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Recurrent *Clostridium difficile* Infection: From Colonization to Cure

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Abstract

Clostridium difficile infection (CDI) is increasingly prevalent, dangerous and challenging to prevent and manage. Despite intense national and international attention the incidence of primary and of recurrent CDI (PCDI and RCDI, respectively) have risen rapidly throughout the past decade. Of major concern is the increase in cases of RCDI resulting in substantial morbidity, mortality and economic burden. RCDI management remains challenging as there is no uniformly effective therapy, no firm consensus on optimal treatment, and reliable data regarding RCDI-specific treatment options is scant. Novel therapeutic strategies are critically needed to rapidly, accurately, and effectively identify and treat patients with, or at-risk for, RCDI. In this review we consider the factors implicated in the epidemiology, pathogenesis and clinical presentation of RCDI, evaluate current management options for RCDI and explore novel and emerging therapies.

Keywords

Antibiotic; fecal microbiota therapy; infection control; infectious diarrhea; nosocomial infection; toxin

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1. INTRODUCTION

Clostridium difficile was originally named for the difficulty encountered in culturing the organism¹. Ironically, in current clinical practice the name remains apt for a different reason in that *Clostridium difficile* infection (CDI) is increasingly prevalent, dangerous and challenging to prevent and manage. *C. difficile* is a notorious nosocomial enteric pathogen that generates substantial morbidity, mortality and economic burden²⁻⁶. Despite intense national and international attention, the incidence of primary and of recurrent CDI (PCDI and RCDI, respectively) has risen rapidly throughout the past decade⁷⁻¹⁰. In the United States alone, the prevalence of CDI more than doubled from 2000 to 2009 and current estimates suggest that *C. difficile* infects >500,000 patients annually, contributing to more than 14,000 deaths^{5, 6, 11-15}.

Of major concern is the increase in cases of RCDI. Recent data indicate that 15–35% of patients with PCDI experience RCDI after discontinuation of antibiotic therapy¹⁶⁻²⁰. By extrapolation this places annual RCDI incidence in the U.S. at 75,000 to 175,000 new cases. Morbidity and mortality aside, this leads to a substantial economic burden especially as caring for an RCDI episode may cost three times more than caring for PCDI²¹. More importantly, the optimal management of RCDI is not well established as there have been no randomized clinical trials specifically for RCDI. Most health care providers follow the current guidelines and use antimicrobials indicated for use in primary infection for a first recurrence^{17, 20}. Treatment with these agents may be prolonged and is increasingly ineffective at reducing the likelihood of subsequent recurrence, as is readily demonstrated by the substantial increase in patients who experience multiply-recurrent CDI^{17, 22}.

Novel therapeutic strategies are critically needed to rapidly, accurately, and effectively identify and treat patients with, or at-risk for, RCDI. In this review we consider the factors implicated in the epidemiology, pathogenesis and clinical presentation of RCDI, evaluate current management options for RCDI and explore novel and emerging therapies.

2. BACTERIAL VIRULENCE DETERMINANTS

C. difficile is an anaerobic, gram-positive, spore-forming bacterium that produces two pathogenic enterotoxins, Toxin A (TcdA) and Toxin B (TcdB)²³, which incite intestinal injury and acute inflammation by promoting epithelial cell cytoskeleton disruption and apoptosis and by activating a brisk inflammatory cell response²⁴⁻²⁶. CDI presents as a toxin-mediated colonic disease with clinical outcomes ranging from asymptomatic carriage or mild, self-limited diarrhea to fulminant pseudomembranous colitis, toxic megacolon, and death²⁷⁻³⁰. Toxin production is a critical bacterial virulence factor: highly toxigenic *C. difficile* strains, such as the epidemic BI/NAP/027 strain, cause severe illness, whereas non-toxigenic *C. difficile* strains are non-pathogenic and do not cause symptomatic disease^{31, 32}.

C. difficile strain or ribotype can play a major role in clinical outcomes, both in terms of disease severity and odds of recurrence. In the early 2000s ribotype 027, also known as the BI/NAP/027 strain, was discovered to be the culprit in a particularly virulent and fatal outbreak of CDI in Canada^{33, 34}. It is a highly toxigenic and sporigenic strain producing, by one estimate, approximately 16 times the amount of toxin as other *C. difficile* strains³¹, and

is associated with increased fulminant illness and high case-mortality^{33, 34} as well as with higher risk of RCDI³⁵. In the outbreak mentioned above one retrospective chart review study conducted at a Canadian medical center found that the probability of recurrence at their site had more than doubled from 20.8% in 1991–2002 to 47.2% during the outbreak in 2003–2004 ($P<0.001$)³⁵. Moreover, at the same site 60% of individuals 65 years of age and older experienced RCDI compared to 25–30% of those younger than 65 years of age^{35, 36} demonstrating the interplay between host and bacterial factors in determining risk of disease recurrence.

A third toxin, called the ADP-ribosyltransferase binary toxin (CDT), may also be responsible for the increased virulence and heightened risk of recurrence associated with the BI/NAP/027 and other outbreak strains. CDT belongs to a class of infamous ADP-ribosylating toxins which include the diphtheria, cholera, and pertussis toxins³⁷. Although the role of CDT in CDI disease pathogenesis is unclear as many pathogenic strains lack it³⁸, its association with virulent strains has suggested that it may augment the effects of TcdA and TcdB³⁹. A recent study found that the binary toxin gene was a significant independent predictor of RCDI among PCDI patients ($P=0.02$)⁴⁰, and another recent study by the same group found that presence of the binary toxin gene within the bacterial stool isolate of PCDI patients was significantly associated with at least one recurrence ($P=0.03$) and with hospital admission for that recurrence ($P=0.03$)⁴¹. While the exact role of CDT in RCDI remains unclear, these results provide evidence that CDT may prove a useful therapeutic target in RCDI management.

3. ENVIRONMENTAL VARIABLES

The *C. difficile* bacillus and its spores are transmitted through the fecal-oral route and may be easily spread among patients and health workers⁴², readily turning high-density care environments such as hospitals and long-term care facilities into loci of endemic disease^{43, 44}. Exposure to such environments as measured by duration of inpatient stay or by number of prior inpatient admissions is a significant and important risk factor for both colonization and development of initial and recurrent infection^{35, 45–47}. However, these factors are clearly compounded by other prominent risk factors (such as advanced age, frequent antibiotic exposure and severe underlying disease).

While classically considered a hospital-acquired infection, in recent years CDI epidemiology has become more widespread. The past decade has seen a marked rise in community-associated CDI (CA-CDI) among individuals who have not had health care environment exposures⁴⁸. This trend promotes the notion that *C. difficile* spore and/or bacillus exposure may be sufficient for the development of active infection regardless of the presence of other major predisposing factors such as older age or underlying comorbidity⁴⁹. Even so, it is important to recognize that the majority of CA-CDI patients do not develop the infection *de novo*, as antibiotic use is still a factor in 50–80% of such cases^{50, 51}. It is unclear, however, whether community-acquisition of *C. difficile* has any effect on a patient's chance of recurrence. One study found that having a community-acquired initial episode of CDI was independently associated with increased risk of RCDI⁵², and a second study found that as much as 28% of patients with CA-CDI developed RCDI⁵³. However, both of these were

retrospective limited-population-based studies and it's unclear whether these trends will be confirmed in the wider literature.

CDI recurrence can occur either through re-activation of persistent vegetative spores or bacteria from the original infection within the host gut (i.e. "relapse") or through the acquisition of the original or a new strain from the environment (i.e. "reinfection"). While it is estimated that reinfection constitutes slightly less than half of all RCDI cases⁵⁴, strain-specific sporulation and germination rates may favor one modality over the other. Spores are resistant to antibiotics and to alcohol-based cleansers and higher sporulation may enable the persistence of the *C. difficile* bacillus within the environment and digestive tract⁵⁵. Efficient germination may contribute to rapid growth of vegetative organisms, facilitating increased recurrence and decreased treatment efficacy⁵⁶. A recent comparative study found that strains with higher germination efficiencies more often infected RCDI than PCDI patients, and that higher germination efficiency was more strongly associated with relapse versus reinfection⁵⁷. Protracted exposure to the healthcare environment and continued antibiotic use may certainly contribute to risk of recurrence via either modality, though in clinical practice it is difficult to differentiate between the two.

Antibiotic-incited destabilization of the host gut microflora is the primary risk factor for all types of CDI^{48, 58, 59}. Persistent disruption of colonic microbial populations is critical in the pathogenesis of RCDI, as patients with RCDI exhibit depleted microflora of lower diversity relative to healthy controls and patients with PCDI^{60, 61}. Duly, continuing or reinstating antibiotic use after successful treatment of PCDI has been shown to substantially increase odds of recurrence^{16, 61}. In its healthy state, the gut microbiota confers protection against infection by *C. difficile*, and other exogenous pathogens, through a number of mechanisms including resource competition and occupation of adhesion sites within the GI tract^{62, 63}. When disrupted by antimicrobial or chemotherapeutic agents, "ecological gaps" can occur in the indigenous microbiota allowing *C. difficile* colonization, replication, and – for toxigenic strains – toxin-mediated symptomatic infection^{64, 65}. Fluoroquinolones and cephalosporins are potent inciting antimicrobials and are associated with a greater predisposition to develop CDI relative to other antibiotics^{66–70}.

Risk of recurrence mounts with each subsequent CDI episode as the antibiotic-propagated injury to the gut microbiota persists and the host and environmental factors predisposing to recurrence become concentrated in multiply recurring patients¹⁷. RCDI risk is strongly predicted by the number of prior CDI episodes experienced^{71–73}: the risk of recurrence for patients with a single prior episode of recurrent CDI is estimated to be approximately 40%, and is estimated to be 60% for patients with two or more prior CDI episodes^{17, 22}. Of note, severity of the preceding infection does not appear to impact risk of subsequent recurrence. One observational study found that while RCDI was associated with more severe abdominal pain at onset the infection itself did not worsen with subsequent recurrence⁷² and others have found that the severity of the preceding infection is not associated with odds of subsequent recurrence^{20, 74}.

4. HOST RISK FACTORS

4.1. Host Characteristics: Age, Health, and Demographics

Older age is an important and well-accepted risk factor for both initial and recurrent CDI, and the increasing age and infirmity of the hospital population has contributed much to the rise in RCDI ^{30, 75}. One of the few existing meta analyses of the risk factors implicated in development of RCDI found that age > 65 years was associated with 62% higher risk of RCDI (OR; 1.62, 95% CI: 1.11 to 2.36; P = 0.0012) ¹⁶.

Unfortunately, treatment outcomes appear to worsen for older individuals with each subsequent decade of life as immune effector functions decrease and severity of underlying diseases increase ⁷⁶. Disease severity for patients' underlying conditions can be categorized using a number of indices and is another well-recognized determinant of both PCDI and RCDI risk ^{77, 78}. The Horn index is a severity score based on clinical assessment of underlying illness ⁷⁹ and is a strong, independent predictor of PCDI ^{77, 80}. A Horn index score of one or two corresponds with an assessment of mild to moderate illness; an Horn index score of 3 or 4 corresponds with an assessment of severe to extremely severe illness ⁷⁹. Increased RCDI incidence has been observed in patients whose Horn indices are higher (3 or 4) ^{73, 81}.

Other demographic factors such as gender, race, or ethnicity have not consistently been found to be significantly associated with odds of developing either PCDI or RCDI. In some instances the incidence of both recurrent and primary CDI appear to be higher in women than men ^{20, 72}, but this trend is not consistent across all studies ^{16, 82, 83}. Associations between CDI risk and race or ethnicity have been similarly inconsistent ^{10, 14}. However, CDI incidence in African Americans in the US may be lower than in other groups ⁸⁴. Whether this reflects differences in genetic predisposition, healthcare utilization patterns or other factors is unknown.

4.2. Host Response: Innate and Adaptive Immunity

Toxin-mediated host immune responses are essential elements in the pathogenesis of CDI and important independent predictors of RCDI. Higher anti-toxin antibody responses to *C. difficile* colonization and initial symptomatic infection are strongly correlated with a lower risk of severe illness and with dramatically lower risk of recurrence ^{75, 81, 85}. Particularly illustrative of this are the results of the prospective study by Kyne et. al ⁸¹, which found that patients with low antitoxin A serum IgG 12 days after a PCDI episode were at 48-fold higher risk of RCDI than those patients with higher antitoxin A serum IgG (95% CI: 3.5 to 663). Although humoral immune responses are not, as yet, practical prospective predictors of RCDI risk ⁷³, the findings suggest that augmenting toxin-mediated humoral immune responses in at-risk individuals may be an effective prophylactic strategy. Vaccines and passive immunotherapy preparations are currently in active clinical development and testing and are discussed in section 7.3.

Innate immunity also influences CDI severity and progression. Toxin A and B prompt gut epithelial cell production of a range of pro-inflammatory cytokines resulting in neutrophil recruitment and tissue injury ^{25, 86, 87}. Intestinal inflammation as measured by fecal

interleukin-8 (IL-8), lactoferrin, and other cytokine concentrations has been strongly associated with persistent infectious symptoms and poor clinical outcomes in patients experiencing PCIDI, and may also be implicated in RCDI predisposition^{88–90}. As a testament to the putative role of host gut inflammation in RCDI risk, the AA genotype of a single nucleotide polymorphism (SNP) at the –251 position in the promoter region of the IL-8 gene has been found to modulate enteric inflammatory response and clinical outcomes for patients with PCIDI⁹¹. The AA genotype was specifically associated with increased fecal IL-8 concentration and with a more severe enteric inflammatory profile in PCIDI patients with impaired humoral immunity⁹². In a subsequent prospective study, the AA genotype was associated with a doubling of RCDI risk relative to the AT/TT genotype (relative risk, 2.1; 95% CI, 1.04 to 4.13; $P=.043$)⁹³. Ultimately, attenuating this inflammatory response may be helpful for the prevention and/or treatment of PCIDI or RCDI, as may a better understanding of the genetic mechanisms behind the cell-mediated and humoral processes that contribute to RCDI risk^{87, 94}.

