A Supplement to

IDSE Infectious Disease SPECIAL EDITION

Gastroenterology & Endoscopy News

PHARMACY PRACTICE NEWS

Special REPORT

Microbiome-Based Therapy:

The Next Frontier in the Management of Clostridioides difficile *Infections and Recurrence*

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The microbiota is a community of microorganisms, such as bacteria, fungi, and viruses, that inhabits a particular location, including the human body.[1-4] The human body is home to about 100 trillion bacteria and other microbes comprising up to 36,000 distinct species of bacteria—collectively known as the microbiome.[4,5] The gut microbes that inhabit the human body outnumber human cells by several times.[6,7] It is recognized that the number of genes in the majority of microbes (microbiome) exceeds the total number of human genes by hundreds-fold.[8] Advances in DNA sequencing and bioinformatics made the progress in human microbiome research possible. Driven by the Human Microbiome Project and European MetaHIT program, there are many groups studying the relationships between the microbiome and human health and disease.[6,7,9] Gut microbiota have roles in health and disease states across several fields, including gastrointestinal diseases (ie, inflammatory bowel disease, fatty liver), metabolic diseases (eg, diabetes, obesity), immunologic diseases (ie, allergic conditions), and brain–gut disorders (eg, autism, Parkinson's disease).[2,4,10-12]

Change in microbiome, known as dysbiosis, is often caused by dietary factors, stress, and the use of broad-spectrum antibiotics, such as cephalosporins or fluoroquinolones.[13-15] Such disruption to the gut microbiome leads to an environment suited for the proliferation of *Clostridioides difficile* (*C. difficile*). Although antimicrobial therapy is currently the standard of care for the treatment of *C. difficile*, these agents are somewhat nonspecific. They target *C. difficile* but also alter the surrounding microbiota milieu, leading to an imbalance of gut microflora and causing recurrence of *C. difficile* infection (CDI).[14,16] Among patients receiving antibiotic treatment for CDI, 20% to 35% experience a recurrence and 40% to 60% of patients have a second recurrence.[17-22] Specifically, the risk for a second recurrence increases to 40%,

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and after 2 or more recurrences, this risk grows to more than 60%.[18,21,22] These repeated infections impose a huge burden on patients and the health care system.

This Special Report describes the gut microbiome, the burden of CDI and recurrent CDI (rCDI), and outlines the current approach to managing infections, including emerging use of microbiome-based therapeutics.

Gut Microbiota: Diversity and Dysbiosis

The terminology of the microbiome is complex and new. The key difference between *microbiome* and *microbiota* is that microbiota includes the entire population of microorganisms that colonizes a particular location or organism, whereas microbiome refers to the genetic makeup of the respective microbiota as well as the environmental conditions.[23,24] The term microbiome was coined by Joshua Lederberg in 2001.[25] The terms microbiome and microbiota are often used interchangeably, although often incorrectly. The science of detecting the hundreds of noncultivable bacterial species is ever changing, and with it comes a range of new terms.

This science is the result of a marked reduction in the costs of gene sequencing such that specific taxa can be found in the microbial flora. It is now possible to generate millions of sequences per specimen. In parallel, computational capabilities also have improved with the availability of multiple management pipelines.[24,26] Among the systems currently available, QIIME is a free platform that imports raw sequence data that can be analyzed to produce measures of inter- and intrasample diversity.[24,27] QIIME can use metadata to create clear visualizations of patterns for further analysis.[24]

The human microbiome is a complex environment composed of an estimated 100 trillion cells.[4] The concentrations and types of bacteria change along the gut.[12,28] Culture-based studies show that all healthy adults share most of the same gut species—a core microbiota. However, non–culture-based sequencing studies have shown a vast array of microbial diversity.

The collective human gut microbiota consists of more than 35,000 bacterial species.[5] Most of these phylotypes belong to just a few phyla. Bacteroidetes and Firmicutes dominate the phyla, whereas Actinobacteria, Proteobacteria, and Verrucomicrobia are less common.[2,29] Despite the consistency of these main components, it is the relative proportions and species that vary significantly across individuals. Awareness of the microbial community alone does not lead to an understanding of how it works. This functional screening originates from studying the cultured isolates that have a well-characterized genome content.[15] It uses shotgun metagenomics, which relies on sequencing the entire microbial flora including those that cannot be cultivated by current methods. As an increasing number of human microbial genomes are sequenced and annotated, it is possible to identify other complementary genomes.

