et al*. Vancomycin prophylaxis for prevention of *Clostridium difficile* infection recurrence in renal transplant patients. *Ann Pharmacother* 2018; 52: 113–119.

65. Knight EM, Schiller DS, Fulman MK, *et al*. Long-term efficacy of oral vancomycin prophylaxis for the prevention of *Clostridium difficile* recurrence. *J Pharm Pract*. Epub ahead of print 11 February 2019. DOI: 10.1177/0897190019825944.

66. Tariq R, Laguio-Vila M, Kamal F, *et al*. Mo1952 – Efficacy of oral vancomycin prophylaxis for prevention of *Clostridioides difficile* infection: a systematic review and meta-analysis. *Gastroenterology* 2019; 156: S-897–S-898.

67. Allegretti JR, Kao D, Phelps E, *et al*. Risk of *Clostridium difficile* infection with systemic antimicrobial therapy following successful fecal

microbiota transplant: should we recommend anti-*Clostridium difficile* antibiotic prophylaxis? *Dig Dis Sci* 2019; 64: 1668–1671

68. Box MJ, Ortwine KN, Goicoechea M, *et al*. No impact of probiotics to reduce *Clostridium difficile* infection in hospitalized patients: a real-world experience. *Open Forum Infect Dis* 2018; 12: ofy192.

69. Williams D and Adcock L. *Probiotics for antibiotic-associated diarrhea and Clostridium difficile infection: a review of clinical effectiveness*. Ottawa: CADTH, 2018.