Patients whose immunity is compromised due to underlying illness or to immunosuppressive treatment may be at increased risk of RCDI. Current data suggest that HIV/AIDS, solid organ transplant, and hematopoietic transplant patients experience rates of RCDI equal to or greater than those seen in the general population^{95, 96}. Inflammatory Bowel Disease (IBD) patients, in particular, encounter a slew of risk factors including frequent hospitalizations, gut microbiota dysbioses, weakened mucosal immunity, and exposure to high-level corticosteroid and antibiotic treatments^{97, 98}. Although there are limited data on RCDI incidence in IBD patients, some estimates suggest that as much as 30–60% of IBD patients with CDI experience subsequent recurrence(s)^{99–101}. Recommendations for therapy in these populations are the same as for other patients^{28, 102, 103}.

5. PREDICTIVE MODELS

A predictive model that effectively harnesses these many contributory factors would be of immense benefit, as rapid identification and targeted treatment of patients at-risk for RCDI could do much to improve clinical outcomes. Several moderately successful predictive models have been designed and validated to-date (Table 1).

Hu et al. constructed a predictive rule using three factors, each of which were independently associated with an increased risk of recurrence: age > 65 years, severe underlying disease (modified Horn index score of 3 or 4), and receipt of additional antibiotics after discontinuation of CDI therapy^{18, 73}. They then validated this rule through a small-scale prospective study and found that the rule successfully predicted RCDI occurrence within a population of 89 patients with PCIDI (AUC of 0.80, 95% CI: 0.67 to 0.92)⁷³. However, despite being simple, easy to use, and fairly reliable the Hu rule is based on a small sample size from a single center study and so its broader applicability to other medical centers and patient populations is unclear.

Eyre et al. devised a predictive model from a long-term population based study of 1678 adults alive after their first CDI case, of which 363 (22%) experienced a recurrence 14 days after their first CDI episode¹⁰⁴. A patient evaluated according to the Eyre model may

receive a score between -2 and 15 depending on which risk factors he or she satisfies. They found the absolute risk of recurrence 4 months after PCDI increased by approximately 5% for every 1-point increase in score. The numerical value correspondent to each risk factor depends on patient age, with higher points per factor given to older patients. Factors used in the model include prior emergency admission, previous methicillin resistant staphylococcus aureus (MRSA) infection, previous receipt of hemodialysis (HD) or chemotherapy, stool frequency (≥ 3 unformed stools per day), prior admission with CDI, elevated C-reactive protein level during PCDI episode, any past admission, prior admission to a GI ward, and PCDI 4–12 weeks after prior hospital discharge ¹⁰⁴. Unfortunately, the number and complexity of factors required by this model make it impractical for clinical use.

Several other predictive models have been published more recently. Hebert et al. conducted an analysis of the factors independently associated with RCDI available in the electronic health records system within a four-hospital healthcare organization ¹⁰⁵. Of the 829 PCDI episodes studied 198 (23.9%) resulted in recurrence. Recurrence was significantly and independently associated with age, fluoroquinolone exposure prior to diagnosis, intensive care unit stay before diagnosis, cephalosporin exposure, proton pump inhibitor use, and metronidazole exposure after diagnosis. Using these risk factors Hebert et al. proposed a predictive risk score tuned to capture just 14.6% of all recurrence cases (AUC of 0.70). Zilberberg et al. retrospectively identified 4,196 PCDI patients at a large urban academic medical center of whom 425 (10.1%) developed recurrence, and found six factors that in a multivariate analysis predicted recurrence with moderate discrimination (C statistic 0.643) and a negative predictive value of 90% or higher. These included age, case status as community-onset healthcare-associated, ≥ 2 hospitalizations in the prior 60 days, new gastric acid suppression, fluoroquinolone use, ICU admission at onset of initial CDI, and high-risk antibiotic use at the onset of initial CDI ⁴⁷. Neither the Hebert nor the Zilberberg models have been translated into easy-to-use scores, which is an encumbrance to their routine use. Finally, D'Agostino et al. developed a simple scoring tool for RCDI risk using a logistic regression model based on data from two large phase 3 clinical trials ⁷¹. Combining data from both studies, they evaluated 1,105 patients with CDI, 16% of whom had experienced a single episode of CDI in the 3 months prior to study enrollment. Of the patients in this study population 962 responded to initial treatment and were used in the derivation of the prediction rule, and 194 (20.2%) of these patients developed a recurrence. The model includes one point for each risk factor including age > 75 years, ≥ 10 unformed bowel movement per day, serum creatinine levels ≥ 1.2 mg/dL and prior episode of CDI (AUC of 0.64, 95% CI: 0.60 to 0.69). While the D'Agostino model, like the Hu model, is simple and – more advantageously – is based on a more diverse patient population, its AUC is only modest and it has yet to be validated in a prospective study.

Despite their shortcomings all of these models include common risk factors that could be used in larger prospective studies to develop a powerful, simple, and convenient score to predict recurrences (Table 1).

6. CURRENT MANAGEMENT

6.1. Standard of Care

Standard of care strategies to-date largely employ the same antimicrobials used in PCIDI with modifications according to the severity and frequency of the recurrence (Table 2). For over 30 years vancomycin and metronidazole have been the cornerstones of CDI treatment. Vancomycin is a poorly-absorbed oral glycopeptide antibiotic that attains high concentrations in the large intestine and that works by interfering with gram-positive bacteria cell wall synthesis¹⁰⁶. Metronidazole is a bactericidal nitroimidazole antibiotic with selective anaerobic activity that prevents DNA replication¹⁰⁷. Classically, metronidazole and vancomycin have been considered equally effective for treatment of first recurrences^{36, 108–110}. However, the data to support this notion are sparse as few studies have investigated the use of either metronidazole or vancomycin specifically for RCDI treatment. Those that exist number in the teens¹⁰⁹ and include old and very small studies of vancomycin efficacy^{111, 112}, a single-center case-series with significant variations in dose and frequency of vancomycin and metronidazole²², and a single-center retrospective analysis of vancomycin versus metronidazole efficacy³⁶. The results of these studies have been mixed and do not strongly favor either metronidazole or vancomycin for RCDI treatment. Moreover, the interpretation and applicability of the results of these studies is restricted due to their limited sizes and study designs.

Although no randomized controlled trials have prospectively compared the efficacy of vancomycin versus metronidazole specifically for RCDI, the recently published results of two large multi-national randomized studies have generated evidence in favor of vancomycin¹¹³. Among the combined study population (n=1,118), comprised of approximately 80% PCIDI and 20% RCDI patients, vancomycin was superior to metronidazole in generating a sustained clinical response (81.1% vs. 72.7%, P=0.02)¹¹³. Rates of recurrence did not significantly differ according to CDI history between the treatment groups and did not differ within any treatment group except the metronidazole group. Among patients treated with metronidazole the rates of recurrence worsened with each subsequent infection: 19.2% of primary, 36.0% of first recurrence and 38.1% of multiply recurrent CDI patients treated with metronidazole subsequently recurred (P=0.040). Conversely, rates of recurrence did not significantly differ according to CDI history among the patients who received vancomycin: 19.3% of primary, 25.0% of first recurrence and 28.6% of multiply recurrent CDI patients treated with vancomycin recurred (P=0.61). Additionally, higher numerical rates of clinical response to vancomycin versus metronidazole were observed among patients treated for a first recurrence (83.3% vs. 67.6%) but not among patients treated for multiply recurrent CDI (65.0% vs. 63.6%). Vancomycin also showed a trend toward being more effective than metronidazole in achieving clinical cure among patients with severe CDI (78.5% vs. 66.3%, P=0.059), echoing the results of a prior small randomized study¹¹⁴. These results provide evidence in favor of use of vancomycin as a first-line agent to treat first recurrences and multiply recurrent CDI. A potential explanation of these observations is that vancomycin is significantly more effective than metronidazole at inducing bacteriologic cure among RCDI patients²². Even so, the apparent clinical benefit of vancomycin may be offset by its high

cost and deleterious effects on commensal gram-positive gut microflora (which may, notably, contribute to further recurrence)¹⁰⁶ and concerns about VRE resistance¹¹⁵. The significance of such concerns will remain ambiguous without further randomized controlled trials.

In May 2011 the U.S. Food and Drug Administration (FDA) approved fidaxomicin for treatment of CDI; the only other FDA-approved therapy is oral vancomycin. Fidaxomicin is an orally administered macrocyclic antibiotic that is bactericidal against *C. difficile* and that, like vancomycin, is not well-absorbed, attaining very high concentrations in the colonic lumen¹¹⁶. Fidaxomicin may be particularly useful in preventing RCDI for several reasons: (1) it inhibits toxin production, (2) it reduces sporulation, which may decrease enteric spore and/or bacterial load, and (3) it has a slightly more narrow spectrum of anaerobic antimicrobial activity than vancomycin, which may reduce or help ameliorate persistent injury to the gut microbiome secondary to CDI treatment^{117, 118}. Indeed, in two recent randomized controlled trials fidaxomicin when used to treat PCIDI resulted in significantly lower risk of RCDI relative to vancomycin (15.4% versus 25.3% respectively, $P=0.005$ in one study and 12.7% versus 26.9% respectively, $P=0.011$ in the second)^{119, 120}. In a subset analysis of the studies, fidaxomicin was found to be superior to vancomycin in preventing secondary recurrences (19.7% vs. 35.5%; 95% CI: 30.4% to -0.3%, $P=0.045$)¹²⁰. While fidaxomicin may be appropriate for patients with or at high risk for RCDI, the current cost of fidaxomicin limits its widespread use¹⁰³. It should additionally be noted that fidaxomicin was not associated with fewer recurrences among patients infected with the BI/NAP/027 strain versus those infected with other *C. difficile* strains¹¹⁹.

6.2. Current Treatment Guidelines

6.2.1. First Recurrence—The hitherto standard recommendations for treating a first recurrence – set forth by the Infectious Diseases Society of America-Society for Healthcare Epidemiology of America (IDSA-SHEA) and American College of Gastroenterology (ACG) in 2010 and 2013, respectively – proposed repeating the treatment used in the PCIDI episode except in severe cases for which only vancomycin should be used (Table 2)^{28, 103}.

Fidaxomicin was not considered by the IDSA-SHEA as those recommendations were made before substantive evidence about fidaxomicin's clinical efficacy was published. The ACG guidelines published in 2013 do not make any recommendation for use of fidaxomicin based on "the limited data available". The recently published European Society of Clinical Microbiology and Infectious Diseases (ESCMID) treatment guidelines provide a comprehensive and current review of the available evidence¹⁰². The ESCMID guidelines recommend fidaxomicin (200 mg orally twice daily for 10 days) or vancomycin (125 mg orally four times daily for 10 days) as the two best treatment options for a first recurrence (Table 2). Although providers can still elect to use metronidazole to treat a first recurrence they should be aware that it is not as effective as vancomycin^{102, 113}.

6.2.2. Second Recurrence—For patients suffering from a second recurrence a tapered or pulsed regimen of oral vancomycin or a 10-day course of fidaxomicin (200 mg orally twice daily for 10 days) is recommended (Table 2)^{28, 102, 103, 120}. A study involving patients who participated in two clinical trials evaluating *Saccharomyces boulardii* or placebo in

combination with antibiotic treatment concluded that tapered or pulsed dosing regimens of vancomycin resulted in significantly better clinical outcome relative to non-tapered, non-pulsed vancomycin or metronidazole ²². However, the antibiotic treatments administered in the study followed physician preference and were not randomized. Various tapering or pulsing strategies are recommended (Table 2) ¹⁰². Although fidaxomicin is superior to vancomycin in reducing risk of second recurrence ^{120, 121}, the ESCMID guidelines recommend pulsed or tapered vancomycin over fidaxomicin because there are no randomized controlled studies of fidaxomicin efficacy in multiply recurrent CDI (Table 2).

6.2.3. Treatment of Subsequent Recurrence(s)—Treatment of patients with multiple CDI recurrences is challenging and requires alternative strategies.

6.2.3.1. Antibiotic Treatments: Rifaximin (Table 3, Agent #1) is a broad-spectrum rifamycin antibiotic that despite strong *in vitro* activity against *C. difficile* does not seem to disrupt the intestinal flora to the same extent as traditional agents ¹²². Rifaximin may be useful against RCDI as an adjunctive therapy following oral vancomycin treatment, the so-called “chaser” approach ^{123–125}. In a recent retrospective study 53% of patients with RCDI had not relapsed 12 weeks after a course of rifaximin (400 mg orally twice daily for 14 days) administered immediately following vancomycin or metronidazole therapy ¹²⁶. In a prospective trial that enrolled PCIDI patients with at least moderately severe underlying illness, a regimen of rifaximin 400 mg orally three times daily for 20 days immediately following standard therapy was associated with decreased RCDI relative to placebo ¹²⁵. While the study was under-powered to detect significant differences, patients administered the rifaximin “chaser” exhibited lower rates of first- and second-recurrences relative to patients given placebo (15% vs. 31%, $P=0.11$; 6% vs. 17%, $P=0.15$; respectively) ¹²⁵. Although *in vitro* studies suggest that *C. difficile* has a low probability of developing rifaximin resistance ¹²⁷, several case studies indicate that this may be possible *in vivo* ^{123, 124, 128}. This potential risk

In a recent case report Johnson et al. described success using a “fidaxomicin chaser” approach in three patients who had experienced more than three RCDI episodes each. In this regimen patients were treated using a 10-day course of fidaxomicin (200 mg orally twice daily) following a prolonged course of low-dose vancomycin. Two of the three patients had experienced no recurrence at the time of the publication (9 and 10 month follow-up periods); the remaining patient experienced a symptomatic recurrence around the 3rd month due to concomitant antibiotics for a urinary tract infection. The success of this regimen was attributed to the inhibition of sporulation by fidaxomicin ¹²⁹.