Factors Affecting the Microbiota

The microbiota is affected by the host's age, sex, genetics, early microbial exposure, diet, and environment.[30] Any change in the composition, number, or health of the gut microbial communities, with respect to healthy individuals, is regarded as dysbiosis.[31] Dietary changes can alter homeostasis and affect gut flora.[32] It has been shown that the composition of the ileal, as well as colonic, microbiota also changes with age[11]: Following birth, exposure to bacteria and other environmental factors affect the microbiota, which will be modified further to encompass the history of microbial exposure through adulthood.[15,33,34] Moreover, women tend to have a lower abundance of Bacteroidetes than men, and there is a significant association between an increased body mass index and alteration of microbiome community composition.[35]

The gut microbiota provides multiple benefits to the host. In addition to providing resistance to colonization, the gut microbiota also shapes the host immune response and is essential for certain metabolic transformations.[33,34] These chemical processes include the fermentation of complex carbohydrates and assembling amino acids into short-chain fatty acids that are vital for intestinal health.[34] These molecules also have been shown to be important in regulating host gene expression, inflammation, cell differentiation, and apoptosis.[36] Additionally, the gut microbiota plays an important role in lipid or bile acid metabolism.[34]

The diversity of the microbiota and microbiome may explain the variation in gut metabolic processes between individuals, including the metabolism of drugs and food.[37] Additionally, there has been much research done to better understand the relationship between a person's physiologic state and the composition of the microbiota. For example, obese individuals have fewer types of microbes in their gut than lean individuals, and have a marked difference in the abundance of specific taxa and functional genes.[38,39] Some of the differences in the microbiota can directly contribute to disease states such as ulcerative colitis, Crohn's disease, and irritable bowel syndrome, as well as *C. difficile*.[5,40,41]

Microbiota and *C. difficile*

Abnormal or disrupted adult gut microbial communities are similar to infant gut communities.[15,42] Yet, both systems react to shifts: *C. difficile* can be a normal adult gut resident, but when the system is altered, it can cause disease. In infants, however, *C. difficile* colonizes up to 65% of gut microbiota and yet most infants are asymptomatic.[15,43] The gut microbiota generally shows colonization resistance by which the native organisms prevent entry and proliferation of pathogenic and potentially harmful microbes.

In a landmark study considering the microbiome and CDI, Chang et al used 16S rRNA clone analysis to compare the fecal microbiota of 3 control patients who had not received antibiotics in the prior 3 months with 4 patients with initial CDI and 3 with rCDI, all identified by ELISA detection of *C. difficile* toxin.[44] Broadly, the microbiota of the control and initial CDI groups are similar in composition.[44] Meanwhile, the Shannon-Wiener diversity index was significantly higher in the control and initial infection groups when compared with the recurrent group (P=0.154).[44]

Recurrent CDI can occur through recrudescence of the initial strain of *C. difficile* or acquisition of a new strain. Current technology does not allow us differentiation of the *C. difficile* strain associated with individual infections. This results in an inability to identify whether a recurrence is a result of the same strain as an original episode or a new strain that invades a patient with a weakening of colonization resistance. In many circumstances, patients are unable to restore colonization resistance against *C. difficile* following the initial infection, leaving them susceptible to recurrent infections (Figure 1).[45] Thus, if the microbiome can be intentionally manipulated to increase colonization resistance, this may prevent rCDI.

Although antibiotics are the standard of care for the treatment of *C. difficile*, they are also a predominant risk factor for recurrence. Use of antibiotics has been shown to disrupt the ecology of the human microbiome and is associated with increased risk for deadly infections such as recurrent *C. difficile*.[16] Disruption of the microbiota increases the risk for *C. difficile* by providing a niche for the infection to flourish.[46] If the intestinal microbiota is disrupted by antibiotics, the effects may be long-lasting and the risk for *C. difficile* may increase during continued therapy. Longer exposure to multiple antibiotics and treatment with multiple antibiotics also may increase the risk.[46]

Pathogenesis of *C. difficile*

C. difficile is a gram-positive, spore-forming anaerobic bacillus that can be transmitted from person to person or through contact with environmental contamination.[46-48] Transmission is particularly effective via the fecal–oral route.[46] The most common symptoms of CDI are severe watery, non-bloody diarrhea and abdominal pain.[49] Untreated, CDI may progress to complications such as dehydration, profuse diarrhea, electrolyte disturbances, hypoalbuminemia, toxic megacolon, volume depletion, renal failure, bowel perforation, sepsis, and death.[50-52]

The symptoms of CDI result from the production of 3 endotoxins: toxin A, toxin B, and binary toxin.[49] Toxins A and B are glycotransferases that modify the actin cytoskeleton of intestinal epithelial cells and the intercellular junctions they afford. The resultant disintegration of the epithelial membrane is responsible for the severe diarrhea associated with CDI. Binary toxin is an ADP-ribosyltransferase that causes affected epithelial cells to produce microtubule-based protrusions on the cell surface, which enhance intestinal permeability.[53,54] Roughly 10% of *C. difficile* strains produce binary toxin.[49] Patients infected with strains, such as NAP1/BI/027, that produce all 3 toxins usually exhibit more severe CDI and present with symptoms including fever, shock or hypotension, severe ileus with cessation of diarrhea, leukocytosis, and elevated serum creatinine

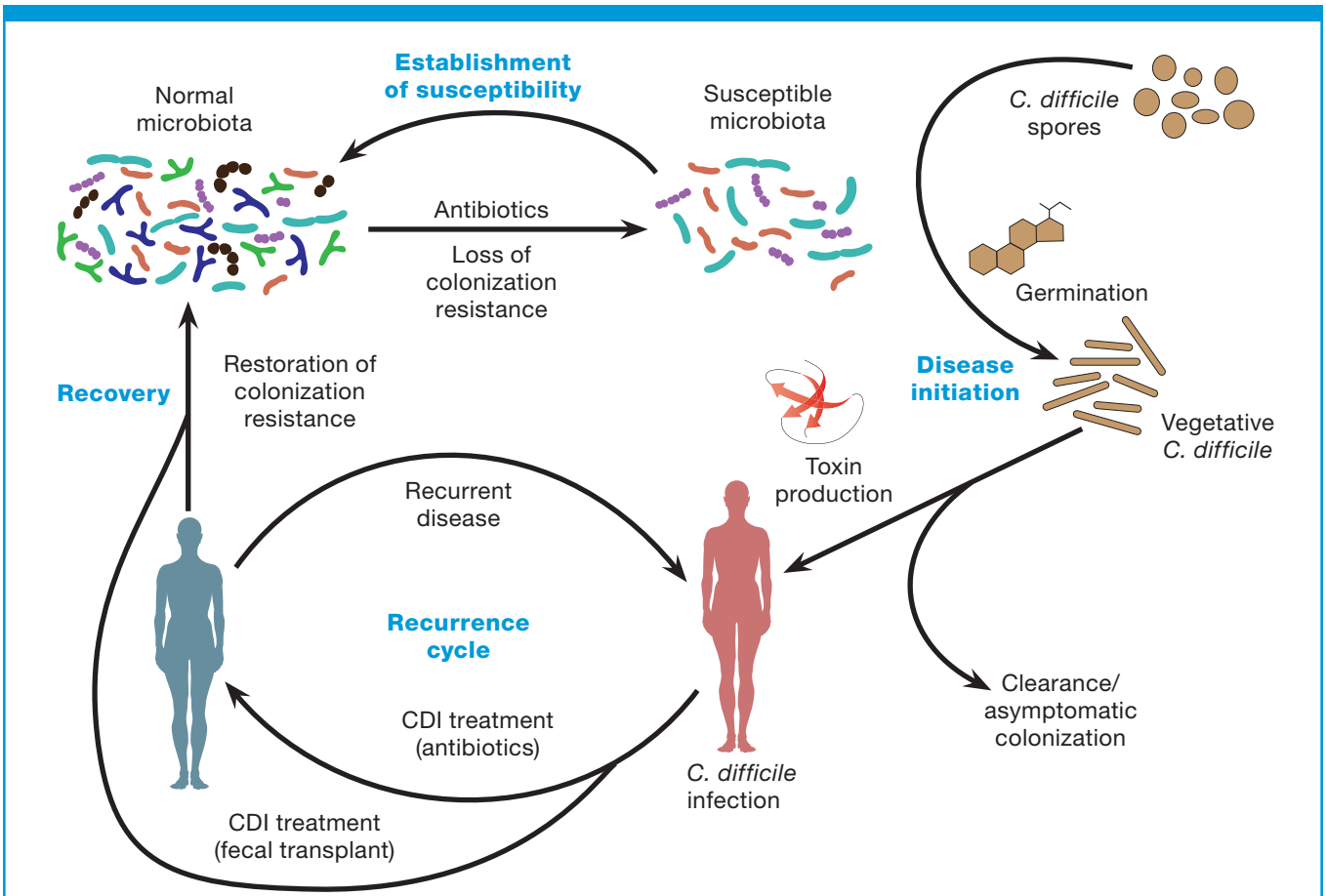


Figure 1. Cycle of CDI.