6.2.3.2. Fecal Microbiota Transplant (FMT): Fecal microbiota transplant (FMT) is a recently “rediscovered” option for treatment of multiply recurrent CDI ^{130,131} and is recommended in combination with oral antibiotic treatment by both the ESCMID and ACG guidelines (Table 2). FMT is based on the principal of restoring the normal ecology of the intestinal microbiota via donor feces, as reintroduction of normal bacteria by FMT can correct intestinal dysbiosis in patients with RCDI ⁶⁰. A recently published study comparing FMT and vancomycin showed that the former was superior in treating RCDI, achieving initial treatment cure rates of 81% ¹³¹. However this study excluded both critically ill and immunocompromised patients. A study published earlier in 2010 showed mean cure rates

approaching 90% in a series of 70 patients with RCDI including some infected with the BI/NAP/027 strain¹³². There is a paucity of literature involving long-term follow-up of patients treated with FMT. Brandt et al. followed 77 patients status-post FMT for a period of 3 months to 10 years. Four of these patients developed an autoimmune disease although no clear relationship between the new disease and FMT was demonstrated¹³³. As of today FMT appears to be safe with few substantial adverse effects or complications directly attributed to the procedure^{134, 135}. FMT is discussed in greater detail in section 7.2.3.

7. NEW DEVELOPMENTS

As CDI has emerged as a substantial and growing healthcare problem the search for better treatments has become more intense. Indeed, several new antibiotics are now under clinical investigation for the treatment of CDI¹³⁶, a weighty testament to the global effort and resources allocated to clinical research and development. Given the step-wise nature of drug development it is not surprising that many new therapeutics have been studied first for PCDI; however, several have also shown promise in primary and secondary prevention. The novel approaches are many and include new antimicrobials, toxin binders, biotherapy, immunotherapy, and approaches to modulate toxin production, sporulation, and host inflammatory responses (Table 3).

7.1. New and Alternative Antimicrobials

Nitazoxanide (Table 3, Agent #2) is a thiazolide agent with activity against anaerobic bacteria and *C. difficile*¹³⁷. A single-site randomized clinical trial found similar cure and relapse rates among patients treated for PCDI with nitazoxanide versus those treated with vancomycin but the study was too small to reach conclusions regarding non-inferiority to vancomycin¹³⁸. The same group used nitazoxanide (500 mg orally twice daily for 10 days) to treat 35 patients who failed treatment with metronidazole for *C. difficile* colitis. They found an initial response of 74% (26/35) to first-round nitazoxanide. RCDI occurred in 27% (7/26) of those with an initial response yielding an overall sustained response rate of 54% (19/35)¹³⁹.

Cadazolid (Table 3, Agent #3) is a new oxazolidinone antibiotic that *in vitro* is potently bactericidal against *C. difficile* and demonstrates low risk for resistance development^{140, 141}. A double-blind randomized active control phase 2 study of varying doses of cadazolid (250 mg, 500 mg, or 1,000 mg orally twice daily for 10 days) versus vancomycin (125 mg orally four times daily for 10 days) found that recurrence rates following PCDI were numerically lower for all doses of cadazolid relative to vancomycin¹⁴². Two phase 3 studies are currently under way (NCT01983683 and NCT01987895, clinicaltrials.gov).

CB-183,315 (surotomycin; Table 3, Agent #4) is a cyclic lipopeptide similar to daptomycin with excellent activity against gram positive bacteria¹⁴³. Its *in vitro* activity against *C. difficile* seems greater than vancomycin and metronidazole, including against resistant isolates and BI/NAP/027 strains^{143, 144}. A small phase 2 clinical trial showed similar efficacy to vancomycin with a ~50% reduction in relapse rates¹⁴⁵ (NCT01085591,

clinicaltrials.gov). A phase 3 study is currently underway (NCT01597505/NCT01598311, clinicaltrials.gov).

Tigecycline (Table 3, Agent #5) is a glycylcycline compound derived from minocycline with a wide antimicrobial spectrum that is very active against *C. difficile*¹²². Some anecdotal reports suggest efficacy in the treatment of severe or refractory cases^{146, 147} but this has not been tested in a controlled study. A phase 3 pharmacokinetics and efficacy study enrolling PCDI and RCDI patients was recently completed; data are pending (NCT01401023, clinicaltrials.gov). Tigecycline should be used with caution due to concerns of increased risk of mortality relative to other antibiotic preparations¹⁴⁸.

Teicoplanin (Table 3, Agent #6) is a glycopeptide antibiotic that is active against *C. difficile* and other Gram-positive anaerobes¹⁴⁹. A Cochrane review found that oral teicoplanin was superior to vancomycin for initial bacteriologic response and symptomatic cure among PCDI patients, but the studies included in the review were of heterogeneous design and small sample size¹⁵⁰. The high cost and lack of availability of this drug have precluded its use in the U.S. Ramoplanin (Table 3, Agent #7), a similar agent classified as a lipoglycopeptide has also shown some efficacy against CDI in phase 2 studies but is not available for clinical use¹⁵¹.

LFF571 (Table 3, Agent #8) is a semisynthetic thiopeptide that has shown very good activity against *C. difficile in vitro* and in animal models^{152, 153}. It also has shown selective activity against most gram-positive anaerobes, sparing the gram negative ones¹⁵². A phase 1 study indicates that the drug is well tolerated and attains good concentration in feces¹⁵⁴. A phase 2 clinical trial was recently completed in patients with moderate PCDI and first-relapse RCDI; results are pending (NCT01232595, clinicaltrials.gov).

7.2. Biotherapy

7.2.1. Probiotics—Although probiotics have been proposed as a remedy to “recolonize” the colon in the setting of RCDI¹⁵⁵, their utility as a therapy or as a prophylactic tool remains unclear^{109, 156}. A recent meta-analysis of the available, albeit limited, data supports the notion that *Saccharomyces boulardii* (*S. boulardii*; Table 3, Agent #9) may be useful as an adjunctive therapy to reduce the risk for RCDI¹⁰⁹. McFarland et. al. observed a 57% decreased risk of recurrence among a mixed population of PCDI and RCDI patients treated with adjunctive *S. boulardii* (1 g, 3×10^{10} colony-forming units, orally once per day) and standard-of-care antibiotics versus antibiotic-only therapy (RR, 0.43; 95% CI, 0.20 to 0.97). Interestingly, this protective effect appeared to be confined to those patients with a prior episode of RCDI (recurrence rate 34.6% compared with 64.7% on placebo; $P=.04$) rather than preventing initial recurrences in patients with PCDI (recurrence rate 19.3% compared with 24.2% on placebo; $P=.86$)¹⁹. While the study’s small sample number prohibited examination of the effects of prior or concurrent antibiotic use on outcomes, antibiotic exposure during the study did not significantly impact *S. boulardii* fecal concentrations¹⁹. However, a second randomized controlled trial by Surawicz et. al. found no significant differences in overall RCDI rates when comparing adjunctive *S. boulardii* therapy to placebo (44% versus 47%).¹⁷⁷ Additionally, other probiotic agents including *Lactobacillus*

GG (Table 3, Agent #10) and *L. Plantarum* (Table 3, Agent #11) have shown no significant benefit either in reduction of clinical symptoms or risk of recurrence^{157, 159}.

Consideration has also been given to the use of probiotics as CDI prophylaxis, although overall the evidence for the use of probiotics to prevent RCDI is heterogeneous and far from consensus^{109, 178}. Additional exploration is warranted.

7.2.2. Non-toxigenic *C. difficile*—Non-toxigenic *C. difficile* (NTCD) is a promising biotherapy that may be useful for both primary and for secondary prophylaxis. Its proposed mechanism of action is out-competing toxigenic *C. difficile* for the same colonization niche. An early study using a hamster model found that colonization with NTCD prior to exposure to toxigenic *C. difficile* resulted in 93% survival compared with 21% survival in the control group¹⁷⁹. The safety and colonization ability of an oral suspension of VP20621 (spores of nontoxigenic *C. difficile* strain M3) were tested in a phase 1, randomized, placebo-controlled study¹⁸⁰. Investigators were able to recover the spores from the stool of all patients receiving multiple doses of VP20621 (Table 3, Agent #12) and colonization with VP20621 was detected in stools on days 7 to 14 after the end of NTCD administration in 44% of subjects. The phase 2 dose, safety, and efficacy trial for this treatment strategy recently finished with highly promising findings (NCT01259726, clinicaltrials.gov). VP20621 exhibited a favorable tolerability profile and lower rates of recurrence were seen in the VP20621 versus the placebo group (11% vs. 30%, $P < 0.001$)¹⁶⁰

7.2.3. Fecal Microbiota Transplantation (FMT)—The therapeutic use of human feces has a long history in medicine and was used for treatment of pseudomembranous colitis even before *C. difficile* was recognized as the cause of the disease^{130, 181}. The first known use of FMT (Table 3, Agent #13) for pseudomembranous colitis occurred in Denver in 1958 in four patients, 3 of whom were critically ill, with good results¹⁸². Since then interest in this therapeutic option has grown given the dramatic increases in disease incidence, mortality and recurrence rates. Meta-analyses indicate that FMT following antibiotic therapy to treat RCDI has unequalled efficacy with cure rates of approximately 90%^{135, 161}. The only published randomized clinical trial of FMT, by van Nood et. al.¹³¹, was terminated early due to the clear benefit of FMT over vancomycin therapy alone. In this study, 13 of the 16 patients (81%) receiving FMT (via nasoduodenal infusion following bowel lavage and vancomycin treatment) had resolution of *C. difficile* -associated diarrhea after the first infusion, and 2/3 of the remaining patients recovered after receiving a second infusion from a different donor. There are also several case reports of severe and fulminant CDI cases treated successfully with FMT^{183, 184}. Successful engraftment following FMT, marked by the similarity of recipient's and donor's intestinal microbiota, correlates with clinical improvement⁶⁴ and may be durable: one study has shown that the recipient's fecal microbiota remains largely stable in composition over a 24-week period following transplantation¹⁸⁵. While the majority of currently published data concerns the efficacy and durability of whole microbiome transplantation for RCDI, a recent publication suggests that targeted, or "precision," microbiome replacement involving just a fraction of the gut microbiome or even a single bacterial species may be therapeutically effective¹⁸⁶. Human studies are needed to explore this hypothesis.

There are a number of ways to administer FMT including duodenal infusion¹³¹, retention enema¹⁸⁷ or instillation during colonoscopy^{132, 133}. Self-administered home fecal transplantation via enema has also been reported to be successful¹⁸⁸. Effectiveness may vary according to route of administration¹⁸⁹. A pooled analysis of 182 cases of recurrent CDI treated with FMT showed that colonoscopic FMT has a slightly higher cure rate than nasogastric/small intestinal FMT (93% vs. 85% percent), although the difference was not statistically significant¹⁹⁰. The efficacy of FMT may also depend upon the technique used to cleanse the colon before administration of the fecal material, as cleansing may help engraftment of the new microbiota. Polyethylene glycol lavage, specifically, may reduce the concentration of *C. difficile* spores and vegetative forms in the luminal gut¹⁹¹. Oral vancomycin is typically prescribed before FMT administration with or without bowel lavage with polyethylene glycol in order to reduce the bacterial load of *C. difficile* within the recipient's gut^{131, 132}.

There are two general approaches to the acquisition of fecal material. Most studies have used donors known to the patient; however, the use of a stable pool of donors or a feces bank is attractive because it can reduce costs, increase safety and provide for prompt and convenient treatment. A case series of 43 patients at the University of Minnesota found good results using feces from only 2 donors¹⁹². A phase 2 study of RBX2660 (Table 3, Agent #14), a microbiota suspension of intestinal microbes derived from the stool of a select few donors, recently finished; overall efficacy was 87.1% with no reported product- or procedure-related significant adverse events (NCT01925417, clinicaltrials.gov)¹⁹³. Other groups are trying to produce bacterial compounds for FMT with the right composition of anaerobic flora required in the gut¹⁹⁴. Successful experiences include two small studies: a case series and a retrospective chart review that used a mixture of 10 intestinal bacterial species delivered via enema^{162, 163} (rectal bacteriotherapy; Table 3, Agent #15). All 6 patients in the case series and 88% (7/8) and of the 8 patients in the retrospective review responded successfully to rectal bacteriotherapy treatment. A group of researchers from the University of Calgary have reported 100% success rate using pills made with the bacterial sediment of donor's feces¹⁶⁴ (Table 3, Agent #16). The only inconvenience was the number of capsules required: between 24 and 34 capsules were necessary to achieve the desired dose. More recently, a group in Cambridge, MA established a not-for-profit company (OpenBiome) that is producing FMT treatment units from screened donors at a very reduced cost to users (Table 3, Agent #17)¹⁹⁵. OpenBiome and others are also providing capsules containing fecal bacteria for oral therapy in recurrent CDI¹⁶⁵. Another group based in Cambridge, MA, Seres Health, is exploring "oral microbiome" therapy using bacterial spores enriched from stool donations from healthy volunteers (Table 3, Agent #18). A recent phase 1/2 study demonstrated clinical cure in 29/30 (96.7%) RCDI patients with no drug-related serious adverse events¹⁶⁶; a phase 3 study is upcoming.

Although donor-screening practices are still evolving, most protocols test for infection with human immunodeficiency virus or for hepatitis A, B or C viruses. In 2011 Bakken and the Fecal Microbiota Transplantation Workgroup published guidelines for treating RCDI using FMT¹⁹⁶. Other exclusion criteria stipulated by these guidelines include high-risk sexual behavior, illicit drug use, tattoo or body piercing within the prior 6 months, risk factors for

variant Creutzfeldt-Jakob disease, travel in the preceding 6 months to areas where diarrheal illnesses are endemic, gastrointestinal comorbid disease (e.g. inflammatory bowel disease, irritable bowel syndrome, chronic constipation, chronic diarrhea, GI malignancy/polypoidosis), use of antibiotics within the prior 3 months, and receipt of immunosuppressant medication or chemotherapy. Donor blood screening as suggested by Bakken et al. includes serology for hepatitis A, B, and C, HIV-1, HIV-2 and syphilis infections ¹⁹⁶. Suggested stool tests include fecal *C. difficile* PCR, routine bacterial culture, Giardia antigen, cryptosporidium antigen, and ova/parasites. Additional stool testing may include *H. pylori* fecal antigen for upper GI tract administration, and cyclospora and isospora smears.

FMT appears to be safe and has not been associated with major complications in most of the published series. There are persisting, albeit theoretical, concerns regarding risks for transmission of pathogens and multidrug resistant organisms ^{196–198}. Further concerns center on the possibility of transmission of metabolic traits such as obesity and metabolic syndrome, as a recent human study has shown that FMT can have a significant impact on whole body glucose metabolism ¹⁹⁹. However, the long-term realities of these concerns remain unexplored and most of the reported complications have in fact been associated with the route or technique of administration, such as those normally accompanying the use of a nasoduodenal tube, enema or colonoscopy ¹⁹⁸. A multicenter long term follow-up study noted that over the follow-up period (3 to 68 months) four patients developed diseases of potential interest after FMT including rheumatoid arthritis, Sjogren syndrome, idiopathic thrombocytopenic purpura, and neuropathy, though these diseases were not clearly related to the procedure ¹³³. Caution has been recommended for patients on immunosuppressive agents or with decompensated cirrhosis, advanced HIV/AIDS, recent bone marrow transplant, or other causes of severe immunodeficiency ¹⁹⁶. However, a recent publication described two solid organ transplant recipients both of whom required two FMTs to achieve resolution of their symptoms and neither of whom developed infectious complications ²⁰⁰. In another report, none of a series of 66 immunocompromised patients who received FMT experienced infectious complications traceable to the procedure ²⁰¹.

Despite its high efficacy and safety the FDA still considers FMT to be an investigational therapy, the use of which requires an investigational new drug (IND) application. However, the FDA has indicated its intention of continuing to exercise discretion in enforcing this requirement when FMT is used to treat CDI not responsive to other therapies ²⁰².

7.3. Immunotherapy

7.3.1. Immunoglobulins & Monoclonal Antibodies—Intravenously administered pooled normal immunoglobulins and anti-toxin antibodies have been explored as methods to passively enhance protective immunity. Intravenous immunoglobulin (IVIG) may have some benefit as an adjunctive therapy in treating severe or recurrent CDI ^{203–205}, though a recent review concluded that the evidence in favor of IVIG was weak and more randomized controlled trials are needed ²⁰³. An exception is patients with hypogammaglobulinemia, for whom the beneficial evidence in favor of IVIG is more robust ²⁰⁶.

Lowy et al. performed a phase 2 randomized, double-blind, placebo-controlled study examining two neutralizing, fully human monoclonal antibodies against *C. difficile* TcdA

(Actoxumab) and TcdB (Bezlotoxumab) administered together as a single infusion (Table 3, Agent #19) in addition to standard antimicrobial therapy ¹⁶⁷. Among the 200 patients enrolled, the rate of RCDI was substantially lower among patients treated with monoclonal antibodies versus placebo (7% vs. 25%, $p<0.001$). Recurrence rates were also lower among patients with the BI/NAP/027 strain treated with monoclonal antibody versus placebo (8% vs. 32%, $p=0.06$) and among patients with at least one prior recurrence (7% vs. 38%, $p=0.006$). This antibody combination, now denoted as MK-3415A, or actoxumab plus bezlotoxumab, (Table 3, Agent #19) is currently being tested further in two phase 3 clinical trials to assess safety and efficacy in preventing RCDI (NCT01513239, Clinical Trials.gov) ²⁰⁷.

Oral administration of immunoglobulins represents another potential tactic in the burgeoning passive immunotherapy arsenal against RCDI. Following a 1993 case report of the effective use of oral immunoglobulin A supplement in treating RCDI in a pediatric case ²⁰⁸, Warny et. al. demonstrated that bovine immunoglobulin concentrate retains *C. difficile* toxin neutralizing activity after passage through the human stomach and small intestine ²⁰⁹. Mattila et. al. carried out the first controlled study comparing orally administered immunoglobulin to standard therapy ¹⁶⁹. Thirty-eight patients with mild to moderately severe RCDI were randomized to receive *C. difficile* immune whey (CDIW; Table 3, Agent #20) or metronidazole. The study was stopped prematurely but preliminary results indicated similar effectiveness between the metronidazole versus the CDIW group (100% vs. 89%, respectively). After two months of follow-up, 55% of patients in the metronidazole arm had no recurrence compared to 56% in the CDIW arm.

7.3.2. Immunization—Direct immunization against *C. difficile* is an active field of research ²¹⁰. Preliminary trials of a parenteral vaccine containing formalin-inactivated TcdA and TcdB (Table 3, Agent #21) toxoids found excellent serum antibody responses in healthy adults ¹⁷⁰. A phase 1 study that randomized adult and elderly volunteers to receive 3 different doses of this *C. difficile* toxoid vaccine or placebo observed 100% seroconversion among the younger volunteers and a variable serologic response dependent on dosage in the elderly ¹⁷². In a small series, the administration of the toxoid vaccine was associated with resolution of multiply recurrent CDI in three patients ¹⁷¹. A phase 2 study aimed to assess recurrence prevention among PCDI patients, but this study was terminated due to poor enrollment (NCT00772343, clinicaltrials.gov). A phase 3 trial using this toxoid vaccine ²¹¹ is underway and aims to evaluate primary prevention in adults at risk for CDI (NCT01887912, clinicaltrials.gov).

Several other vaccines have been developed and are under investigation. A phase 1 clinical trial has been completed for a recombinant toxoid-based vaccine (Table 3, Agent #22) consisting of genetically modified toxins derived from non-sporulating *C. difficile* strains (NCT01706367, clinicaltrials.gov) but the results are not available yet ¹⁷³. Another vaccine under exploration uses recombinant peptide antigens targeting the toxins' receptor binding domains. This vaccine (Table 3, Agent #23) is delivered either intramuscularly as a recombinant fusion protein ¹⁷⁴ or orally as a surface-expressed protein on *Bacillus* spores ²¹² and has been found safe, tolerable, and immunogenic in a phase 1 study.

7.4. Other approaches

7.4.1. Toxin Binders—Anion binding resins like cholestyramine and colestipol have been used to treat RCDI (Table 3, Agent #24). An old, small, uncontrolled case series found that adjunctive use of colestipol following vancomycin taper (4 g orally once daily started during the last 2 weeks of tapered-pulsed vancomycin regimen) was successful in treating RCDI¹⁷⁵. However, while early studies reported that cholestyramine could remove up to 99% of the cytotoxic activity of *C. difficile* toxin²¹³, these agents may also bind to vancomycin and could potentially block its antibiotic effect²¹⁴. No recent studies have been conducted exploring either cholestyramine or colestipol for RCDI treatment. Newer toxin adsorbents such as Synsorb 90 (Table 3, Agent #25) and tolevamer (Table 3, Agent #26) have been tested without any clear benefit¹⁷⁶. In a recent large-scale randomized controlled trial tolevamer was found inferior to both metronidazole and vancomycin for treatment of CDI ($P < .001$)¹¹³. Recurrence rates among the patients who achieved clinical success on tolevamer were markedly lower than those achieving clinical success with either metronidazole or vancomycin (4.5% vs. 23.0% vs. 20.6%, respectively; $P < 0.001$). Despite this the authors concluded that tolevamer showed insufficient benefit to be considered a viable treatment option¹¹³.

7.4.2. Anti-inflammatory agents—Strategies to control the host innate immune and inflammatory responses are being studied as severity of disease and even recurrence are associated with mucosal inflammation⁸⁸. A multitude of *in vitro* and animal studies have indicated beneficial effects from inhibition of various aspects of the host innate immune response in CDI^{75, 87, 215–218}. In addition to IL-8, lactoferrin, adenosine deaminase and adenosine A2A receptor (A2AAR) have been associated with toxin-mediated inflammation. For example, infected mice treated with both vancomycin and an A2AAR agonist had better long-term survival than mice treated with vancomycin alone, and also had comparatively lower levels of IFN γ and blood TNF α ²¹⁹. Interestingly, some antimicrobial agents including coprisin,²²⁰ cathelicidin,²²¹ as well as fidaxomicin²²² have shown activity in mouse models via reduction of inflammation and mucosal damage.

8. CONCLUSION

RCDI management remains challenging: there is no uniformly effective therapy, no firm consensus on optimal treatment¹⁰⁹, and reliable data regarding RCDI-specific treatment options is scant. Even so, consideration of the currently available evidence reveals certain encouraging trends that should prompt serious reconsideration of the standard approaches to RCDI care. Evidence has emerged favoring vancomycin and fidaxomicin over metronidazole for treatment of first and second recurrences. FMT is rapidly becoming the obvious best choice for multiply recurrent CDI, though the costs and risks of FMT should be balanced with those of antimicrobial therapy. And while the therapeutic arsenal against RCDI remains small, the pool of promising novel agents is growing. Research on use of narrow spectrum agents directed mainly at *C. difficile* itself, while sparing the normal microbiota, may decrease the number of patients with multiple recurrences, and reduce the need for FMT. Only with further research and development of these and standard of care

agents can we hope to make RCDI care, and management of *C. difficile* infection in general, less difficult.

ABBREVIATIONS

CDI	<i>Clostridium difficile</i> infection
PCDI	Primary <i>Clostridium difficile</i> infection
RCDI	Recurrent <i>Clostridium difficile</i> infection
FMT	Fecal microbiota therapy
Tcd	Toxin

References

- Hall IC, O'Toole E. Intestinal flora in new-born infants: with a description of a new pathogenic anaerobe, *Bacillus difficilis*. American Journal of Diseases of Children. 1935; 49(2):390–402.
- Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. Clinical Infectious Diseases. 2008; 46(Supplement 1):S12–S18. [PubMed: 18177217]
- Dubberke ER, Olsen MA. Burden of *Clostridium difficile* on the healthcare system. Clinical Infectious Diseases. 2012; 55(suppl 2):S88–S92. [PubMed: 22752870]
- Kyne L, Hamel MB, Polavaram R, et al. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clinical Infectious Diseases. 2002; 34(3):346–353. [PubMed: 11774082]
- Lucado, J.; Gould, C.; Elixhauser, A. *Clostridium difficile* infections (CDI) in hospital stays, 2009. Apr 30. 2014 Available from: <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf>
- Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology. 2012; 143(5):1179–1187.e3. [PubMed: 22885331]
- Aslam S, Hamill RJ, Musher DM. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. The Lancet Infectious Diseases. 2005; 5(9):549–557. [PubMed: 16122678]
- Bauer MP, Notermans DW, Van Benthem BH, et al. *Clostridium difficile* infection in Europe: a hospital-based survey. The Lancet. 2011; 377(9759):63–73.
- Dubberke ER, Butler AM, Yokoe DS, et al. A Multicenter Study of *Clostridium difficile* Infection Rates from 2000–2006. Infection Control & Hospital Epidemiology. 2010; 31(10):1030. [PubMed: 20695799]
- VerLee KE, Finks JL, Wilkins MJ, et al. Michigan *Clostridium difficile* hospital discharges: frequency, mortality, and charges, 2002–2008. Public Health Reports. 2012; 127(1):62. [PubMed: 22298923]
- Campbell RJ, Giljahn L, Machesky K, et al. *Clostridium difficile* infection in Ohio hospitals and nursing homes during 2006. Infection Control & Hospital Epidemiology. 2009; 30(6):526–533. [PubMed: 19419272]
- Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. New England Journal of Medicine. 2015; 372(9):825–834. [PubMed: 25714160]
- Centers for Disease Control and Prevention (CDC). Vital signs: preventing *Clostridium difficile* infections. MMWR Morbidity and Mortality Weekly Report. 2012; 61(9):157. [PubMed: 22398844]
- Ricciardi R, Rothenberger DA, Madoff RD, et al. Increasing prevalence and severity of *Clostridium difficile* colitis in hospitalized patients in the United States. Archives of Surgery. 2007; 142(7):624–631. [PubMed: 17638799]
- Rupnik M, Wilcox MH, Gerding DN. *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. Nature Reviews Microbiology. 2009; 7(7):526–536.

16. Garey K, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. *Journal of Hospital Infection*. 2008; 70(4):298–304. [PubMed: 18951661]
17. Johnson S. Recurrent *Clostridium difficile* infection: A review of risk factors, treatments, and outcomes. *Journal of Infection*. 2009; 58(6):403–410. [PubMed: 19394704]
18. Kelly C. Can we identify patients at high risk of recurrent *Clostridium difficile* infection? *Clinical Microbiology and Infection*. 2012; 18(s6):21–27. [PubMed: 23121551]
19. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *Journal of the American Medical Association*. 1994; 271(24):1913–1918. [PubMed: 8201735]
20. McFarland LV, Surawicz CM, Rubin M, et al. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. *Infection Control & Hospital Epidemiology*. 1999; 20(1):43–50. [PubMed: 9927265]
21. Ghantaji S, Sail K, Lairson D, et al. Economic healthcare costs of *Clostridium difficile* infection: a systematic review. *Journal of Hospital Infection*. 2010; 74(4):309–318. [PubMed: 20153547]
22. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *The American Journal of Gastroenterology*. 2002; 97(7):1769–1775. [PubMed: 12135033]
23. Taylor N, Thorne G, Bartlett J. Comparison of two toxins produced by *Clostridium difficile*. *Infection and Immunity*. 1981; 34(3):1036–1043. [PubMed: 7333662]
24. Genth H, Dreger SC, Huelsenbeck J, et al. *Clostridium difficile* toxins: More than mere inhibitors of Rho proteins. *The International Journal of Biochemistry & Cell Biology*. 2008; 40(4):592–597. [PubMed: 18289919]
25. Savidge TC, Pan W-h, Newman P, et al. *Clostridium difficile* toxin B is an inflammatory enterotoxin in human intestine. *Gastroenterology*. 2003; 125(2):413–420. [PubMed: 12891543]
26. Sun X, He X, Tzipori S, et al. Essential role of the glucosyltransferase activity in *Clostridium difficile* toxin-induced secretion of TNF- α by macrophages. *Microbial Pathogenesis*. 2009; 46(6):298–305. [PubMed: 19324080]
27. Bartlett JG, Chang TW, Gurwith M, et al. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *New England Journal of Medicine*. 1978; 298(10):531–534. [PubMed: 625309]
28. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infection Control & Hospital Epidemiology*. 2010; 31(5):431–455. [PubMed: 20307191]
29. Gerding DN, Johnson S, Peterson LR, et al. *Clostridium difficile*-associated diarrhea and colitis. *Infection Control & Hospital Epidemiology*. 1995; 16(8):459–77. [PubMed: 7594392]
30. Kelly CP, LaMont JT. *Clostridium difficile*—more difficult than ever. *New England Journal of Medicine*. 2008; 359(18):1932–1940. [PubMed: 18971494]
31. Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *The Lancet*. 2005; 366(9491):1079–1084.
32. Carter GP, Rood JJ, Lyras D. The role of toxin A and toxin B in the virulence of *Clostridium difficile*. *Trends in Microbiology*. 2011; 20(1):21–29. [PubMed: 22154163]
33. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *New England Journal of Medicine*. 2005; 353(23):2442–2449. [PubMed: 16322602]
34. Ppin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *Canadian Medical Association Journal*. 2004; 171(5):466–472. [PubMed: 15337727]
35. Ppin J, Alary ME, Valiquette L, et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. *Clinical Infectious Diseases*. 2005; 40(11):1591–1597. [PubMed: 15889355]

36. Pépin J, Routhier S, Gagnon S, et al. Management and outcomes of a first recurrence of *Clostridium difficile*-associated disease in Quebec, Canada. *Clinical Infectious Diseases*. 2006; 42(6):758–764. [PubMed: 16477549]
37. Holbourn KP, Shone CC, Acharya K. A family of killer toxins. *FEBS Journal*. 2006; 273(20): 4579–4593. [PubMed: 16956368]
38. Perelle S, Gibert M, Bourlioux P, et al. Production of a complete binary toxin (actin-specific ADP-ribosyltransferase) by *Clostridium difficile* CD196. *Infection and Immunity*. 1997; 65(4):1402–1407. [PubMed: 9119480]
39. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *New England Journal of Medicine*. 2005; 353(23):2433–2441. [PubMed: 16322603]
40. Stewart DB, Berg A, Hegarty J. Predicting recurrence of *C. difficile* colitis using bacterial virulence factors: binary toxin is the key. *Journal of Gastrointestinal Surgery*. 2013; 17(1):118–125. [PubMed: 23086451]
41. Stewart DB, Berg AS, Hegarty JP. Single Nucleotide Polymorphisms of the *tcdC* Gene and Presence of the Binary Toxin Gene Predict Recurrent Episodes of *Clostridium difficile* Infection. *Annals of Surgery*. 2013
42. Fekety R, Kim KH, Brown D, et al. Epidemiology of antibiotic-associated colitis: isolation of *Clostridium difficile* from the hospital environment. *The American Journal of Medicine*. 1981; 70(4):906–908. [PubMed: 7211925]
43. Gerding DN, Muto CA, Owens RC. Measures to control and prevent *Clostridium difficile* infection. *Clinical Infectious Diseases*. 2008; 46(Supplement 1):S43–S49. [PubMed: 18177221]
44. McFarland LV, Mulligan ME, Kwok RY, et al. Nosocomial acquisition of *Clostridium difficile* infection. *New England Journal of Medicine*. 1989; 320(4):204–210. [PubMed: 2911306]
45. Cartmill T, Shrimpton S, Panigrahi H, et al. Nosocomial diarrhoea due to a single strain of *Clostridium difficile*: a prolonged outbreak in elderly patients. *Age and Ageing*. 1992; 21(4):245–249. [PubMed: 1514452]
46. Moshkowitz M, Ben-Baruch E, Kline Z, et al. Risk factors for severity and relapse of pseudomembranous colitis in an elderly population. *Colorectal Disease*. 2007; 9(2):173–177. [PubMed: 17223943]
47. Zilberberg MD, Reske K, Olsen M, et al. Development and validation of a recurrent *Clostridium difficile* risk-prediction model. *Journal of Hospital Medicine*. 2014
48. Gupta A, Khanna S. Community-acquired *Clostridium difficile* infection: an increasing public health threat. *Infection and Drug Resistance*. 2014; 7:63. [PubMed: 24669194]
49. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *The American Journal of Gastroenterology*. 2011; 107(1):89–95. [PubMed: 22108454]
50. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *The American Journal of Gastroenterology*. 2012; 107(1):89–95. [PubMed: 22108454]
51. Collins CE, Ayturk MD, Flahive JM, et al. Epidemiology and Outcomes of Community-Acquired *Clostridium difficile* Infections in Medicare Beneficiaries. *Journal of the American College of Surgeons*. 2014; 218(6):1141–1147.e1. [PubMed: 24755188]
52. Do AN, Fridkin SK, Yechouren A, et al. Risk factors for early recurrent *Clostridium difficile*-associated diarrhea. *Clinical Infectious Diseases*. 1998; 26(4):954–959. [PubMed: 9564482]
53. Khanna S, Pardi DS, Aronson SL, et al. Outcomes in community-acquired *Clostridium difficile* infection. *Alimentary Pharmacology & Therapeutics*. 2012; 35(5):613–618. [PubMed: 22229532]
54. Barbut F, Richard A, Hamadi K, et al. Epidemiology of recurrences or reinfections of *Clostridium difficile*-associated diarrhea. *Journal of Clinical Microbiology*. 2000; 38(6):2386–2388. [PubMed: 10835010]
55. Jabbar U, Leischner J, Kasper D, et al. Effectiveness of Alcohol-Based Hand Rubs for Removal of *Clostridium difficile* Spores from Hands. *Infection Control & Hospital Epidemiology*. 2010; 31(6): 565–570. [PubMed: 20429659]

56. Moore P, Kyne L, Martin A, et al. Germination efficiency of clinical *Clostridium difficile* spores and correlation with ribotype, disease severity and therapy failure. *Journal of Medical Microbiology*. 2013; 62(Pt 9):1405–13. [PubMed: 23518657]
57. Oka K, Osaki T, Hanawa T, et al. Molecular and microbiological characterization of *Clostridium difficile* isolates from single, relapse, and reinfection cases. *Journal of Clinical Microbiology*. 2012; 50(3):915–921. [PubMed: 22205786]
58. Centers for Disease Control and Prevention (CDC). Severe *Clostridium difficile*-associated disease in populations previously at low risk--four states 2005. *MMWR Morbidity and Mortality Weekly Report*. 2005; 54(47):1201. [PubMed: 16319813]
59. Young VB, Schmidt TM. Antibiotic-associated diarrhea accompanied by large-scale alterations in the composition of the fecal microbiota. *Journal of Clinical Microbiology*. 2004; 42(3):1203–1206. [PubMed: 15004076]
60. Chang JY, Antonopoulos DA, Kalra A, et al. Decreased Diversity of the Fecal Microbiome in Recurrent *Clostridium difficile*—Associated Diarrhea. *Journal of Infectious Diseases*. 2008; 197(3):435–438. [PubMed: 18199029]
61. Nair S, Yadav D, Corpuz M, et al. *Clostridium difficile* colitis: factors influencing treatment failure and relapse—a prospective evaluation. *The American Journal of Gastroenterology*. 1998; 93(10):1873–1876. [PubMed: 9772047]
62. Berg RD. The indigenous gastrointestinal microflora. *Trends in Microbiology*. 1996; 4(11):430–435. [PubMed: 8950812]
63. Vollaard E, Clasener H. Colonization resistance. *Antimicrobial Agents and Chemotherapy*. 1994; 38(3):409. [PubMed: 8203832]
64. Khoruts A, Dicksved J, Jansson JK, et al. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent *Clostridium difficile*-associated diarrhea. *Journal of Clinical Gastroenterology*. 2010; 44(5):354–360. [PubMed: 20048681]
65. Wilson KH. The microecology of *Clostridium difficile*. *Clinical Infectious Diseases*. 1993; 16(Supplement 4):S214–S218. [PubMed: 8324122]
66. Kelly CP. Current strategies for management of initial *Clostridium difficile* infection. *Journal of Hospital Medicine*. 2012; 7(S3):S5–S10. [PubMed: 22407996]
67. Dial S, Kezouh A, Dascal A, et al. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. *Canadian Medical Association Journal*. 2008; 179(8):767–772. [PubMed: 18838451]
68. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infection Control & Hospital Epidemiology*. 2005; 26(3):273–280. [PubMed: 15796280]
69. Pépin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clinical Infectious Diseases*. 2005; 41(9):1254–1260. [PubMed: 16206099]
70. Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy*. 2013; dkt477.
71. D'Agostino RB, Collins SH, Pencina KM, et al. Risk Estimation for Recurrent *Clostridium Difficile* Infection Based on Clinical Factors. *Clinical Infectious Diseases*. 2014; 58(10):1386–93. [PubMed: 24599770]
72. Fekety R, McFarland LV, Surawicz CM, et al. Recurrent *Clostridium difficile* diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. *Clinical Infectious Diseases*. 1997; 24(3):324–333. [PubMed: 9114180]
73. Hu MY, Katchar K, Kyne L, et al. Prospective Derivation and Validation of a Clinical Prediction Rule for Recurrent *Clostridium difficile* Infection. *Gastroenterology*. 2009; 136(4):1206–1214. [PubMed: 19162027]
74. Venugopal AA, Szpunar S, Sanchez K, et al. Assessment of 30-day all-cause mortality in metronidazole-treated patients with *Clostridium difficile* infection. *Scandinavian Journal of Infectious Diseases*. 2013; 45(10):786–790. [PubMed: 23746336]

75. Kelly CP, Kyne L. The host immune response to *Clostridium difficile*. *Journal of Medical Microbiology*. 2011; 60(8):1070–1079. [PubMed: 21415200]
76. Louie TJ, Miller MA, Crook DW, et al. Effect of age on treatment outcomes in *Clostridium difficile* infection. *Journal of the American Geriatrics Society*. 2013; 61(2):222–230. [PubMed: 23379974]
77. Kyne L, Sougioultzis S, McFarland LV, et al. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. *Infection Control & Hospital Epidemiology*. 2002; 23(11):653–659. [PubMed: 12452292]
78. Vesta KS, Wells PG, Gentry CA, et al. Specific risk factors for *Clostridium difficile*-associated diarrhea: A prospective, multicenter, case control evaluation. *American Journal of Infection Control*. 2005; 33(8):469–472. [PubMed: 16216661]
79. Horn SD, Sharkey PD, Bertram DA. Measuring severity of illness: homogeneous case mix groups. *Medical Care*. 1983:14–30. [PubMed: 6403781]
80. Arora V, Kachroo S, Ghantaji SS, et al. High Horn's index score predicts poor outcomes in patients with *Clostridium difficile* infection. *Journal of Hospital Infection*. 2011; 79(1):23–26. [PubMed: 21700363]
81. Kyne L, Warny M, Qamar A, et al. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *The Lancet*. 2001; 357(9251):189–193.
82. Henrich TJ, Krakower D, Bitton A, et al. Clinical risk factors for severe *Clostridium difficile*-associated disease. *Emerging Infectious Diseases*. 2009; 15(3):415. [PubMed: 19239754]
83. Rodríguez-Pardo D, Almirante B, Bartolomé RM, et al. Epidemiology of *Clostridium difficile* infection and risk factors for unfavorable clinical outcomes: results of a hospital-based study in Barcelona, Spain. *Journal of Clinical Microbiology*. 2013; 51(5):1465–1473. [PubMed: 23447638]
84. Redelings MD, Sorvillo F, Mascola L. Increase in *Clostridium difficile*-related mortality rates, United States, 1999–2004. *Emerging Infectious Diseases*. 2007; 13(9):1417. [PubMed: 18252127]
85. Warny M, Vaerman JP, Avesani V, et al. Human antibody response to *Clostridium difficile* toxin A in relation to clinical course of infection. *Infection and Immunity*. 1994; 62(2):384–389. [PubMed: 8300199]
86. Hippenstiel S, Soeth S, Kellas B, et al. Rho proteins and the p38-MAPK pathway are important mediators for LPS-induced interleukin-8 expression in human endothelial cells. *Blood*. 2000; 95(10):3044–3051. [PubMed: 10807767]
87. Warny M, Keates AC, Keates S, et al. p38 MAP kinase activation by *Clostridium difficile* toxin A mediates monocyte necrosis, IL-8 production, and enteritis. *Journal of Clinical Investigation*. 2000; 105(8):1147–1156. [PubMed: 10772660]
88. El Feghaly RE, Stauber JL, Deych E, et al. Markers of intestinal inflammation, not bacterial burden, correlate with clinical outcomes in *Clostridium difficile* infection. *Clinical Infectious Diseases*. 2013; 56(12):1713–1721. [PubMed: 23487367]
89. Yacyshyn MB, Yacyshyn B. Editorial Commentary: The Role of Gut Inflammation in Recurrent *Clostridium difficile*-Associated Disease. *Clinical Infectious Diseases*. 2013; 56(12):1722–1723. [PubMed: 23487370]
90. Boone J, Archbald-Pannone L, Wickham K, et al. Ribotype 027 *Clostridium difficile* infections with measurable stool toxin have increased lactoferrin and are associated with a higher mortality. *European Journal of Clinical Microbiology & Infectious Diseases*. 2014; 33(6):1045–1051. [PubMed: 24449345]
91. Jiang ZD, Okhuysen PC, Guo DC, et al. Genetic susceptibility to enteroaggregative *Escherichia coli* diarrhea: polymorphism in the interleukin-8 promoter region. *Journal of Infectious Diseases*. 2003; 188(4):506–511. [PubMed: 12898436]
92. Jiang ZD, Garey KW, Price M, et al. Association of Interleukin-8 Polymorphism and Immunoglobulin G Anti-Toxin A in Patients With *Clostridium difficile*-Associated Diarrhea. *Clinical Gastroenterology and Hepatology*. 2007; 5(8):964–968. [PubMed: 17618838]
93. Garey KW, Jiang ZD, Ghantaji S, et al. A common polymorphism in the interleukin-8 gene promoter is associated with an increased risk for recurrent *Clostridium difficile* infection. *Clinical Infectious Diseases*. 2010; 51(12):1406–1410. [PubMed: 21058913]

94. Kim H, Kokkotou E, Na X, et al. Clostridium difficile Toxin A–Induced Colonocyte Apoptosis Involves p53-Dependent p21 (WAF1/CIP1) Induction via p38 Mitogen-Activated Protein Kinase. *Gastroenterology*. 2005; 129(6):1875–1888. [PubMed: 16344056]
95. Collini PJ, Bauer M, Kuijper E, et al. Clostridium difficile infection in HIV-seropositive individuals and transplant recipients. *Journal of Infection*. 2012; 64(2):131–147. [PubMed: 22178989]
96. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. *The American Journal of Gastroenterology*. 2014; 109(7):1065–1071. [PubMed: 24890442]
97. Hashash JG, Binion DG. Managing Clostridium difficile in Inflammatory Bowel Disease (IBD). *Current Gastroenterology Reports*. 2014; 16(7):1–6.
98. Nitzan O, Elias M, Chazan B, et al. Clostridium difficile and inflammatory bowel disease: role in pathogenesis and implications in treatment. *World Journal of Gastroenterology*. 2013; 19(43):7577. [PubMed: 24282348]
99. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. *Clinical Gastroenterology and Hepatology*. 2007; 5(3):345–351. [PubMed: 17368234]
100. Kelsen JR, Kim J, Latta D, et al. Recurrence rate of Clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2011; 17(1):50–55. [PubMed: 20722068]
101. Libot A, Issa M, Zadornova Y, et al. Initial vancomycin monotherapy is associated with higher rates of subsequent Clostridium difficile infection in inflammatory bowel disease population. *Gastroenterology*. 2011; 140(5):S-159.
102. Debast S, Bauer M, Kuijper E. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clinical Microbiology and Infection*. 2014; 20(s2):1–26. [PubMed: 24118601]
103. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *The American Journal of Gastroenterology*. 2013; 108(4):478–498. [PubMed: 23439232]
104. Eyre DW, Walker AS, Wyllie D, et al. Predictors of first recurrence of Clostridium difficile infection: implications for initial management. *Clinical Infectious Diseases*. 2012; 55(suppl 2):S77–S87. [PubMed: 22752869]
105. Hebert C, Du H, Peterson LR, et al. Electronic Health Record-Based Detection of Risk Factors for Clostridium difficile Infection Relapse. *Infection Control & Hospital Epidemiology*. 2013; 34(4):407–414. [PubMed: 23466915]
106. Marsh JW, Curry SR. Therapeutic Approaches for Clostridium difficile Infections. *Current Protocols in Microbiology*. 2012; 9A. 3.1–9A. 3.9.
107. Edwards DI, Thompson EJ, Tomusange J, et al. Inactivation of metronidazole by aerobic organisms. *Journal of Antimicrobial Chemotherapy*. 1979 May; 5(3):315–6. [PubMed: 113378]
108. Drekonja DM, Butler M, MacDonald R, et al. Comparative Effectiveness of Clostridium difficile Treatments A Systematic Review. *Annals of Internal Medicine*. 2011; 155(12):839–847. [PubMed: 22184691]
109. O'Horo J, Jindai K, Kunzer B, et al. Treatment of recurrent Clostridium difficile infection: a systematic review. *Infection*. 2014; 42(1):43–59. [PubMed: 23839210]
110. Nelson RL, Kelsey P, Leeman H, et al. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. *Cochrane Database of Systematic Reviews*. 2011; 9.
111. Tedesco FJ, Gordon D, Fortson WC. Approach to patients with multiple relapses of antibiotic-associated pseudomembranous colitis. *The American Journal of Gastroenterology*. 1985; 80(11):867–868. [PubMed: 4050760]
112. Buggy BP, Fekety R, Silva J Jr. Therapy of relapsing Clostridium difficile associated diarrhea and colitis with the combination of vancomycin and rifampin. *Journal of Clinical Gastroenterology*. 1987; 9(2):155–159. [PubMed: 3571889]
113. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, Metronidazole, or Tolevamer for Clostridium difficile Infection: Results From Two Multinational, Randomized, Controlled Trials. *Clinical Infectious Diseases*. 2014; ciu313.

114. Zar FA, Bakkanagari SR, Moorthi K, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clinical Infectious Diseases*. 2007; 45(3):302–307. [PubMed: 17599306]
115. Bishara J, Wattad M, Paul M. Vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea. *Clinical Infectious Diseases*. 2007; 45(12):1646–7. [PubMed: 18190329]
116. Venugopal AA, Johnson S. Fidaxomicin: a novel macrocyclic antibiotic approved for treatment of *Clostridium difficile* infection. *Clinical Infectious Diseases*. 2012; 54(4):568–574. [PubMed: 22156854]
117. Babakhani F, Bouillaut L, Sears P, et al. Fidaxomicin inhibits toxin production in *Clostridium difficile*. *Journal of Antimicrobial Chemotherapy*. 2013; 68(3):515–522. [PubMed: 23208832]
118. Credito KL, Appelbaum PC. Activity of OPT-80, a novel macrocycle, compared with those of eight other agents against selected anaerobic species. *Antimicrobial Agents and Chemotherapy*. 2004; 48(11):4430–4434. [PubMed: 15504874]
119. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *New England Journal of Medicine*. 2011; 364(5):422–431. [PubMed: 21288078]
120. 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, randomised controlled trial. *The Lancet Infectious Diseases*. 2012; 12(4):281–289. [PubMed: 22321770]
121. Louie TJ, Cannon K, Byrne B, et al. Fidaxomicin preserves the intestinal microbiome during and after treatment of *Clostridium difficile* infection (CDI) and reduces both toxin reexpression and recurrence of CDI. *Clinical Infectious Diseases*. 2012; 55(suppl 2):S132–S142. [PubMed: 22752862]
122. Hecht DW, Galang MA, Sambol SP, et al. In vitro activities of 15 antimicrobial agents against 110 toxigenic *Clostridium difficile* clinical isolates collected from 1983 to 2004. *Antimicrobial Agents and Chemotherapy*. 2007; 51(8):2716–2719. [PubMed: 17517836]
123. Johnson S, Schriever C, Galang M, et al. Interruption of recurrent *Clostridium difficile*-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clinical Infectious Diseases*. 2007; 44(6):846–848. [PubMed: 17304459]
124. Johnson S, Schriever C, Patel U, et al. Rifaximin Redux: Treatment of recurrent *Clostridium difficile* infections with Rifaximin immediately post-vancomycin treatment. *Anaerobe*. 2009; 15(6):290–291. [PubMed: 19698797]
125. Garey KW, Ghantaji SS, Shah DN, et al. A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with *Clostridium difficile* infection. *Journal of Antimicrobial Chemotherapy*. 2011; 66(12):2850–2855. [PubMed: 21948965]
126. Mattila E, Arkkila P, Mattila P, et al. Rifaximin in the treatment of recurrent *Clostridium difficile* infection. *Alimentary Pharmacology & Therapeutics*. 2013; 37(1):122–128. [PubMed: 23095030]
127. Marchese A, Salerno A, Pesce A, et al. In vitro activity of rifaximin, metronidazole and vancomycin against *Clostridium difficile* and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. *Chemotherapy*. 1999; 46(4):253–266. [PubMed: 10859431]
128. Carman RJ, Boone JH, Grover H, et al. In vivo selection of rifamycin-resistant *Clostridium difficile* during rifaximin therapy. *Antimicrobial Agents and Chemotherapy*. 2012; 56(11):6019–6020. [PubMed: 22908175]
129. Johnson S, Gerding DN. Fidaxomicin “chaser” regimen following vancomycin for patients with multiple *Clostridium difficile* recurrences. *Clinical Infectious Diseases*. 2013; 56(2):309–310. [PubMed: 23024296]
130. Kelly CP. Fecal microbiota transplantation—an old therapy comes of age. *New England Journal of Medicine*. 2013; 368(5):474–475. [PubMed: 23323865]

131. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *New England Journal of Medicine*. 2013; 368(5):407–415. [PubMed: 23323867]
132. Mattila E, Uusitalo-Seppälä R, Wuorela M, et al. Fecal Transplantation, Through Colonoscopy, Is Effective Therapy for Recurrent *Clostridium difficile* Infection. *Gastroenterology*. 2012; 142(3):490–496. [PubMed: 22155369]
133. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *The American Journal of Gastroenterology*. 2012; 107(7):1079–1087. [PubMed: 22450732]
134. Bakken JS, Borody T, Brandt LJ, et al. Treating *Clostridium difficile* Infection With Fecal Microbiota Transplantation. *Clinical Gastroenterology and Hepatology*. 2011; 9(12):1044–1049. [PubMed: 21871249]
135. Kassam Z, Lee CH, Yuan Y, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *The American Journal of Gastroenterology*. 2013; 108(4):500–508. [PubMed: 23511459]
136. Butler MS, Blaskovich MA, Cooper MA. Antibiotics in the clinical pipeline in 2013. *The Journal of Antibiotics*. 2013; 66(10):571–591. [PubMed: 24002361]
137. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of *Clostridium difficile* colitis. *Clinical Infectious Diseases*. 2006; 43(4):421–427. [PubMed: 16838229]
138. Musher DM, Logan N, Bressler AM, et al. Nitazoxanide versus vancomycin in *Clostridium difficile* infection: a randomized, double-blind study. *Clinical Infectious Diseases*. 2009; 48(4):e41–e46. [PubMed: 19133801]
139. Musher DM, Logan N, Mehendiratta V, et al. *Clostridium difficile* colitis that fails conventional metronidazole therapy: response to nitazoxanide. *Journal of Antimicrobial Chemotherapy*. 2007; 59(4):705–710. [PubMed: 17337513]
140. Baldoni D, Gutierrez M, Timmer W, et al. Cadazolid, a novel antibiotic with potent activity against *Clostridium difficile*: safety, tolerability and pharmacokinetics in healthy subjects following single and multiple oral doses. *Journal of Antimicrobial Chemotherapy*. 2014; 69(3): 706–714. [PubMed: 24106141]
141. Locher, H.; Ritz, D.; Schroeder, S., et al. Cadazolid, a novel quinolonyl-oxazolidinone antibiotic: mode of action and effect on *Clostridium difficile* toxin and spore formation. Poster (C1-1347) presented at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2012;
142. Actelion. [Accessed January 9, 2015] Cadazolid. Available from: <http://www1.actelion.com/en/scientists/development-pipeline/phase-3/cadazolid.page>
143. Citron DM, Tyrrell KL, Merriam CV, et al. In vitro activities of CB-183,315, vancomycin, and metronidazole against 556 strains of *Clostridium difficile*, 445 other intestinal anaerobes, and 56 *Enterobacteriaceae* species. *Antimicrobial Agents and Chemotherapy*. 2012; 56(3):1613–5. [PubMed: 22183166]
144. Snyderman D, Jacobus N, McDermott L. Activity of a novel cyclic lipopeptide, CB-183,315, against resistant *Clostridium difficile* and other Gram-positive aerobic and anaerobic intestinal pathogens. *Antimicrobial Agents and Chemotherapy*. 2012; 56(6):3448–3452. [PubMed: 22391542]
145. Chesnel L, Sambol S, Gerding D. Treatment of CDAD with oral CB-183 315: time to recurrence, relapse and re-infection rates compared with vancomycin. *Clinical Microbiology and Infection*. 2012; 18(Suppl 3):380.
146. Herpers BL, Vlamincx B, Burkhardt O, et al. Intravenous tigecycline as adjunctive or alternative therapy for severe refractory *Clostridium difficile* infection. *Clinical Infectious Diseases*. 2009; 48(12):1732–1735. [PubMed: 19435431]
147. Lu CL, Liu CY, Liao CH, et al. Severe and refractory *Clostridium difficile* infection successfully treated with tigecycline and metronidazole. *International Journal of Antimicrobial Agents*. 2010; 35(3):311–312. [PubMed: 20045292]

148. Food and Drug Administration. [Accessed 6/21/2014] FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm>
149. Musgrave CR, Bookstaver PB, Sutton SS, et al. Use of alternative or adjuvant pharmacologic treatment strategies in the prevention and treatment of *Clostridium difficile* infection. *International Journal of Infectious Diseases*. 2011; 15(7):e438–e448. [PubMed: 21596604]
150. Nelson R. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database of Systematic Reviews*. 2007;3.
151. Fulco P, Wenzel RP. Ramoplanin: a topical lipoglycopeptide antibacterial agent. *Expert Review of Anti-infective Therapy*. 2006; 4(6):939–45. [PubMed: 17181409]
152. Citron DM, Tyrrell KL, Merriam CV, et al. Comparative in vitro activities of LFF571 against *Clostridium difficile* and 630 other intestinal strains of aerobic and anaerobic bacteria. *Antimicrobial Agents and Chemotherapy*. 2012; 56(5):2493–2503. [PubMed: 22290948]
153. Trzasko A, Leeds JA, Praestgaard J, et al. Efficacy of LFF571 in a hamster model of *Clostridium difficile* infection. *Antimicrobial Agents and Chemotherapy*. 2012; 56(8):4459–4462. [PubMed: 22644020]
154. Ting LS, Praestgaard J, Grunenberg N, et al. A first-in-human, randomized, double-blind, placebo-controlled, single-and multiple-ascending oral dose study to assess the safety and tolerability of LFF571 in healthy volunteers. *Antimicrobial Agents and Chemotherapy*. 2012; 56(11):5946–5951. [PubMed: 22964250]
155. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. *PLoS One*. 2012; 7(4):e34938. [PubMed: 22529959]
156. D'Souza AL, Rajkumar C, Cooke J, et al. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ*. 2002; 324(7350):1361. [PubMed: 12052801]
157. Lawrence SJ, Korzenik JR, Mundy LM. Probiotics for recurrent *Clostridium difficile* disease. *Journal of Medical Microbiology*. 2005; 54(9):905–906. [PubMed: 16091446]
158. Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. *Cochrane Database of Systematic Reviews*. 2008; 1(1)
159. Wullt M, Hagslätt M-IJ, Odenholt I. *Lactobacillus plantarum* 299v for the treatment of recurrent *Clostridium difficile*-associated diarrhoea: a double-blind, placebo-controlled trial. *Scandinavian Journal of Infectious Diseases*. 2003; 35(6–7):365–367. [PubMed: 12953945]
160. ViroPharma Incorporated. [Accessed January 9, 2015] Treatment With VP20621 (Non-Toxigenic *Clostridium difficile*; NTCD). A Phase 2 Study Resulted In High Rates Of Colonization And Statistically Significant Reductions In Recurrence Of *C. difficile* Infection. Available from: <http://www.prnewswire.com/news-releases/treatment-with-vp20621-non-toxigenic-clostridium-difficile-ntcd-in-a-phase-2-study-resulted-in-high-rates-of-colonization-and-statistically-significant-reductions-in-recurrence-of-c-difficile-infection-204069451.html>
161. Sha S, Liang J, Chen M, et al. Systematic review: faecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children. *Alimentary Pharmacology & Therapeutics*. 2014; 39(10):1003–1032. [PubMed: 24641570]
162. Emanuelsson F, Claesson BE, Ljungström L, et al. Faecal microbiota transplantation and bacteriotherapy for recurrent *Clostridium difficile* infection: A retrospective evaluation of 31 patients. *Scandinavian Journal of Infectious Diseases*. 2014; 46(2):89–97. [PubMed: 24354958]
163. Tvede M, Rask-Madsen J. Bacteriotherapy for chronic relapsing *Clostridium difficile* diarrhoea in six patients. *The Lancet*. 1989; 333(8648):1156–1160.
164. Louie, T.; Cannon, K.; O'grady, H., et al. IDWeek. San Francisco, CA: 2013. Fecal microbiome transplantation (FMT) via oral fecal microbial capsules for recurrent *Clostridium difficile* infection (rCDI) (Abstract 89).
165. Youngster I, Russell GH, Pindar C, et al. Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection. *Journal of the American Medical Association*. 2014; 312(17):1772–1778. [PubMed: 25322359]
166. Seres Health. [Accessed April 14, 2015] Seres Health Presents Final Data for Study of SER-109 in Recurrent *Clostridium difficile* Infection at ICAAC 2014 Conference. Available from: <http://sereshealth.com/news/newsroom/>

[seres_health_presents_final_data_for_study_of_ser-109_in_recurrent_clostridium_difficile_infection_at_icaac_2014_conference/](#)

167. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *New England Journal of Medicine*. 2010; 362(3):197. [PubMed: 20089970]
168. Numan SC, Veldkamp P, Kuijper EJ, et al. *Clostridium difficile*-associated diarrhoea: bovine anti-*Clostridium difficile* whey protein to help aid the prevention of relapses. *Gut*. 2007; 56(6): 888–889. [PubMed: 17519495]
169. Mattila E, Anttila VJ, Broas M, et al. A randomized, double-blind study comparing *Clostridium difficile* immune whey and metronidazole for recurrent *Clostridium difficile*-associated diarrhoea: efficacy and safety data of a prematurely interrupted trial. *Scandinavian Journal of Infectious Diseases*. 2008; 40(9):702–708. [PubMed: 19086244]
170. Kotloff KL, Wasserman SS, Losonsky GA, et al. Safety and Immunogenicity of Increasing Doses of a *Clostridium difficile* Toxoid Vaccine Administered to Healthy Adults. *Infection and Immunity*. 2001; 69(2):988–995. [PubMed: 11159994]
171. Sougioultzis S, Kyne L, Drudy D, et al. *Clostridium difficile* toxoid vaccine in recurrent *C. difficile*-associated diarrhea. *Gastroenterology*. 2005; 128(3):764–770. [PubMed: 15765411]
172. Greenberg RN, Marbury TC, Foglia G, et al. Phase I dose finding studies of an adjuvanted *Clostridium difficile* toxoid vaccine. *Vaccine*. 2012; 30(13):2245–2249. [PubMed: 22306375]
173. Donald RG, Flint M, Kalyan N, et al. A novel approach to generate a recombinant toxoid vaccine against *Clostridium difficile*. *Microbiology*. 2013; 159(Pt 7):1254–1266. [PubMed: 23629868]
174. Tian JH, Fuhrmann SR, Kluepfel-Stahl S, et al. A novel fusion protein containing the receptor binding domains of *C. difficile* toxin A and toxin B elicits protective immunity against lethal toxin and spore challenge in preclinical efficacy models. *Vaccine*. 2012; 30(28):4249–4258. [PubMed: 22537987]
175. Tedesco FJ. Treatment of recurrent antibiotic-associated pseudomembranous colitis. *The American Journal of Gastroenterology*. 1982; 77(4):220–221. [PubMed: 7072692]
176. Weiss K. Toxin-binding treatment for *Clostridium difficile*: a review including reports of studies with tolevamer. *International Journal of Antimicrobial Agents*. 2009; 33(1):4–7. [PubMed: 18804351]
177. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. *Clinical Infectious Diseases*. 2000; 31(4):1012–1017. [PubMed: 11049785]
178. Dendukuri N, Costa V, McGregor M, et al. Probiotic therapy for the prevention and treatment of *Clostridium difficile*-associated diarrhea: a systematic review. *Canadian Medical Association Journal*. 2005; 173(2):167–170. [PubMed: 16027434]
179. Wilson KH, Sheagren JN. Antagonism of toxigenic *Clostridium difficile* by nontoxigenic *C. difficile*. *Journal of Infectious Diseases*. 1983; 147(4):733–736. [PubMed: 6842009]
180. Villano SA, Seiberling M, Tatarowicz W, et al. Evaluation of an oral suspension of VP20621, spores of nontoxigenic *Clostridium difficile* strain M3, in healthy subjects. *Antimicrobial Agents and Chemotherapy*. 2012; 56(10):5224–5229. [PubMed: 22850511]
181. Petrof EO, Khoruts A. From Stool Transplants to Next-generation Microbiota Therapeutics. *Gastroenterology*. 2014
182. Eiseman B, Silen W, Bascom G, et al. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery*. 1958; 44(5):854–859. [PubMed: 13592638]
183. You DM, Franzos MA, Holman RP. Successful treatment of fulminant *Clostridium difficile* infection with fecal bacteriotherapy. *Annals of Internal Medicine*. 2008; 148(8):632–3. [PubMed: 18413636]
184. Trubiano JA, Gardiner B, Kwong JC, et al. Faecal microbiota transplantation for severe *Clostridium difficile* infection in the intensive care unit. *European Journal of Gastroenterology & Hepatology*. 2013; 25(2):255–257. [PubMed: 23117471]
185. Grehan MJ, Borody TJ, Leis SM, et al. Durable alteration of the colonic microbiota by the administration of donor fecal flora. *Journal of Clinical Gastroenterology*. 2010; 44(8):551–561. [PubMed: 20716985]

186. Buffie CG, Bucci V, Stein RR, et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature*. 2015; 517(7533):205–208. [PubMed: 25337874]
187. Kassam Z, Hundal R, Marshall JK, et al. Fecal transplant via retention enema for refractory or recurrent *Clostridium difficile* infection. *Archives of Internal Medicine*. 2012; 172(2):191–193. [PubMed: 22271132]
188. Silverman MS, Davis I, Pillai DR. Success of Self-Administered Home Fecal Transplantation for Chronic *Clostridium difficile* Infection. *Clinical Gastroenterology and Hepatology*. 2010; 8(5): 471–473. [PubMed: 20117243]
189. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clinical Infectious Diseases*. 2011; 53(10):994–1002. [PubMed: 22002980]
190. Postigo R, Kim J. Colonoscopic versus nasogastric fecal transplantation for the treatment of *Clostridium difficile* infection: a review and pooled analysis. *Infection*. 2012; 40(6):643–648. [PubMed: 22847629]
191. Persky SE, Brandt LJ. Treatment of recurrent *Clostridium difficile*–associated diarrhea by administration of donated stool directly through a colonoscope. *The American Journal of Gastroenterology*. 2000; 95(11):3283–3285. [PubMed: 11095355]
192. Hamilton MJ, Weingarden AR, Sadowsky MJ, et al. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *The American Journal of Gastroenterology*. 2012; 107(5):761–767. [PubMed: 22290405]
193. Ray A, Hardi R, Ramesh M, et al. Enema Administration of RBX2660 (Microbiota Suspension) for Recurrent *C. difficile* Infection: Lessons Learned from the PUNCH CD Study. *American College of Gastroenterology*. 2014; 109:S192–S193.
194. Petrof EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: ‘RePOOPulating’ the gut. *Microbiome*. 2013; 1(1):1–12. [PubMed: 24467924]
195. [Accessed April 15, 2015] openbiome.org
196. Bakken JS. Fecal bacteriotherapy for recurrent *Clostridium difficile* infection. *Anaerobe*. 2009; 15(6):285–289. [PubMed: 19778623]
197. Kassam Z, Lee CH, Yuan Y, et al. Navigating long-term safety in fecal microbiota transplantation. *The American Journal of Gastroenterology*. 2013; 108(108):1538. [PubMed: 24005359]
198. Gens KD, Elshaboury RH, Holt JS. Fecal Microbiota Transplantation and Emerging Treatments for *Clostridium difficile* Infection. *Journal of Pharmacy Practice*. 2013; 26(5):498–505. [PubMed: 23966282]
199. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012; 143(4):913–916.e7. [PubMed: 22728514]
200. Friedman-Moraco R, Mehta A, Lyon G, et al. Fecal microbiota transplantation for refractory *Clostridium difficile* colitis in solid organ transplant recipients. *American Journal of Transplantation*. 2014; 14(2):477–480. [PubMed: 24433460]
201. Ihunnah, C.; Kelly, C.; Hohmann, E., et al. Fecal Microbiota Transplantation (FMT) for Treatment of *Clostridium difficile* Infection (CDI) in Immunocompromised Patients (Abstract 10). American College of Gastroenterology (ACG) Annual Scientific Meeting; 2013; San Diego, California.
202. U.S. Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA). Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies. Apr 30. 2014 Available from: <http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm361379.htm>
203. Abougergi MS, Kwon JH. Intravenous immunoglobulin for the treatment of *Clostridium difficile* infection: a review. *Digestive Diseases and Sciences*. 2011; 56(1):19–26. [PubMed: 20924675]

204. Abougergi MS, Broor A, Cui W, et al. Intravenous immunoglobulin for the treatment of severe *Clostridium difficile* colitis: an observational study and review of the literature. *Journal of Hospital Medicine*. 2010; 5(1):E1–E9. [PubMed: 20063275]
205. O'Horo J, Safdar N. The role of immunoglobulin for the treatment of *Clostridium difficile* infection: a systematic review. *International Journal of Infectious Diseases*. 2009; 13(6):663–667. [PubMed: 19186089]
206. Muñoz P, Giannella M, Alcalá L, et al. *Clostridium difficile*–associated Diarrhea in Heart Transplant Recipients: Is Hypogammaglobulinemia the Answer? *The Journal of Heart and Lung Transplantation*. 2007; 26(9):907–914. [PubMed: 17845929]
207. Reichert JM. Antibodies to watch in 2013: Mid-year update. *MAbs*. 2013
208. Tjellström B, Stenhammar L, Eriksson S, et al. Oral immunoglobulin A supplement in treatment of *Clostridium difficile* enteritis. *The Lancet*. 1993; 341(8846):701–702.
209. Warny M, Fatimi A, Bostwick E, et al. Bovine immunoglobulin concentrate-*Clostridium difficile* retains C difficile toxin neutralising activity after passage through the human stomach and small intestine. *Gut*. 1999; 44(2):212–217. [PubMed: 9895380]
210. Leuzzi R, Adamo R, Scarselli M. Vaccines against *Clostridium difficile*. *Human Vaccines & Immunotherapeutics*. 2014; 10(6):0–1.
211. Foglia G, Shah S, Luxemburger C, et al. *Clostridium difficile*: Development of a novel candidate vaccine. *Vaccine*. 2012; 30(29):4307–4309. [PubMed: 22682287]
212. Permpoonpattana P, Hong HA, Phetcharaburanin J, et al. Immunization with *Bacillus* spores expressing toxin A peptide repeats protects against infection with *Clostridium difficile* strains producing toxins A and B. *Infection and Immunity*. 2011; 79(6):2295–2302. [PubMed: 21482682]
213. Kreutzer E, Milligan F. Treatment of antibiotic-associated pseudomembranous colitis with cholestyramine resin. *The Johns Hopkins Medical Journal*. 1978; 143(3):67–72. [PubMed: 691920]
214. Taylor NS, Bartlett JG. Binding of *Clostridium difficile* cytotoxin and vancomycin by anion-exchange resins. *Journal of Infectious Diseases*. 1980; 141(1):92–97. [PubMed: 7365273]
215. Kelly CP, Becker S, Linevsky JK, et al. Neutrophil recruitment in *Clostridium difficile* toxin A enteritis in the rabbit. *Journal of Clinical Investigation*. 1994; 93(3):1257–65. [PubMed: 7907603]
216. Kelly CP, Kyne L. The host immune response to *Clostridium difficile*. *J Med Microbiol*. 2011; 60(Pt 8):1070–9. [PubMed: 21415200]
217. Linevsky JK, Pothoulakis C, Keates S, et al. IL-8 release and neutrophil activation by *Clostridium difficile* toxin-exposed human monocytes. *American Journal of Physiology*. 1997; 273(6 Pt 1):G1333–40. [PubMed: 9435559]
218. Warny M, Keates AC, Keates S, et al. p38 MAP kinase activation by *Clostridium difficile* toxin A mediates monocyte necrosis, IL-8 production, and enteritis. *J Clin Invest*. 2000; 105(8):1147–56. [PubMed: 10772660]
219. Li Y, Figler RA, Kolling G, et al. Adenosine A2A receptor activation reduces recurrence and mortality from *Clostridium difficile* infection in mice following vancomycin treatment. *BMC Infectious Diseases*. 2012; 12(1):342. [PubMed: 23217055]
220. Kang JK, Hwang JS, Nam HJ, et al. The insect peptide coprisin prevents *Clostridium difficile*-mediated acute inflammation and mucosal damage through selective antimicrobial activity. *Antimicrobial Agents and Chemotherapy*. 2011; 55(10):4850–4857. [PubMed: 21807975]
221. Hing TC, Ho S, Shih DQ, et al. The antimicrobial peptide cathelicidin modulates *Clostridium difficile*-associated colitis and toxin A-mediated enteritis in mice. *Gut*. 2013; 62(9):1295–1305. [PubMed: 22760006]
222. Koon HW, Ho S, Hing TC, et al. Fidaxomicin inhibits *Clostridium difficile* toxin A—mediated enteritis in mouse ileum. *Antimicrobial Agents and Chemotherapy*. 2014 AAC.02783-14.

HIGHLIGHTS

- Recurrent CDI (RCDI) is a common complication following ~25% of initial CDI cases.
- RCDI is challenging: there is no uniformly effective therapy and few reliable data.
- We evaluate current and novel RCDI treatments and propose treatment approaches.
- New evidence favors vancomycin and fidaxomicin over metronidazole for RCDI therapy.
- FMT has emerged as a leading choice for treatment of multiply recurrent CDI.

Table 1

Prediction models for RCDI

Prediction Model	Sample size; Number of recurrences (%recurred)	Risk Factors	Prediction
Hu et al. ^{18, 73} (Score based on logistic regression)	89; 13 (15%)	<ul style="list-style-type: none"> Age >65 years Severe underlying disease (modified Horn index score of 3 or 4) Use of additional antibiotics after discontinuation of CDI therapy 	AUC of 0.80 (95% CI: 0.67 to 0.92)
Eyre et al. ¹⁰⁴ (Score based on hazard regression)	1,678; 363 (22%)	<ul style="list-style-type: none"> Age (per 10 years older) Emergency admission Previous MRSA Previous HD or chemotherapy Stool frequency 3 unformed stools/day Admission with CDI C-reactive protein level 85 mg/L Any past admission Past admission to GI ward PCDI 4–12 weeks after hospital discharge. 	Absolute risk of recurrence 4 months after initial CDI increased by approximately 5% for every one point increase in score.
Hebert et al. ¹⁰⁵ (Prediction model)	829; 198 (23.9%)	<ul style="list-style-type: none"> Age (per every year) Fluoroquinolone in past 90 days ICU stay 30 days before diagnosis Cephalosporin given after diagnosis PPI given after diagnosis Metronidazole exposure after diagnosis 	AUC of 0.70
Zilberberg et al. ⁴⁷ (Prediction model)	4,196; 425 (10.1%)	<ul style="list-style-type: none"> Age (per every 10 years) Case status as community-onset healthcare-associated 2 hospitalizations in the prior 60 days New gastric acid suppression at onset of initial CDI Fluoroquinolone use at onset of initial CDI ICU at the onset of initial CDI High-risk antibiotic use at the onset of initial CDI 	AUC of 0.643 and Brier score 0.089
D'Agostino et al. ⁷¹ (Score based on logistic regression)	962; 194 (20%)	<ul style="list-style-type: none"> Age >75 years 10 unformed bowel movement per day Serum creatinine levels 1.2 mg/dL Prior episode of CDI 	AUC of 0.64 (95% CI: 0.60 to 0.69)

Table 2

Summary of current recommendations for treatment of RCDI

Treatment Guidelines* ESCMID ¹⁰²	IDSA-SHEA ²⁸	ACG ¹⁰³
FIRST RECURRENCE		
Fidaxomicin or vancomycin recommended over metronidazole.	Repeat treatment as in initial episode. Vancomycin recommended in severe[#] cases.	Repeat treatment as in initial episode. Vancomycin recommended in severe^{&} cases.
Fidaxomicin orally 200 mg twice daily for 10 days	Metronidazole orally 500 mg three times daily for 10–14 days	Metronidazole orally 500 mg three times daily for 10 days
Vancomycin orally 125 mg four times daily for 10 days	Vancomycin orally 125 mg four times daily for 10–14 days	Vancomycin orally 125 mg four times daily for 10 days
Metronidazole orally 500 mg three times daily for 10 days		
SECOND RECURRENCE		
Pulsed/tapered vancomycin or fidaxomicin.	Vancomycin in a tapered and/or pulsed regimen.	Pulsed vancomycin regimen.
Vancomycin orally 125 mg four times daily for 10 days followed by pulse strategy (125–500 mg/day every 2–3 days for at least 3 weeks)	Vancomycin orally 125 mg four times daily for 10–14 days, 125 mg twice daily for a week, 125 mg once daily for a week, and then 125 mg every 2 or 3 days for 2–8 weeks	Vancomycin orally 125 mg four times daily for 10 days followed by 125 mg daily pulsed every 3 days for ten doses
Vancomycin orally 125 mg four times daily for 10 days followed by taper strategy (gradually decreasing the dose to 125 mg per day)		
Fidaxomicin orally 200 mg twice daily for 10 days		
SUBSEQUENT RECURRENCE NONRESPONSIVE TO ANTIBIOTIC THERAPY		
FMT in combination with oral antibiotic treatment is strongly recommended.	No recommendation.	Fecal microbiota transplant (FMT) should be considered.
No specific regimen recommended		No specific regimen recommended

* Guidelines are summarized and accompanied by recommended treatment regimens

[#] Severe: white blood cell count (WBC) 15,000 cells/mL[&] Severe: serum albumin < 3 g/dl plus WBC 15,000 cells/mL and/or abdominal tenderness

Table 3

Novel therapies: usage, availability, and effectiveness

Agent #	Class	Administration	USA Availability	Effectiveness
NEW ANTIMICROBIALS				
1	Rifaximin	400 mg orally twice daily for 14 days or three times daily for 20 days following standard therapy	Xifaxan (Salix) Additional clinical trials needed	A retrospective study showed effectiveness. ¹²⁶ Chaser treatment after vancomycin could be effective for recurrence. ¹²³⁻¹²⁵
2	Nitazoxanide	500 mg orally twice daily for 10 days	Alinia (Romark) Additional clinical trials needed	A randomized clinical trial in PCDI patients showed similar symptomatic cure and recurrence rates versus vancomycin. ¹³⁸
3	Cadazolid	N/A	Former ACT-179811 (Actelion) RCT phase 3 NCT01983683 RCT phase 3 NCT01987895	A phase 2 study has shown efficacy and tolerability in CDI patients; rates of recurrence were numerically lower versus vancomycin. ¹⁴⁰
4	CB-183,315	N/A	Surotomycin (Cubist) RCT phase 3 NCT01597505 RCT phase 3 NCT01598311	A small phase 2 clinical trial showed similar efficacy to vancomycin but also showed lower relapse rates. ¹⁴⁵
5	Tigecycline	50 mg IV twice daily after a loading dose of 100 mg	Tygaril (Pfizer-Wyeth) No active clinical trials	Some success in severe or refractory cases. ^{146, 147} A phase 3 study was recently completed; data pending (NCT01401023). FDA warning regarding increased risk of mortality associated with tigecycline.
6	Teicoplanin	100 mg orally twice daily	Limited use in US	Cochrane review found that oral teicoplanin was superior to vancomycin for bacteriologic cure following PCDI. ¹¹⁰ Data regarding efficacy in treating recurrences is lacking.
7	Ramoplanin	N/A	(Nanotherapeutics) No active clinical trials	Shown efficacy against CDI in phase 2 studies. ¹⁵¹
8	LFF571	N/A	(Novartis) No active clinical trials	A randomized, double-blind, placebo- controlled study showed that the drug is well tolerated. ¹⁵⁴ A phase 2 safety and efficacy study was recently completed; results pending (NCT01232595).
BIOOTHERAPY				
9	<i>S. Boulardii</i>	3 x 10 ¹⁰ colony- forming units orally once per day	Multiple products, alone or in combination	Effective at preventing second recurrences as an adjunctive therapy to standard vancomycin or metronidazole therapy. ¹⁹
10	<i>Lactobacillus GG</i>	2.8x10 ¹¹ colony- forming units orally once per day	Multiple products, alone or in combination	No statistically significant clinical benefit; not effective at preventing recurrences. ^{157, 158}
11	<i>L. plantarum</i>	5x10 ¹⁰ colony- forming units orally once per day	Multiple products, alone or in combination	Apparently not effective at preventing recurrence; sample size too small for statistical comparisons. ^{158, 159}

Agent #	Class	Administration	USA Availability	Effectiveness
12	Non-toxicogenic <i>C. difficile</i>	N/A	VP20621 (Shire) No active clinical trials	A recent phase 2 trial demonstrated favorable tolerability and lower rates of recurrence versus placebo (NCT01259726) ¹⁶⁰ .
13	Fecal Microbiota Transplant	Duodenal infusion Retention enema Colonoscopy	Local compounding Fecal banks Several active studies	A small randomized clinical trial ¹³¹ and meta-analyses ¹⁶¹ show benefit in the treatment of recurrent CDI.
14	Microbiota Suspension	Retention enema	RBX2660 (Rebiotix) No active clinical trials	A phase 2 trial was recently completed demonstrating 87.1% efficacy; the retention enema was well-tolerated (NCT01925417).
15	Rectal Bacteriotherapy	Variable	Local research compounding (University of Copenhagen, Copenhagen, Denmark/Skårborgs Hospital Skövde, Sweden) Additional clinical trials needed	Two small studies using a mixture of 10 intestinal bacterial species via enema demonstrated success ^{162, 163} .
16	Bacterial Sediment	Oral fecal microbial capsules	Local research compounding (University of Calgary, AB, Canada) Additional clinical trials needed	A case-series of 27 patients administered the oral fecal microbial capsules observed arrested RCDI in all 27 patients ¹⁶⁴ .
17	Frozen Fecal Microbiota Transplant	Oral capsulized frozen fecal microbiota	Local research compounding (Openbiome) Additional clinical trials needed	A small open-label single-group study observed diarrhea resolution among 18/20 (90%) patients treated with frozen FMT. No serious adverse events were observed ¹⁶⁵ .
18	Bacterial spore therapy	Oral capsulized fecal bacterial spores	SER-109 (Seres Health) No active clinical trials; a phase 3 trial is upcoming	A small single-arm open label phase 1/2 study saw clinical cure among 29/30 (96.7%) RCDI patients treated with SER-109. No serious adverse events were observed ¹⁶⁶ .
IMMUNOTHERAPY				
19	Anti-toxin A and anti-toxin B human monoclonal antibodies	N/A	Actoxumab/bezlotoxumab (Merck) RCT phase 3 NCT01513239 RCT phase 3 NCT01241552	A phase 2 randomized, double-blind, placebo-controlled study showed lower recurrences among patients treated with these antibodies plus standard-of-care treatment, including infections due to BI/NAP/027 strain ¹⁶⁷ . Two phase 3 studies are ongoing.
20	<i>C. difficile</i> immune whey	Oral immunoglobulin	(Novatreat) No new studies done	An open-label study showed efficacy ¹⁶⁸ . A randomized, double-blind study showed similar efficacy between CDIW and oral metronidazole ¹⁶⁹ .
21	Highly purified toxoid A and B	Toxoid vaccine	ACAM-CDiff (Acambis/Sanofi Pasteur) RCT phase 3 NCT01887912	Purified toxoid A and B were tolerated and elicited good response among healthy adults ¹⁷⁰ . An open-label study ¹⁷¹ and a phase 1 randomized clinical trial ¹⁷² with highly purified toxoid showed good seroconversion rates.
22	Genetically modified full-length TcdA and B	Toxoid vaccine	(Pfizer) RCT phase 1 NCT02052726 RCT phase 2 NCT02117570	Genetically modified toxins in non-sporulating <i>C. difficile</i> strains ¹⁷³ . A phase 1 study (NCT01706367) has been completed but results are not yet available.

Agent #	Class	Administration	USA Availability	Effectiveness
23	IC84 recombinant fusion protein	Recombinant vaccine	N/A	C-terminal receptor binding domains of TcdA and TcdB incorporated into a recombinant fusion protein ¹⁷⁴ have shown to be safe and tolerable, and induced antibodies against TcdA and B in a phase I study (NCT01296386).
OTHER APPROACHES				
24	Cholestyramine/Colestipol	Toxin binding polymer	4 g orally once daily started during the last 2 weeks of tapered- pulsed vancomycin regimen	No new studies done
25	Synsorb 90	Toxin binding polymer	N/A	(Synsorb Biotech) Development halted
26	Tolevamer	Toxin binding polymer	9 g (loading dose) followed by 3 g every 8 hours for 14 days	Exodif, GT267-004 (Genzyme) Development halted
				Two randomized phase 3 trials showed that tolevamer was inferior to metronidazole or vancomycin ^{113, 176} .