Antibiotic administration alters the indigenous intestinal microbiota, producing an environment that permits germination of *C. difficile* spores and expansion of the pathogen. *C. difficile* produces toxins that cause colitis and resulting symptoms. Antibiotics directed against *C. difficile* can decrease the load of the pathogen and toxin production. Returning the microbiota to a state of colonization resistance cures CDI. However, if the microbiota is unable to restore resistance to colonization by *C. difficile*, then patients have recurring CDI. In certain cases, repeat courses of anti–*C. difficile* antibiotic therapy can eradicate the pathogen. In other cases, therapeutic restoration of a diverse microbiota via fecal microbiota transplantation is required to overcome CDI.

CDI, *Clostridium difficile* infection

Reprinted from *Gastroenterology*, 146(7). Britton RA, Young VB. Role of intestinal microbiota in resistance to colonization by *Clostridium difficile*. 1547-1553, 2014, with permission from Elsevier.

levels.[55,56] Patients infected by strains that produce all 3 toxins also have higher mortality rates than patients who carry other strains of *C. difficile*.[57]

In addition to gastrointestinal damage, CDI can be complicated by the development of nosocomial infections and bloodstream infections with enteric pathogens as the main causative pathogen.[58] It has been hypothesized that the altered gut integrity enables microbial translocation from the gut to the systemic circulation.[59] Translocation is the increased intestinal permeability due to disruption of the gut barrier function. Moreover, intestinal overgrowth and general changes in the bacterial microbiota are associated with CDI. Translocation leads to the release of lipopolysaccharides (LPS), a component of the gram-negative cell wall, into the bloodstream.[60] This induces production of host response proteins and consumption of neutralization antibodies against LPS antigens.[60] Following translocation, this cascade can lead to sepsis in initial CDI (16%), and can increase significantly with recurrent episodes: 27.3% with the first recurrence, 33.1% with the second, and 43.3% with more.[61]

Epidemiology and Burden of CDI

Recent studies on the incidence of *C. difficile* in the United States show a decrease in overall numbers but a growing proportion of community-acquired infections.[62] The estimated national burden of both community-associated and health care–associated *C. difficile* is 428,600 cases (95% CI, 428,600-495,600 cases).[62] Although the adjusted estimate of the national burden of health care–associated CDI decreased by 36% (95% CI, 24%-54%), the adjusted estimate of the national burden of community-acquired CDI has remained unchanged over time.[62] The overall national burden estimate in 2017 for health care–associated CDI was 462,100 cases (95% CI, 428,600-495,600 cases), and the incidence was estimated as 143.6 (95% CI, 133.2-154.0) per 100,000 population.[62] In 2017, the estimated national burden of health care–associated CDI was 235,700 cases (95% CI, 221,700-249,700 cases) with an estimated incidence of 73.3 (95% CI, 68.9-77.6) per 100,000 population.[62] The burden of community-associated CDI was 226,400 cases (95% CI, 206,900-245,900 cases) with an estimated incidence of 70.4 (95% CI, 64.3-76.4) per 100,000 population.[62] Most estimates of CDI incidence are likely underestimates because data are typically only reported in terms of cases admitted to the hospital for CDI, and therefore do not include people treated as outpatients.[62] Thus, the ratio shifted toward a higher incidence in the community setting from the health care setting because of a lack of antibiotic stewardship programs.[62]

Another factor that frames the data reported above involves hospitals being penalized for their rates of CDI (especially for rCDI) in the United States.[63] Given this financial consideration, there is sometimes a reluctance to test patients with classic symptoms for CDI and a recent infection.[63] In that clinical scenario, empiric therapy is usually started and likely effective but the patient is not accounted for epidemiologically as having a recurrence.[63] Under the Hospital-Acquired Condition Reduction Program of the Centers for Medicare & Medicaid Services, hospitals' reimbursement is reduced if their rates of hospital-acquired CDI are elevated.[64] The estimated frequency of first recurrence of CDI, hospitalizations for CDI regardless of site of acquisition, and in-hospital deaths are shown in Table 1.[62]

The rates of CDI have decreased recently, but still remain very high; however, the infections that patients get seem to be more refractory to antimicrobial therapy resulting in recurrence. In 2017, Ma et al studied the incidence of rCDI in the United States using a database of almost 39 million commercially insured people, of whom 45,341 developed CDI between 2001 and 2012.[65] During this period, the annual incidence of CDI increased by 42.7%, from 0.4408 to 0.6289

Table 1. Estimates of First Recurrence, Hospitalization, and In-Hospital Deaths Associated With CDI in the United States: 2017

	Estimated First Recurrence	Estimated Hospitalizations	Estimated In-Hospital Deaths
Community-associated CDI, n (95% CI)	31,300 (26,600-36,000)	69,900 (61,100-78,600)	4,300 (2,300-6,300)
Estimated total: 235,700 cases	13.3%		1.8%
Incidence per 100,000 persons (95% CI)	9.7 (8.3-11.2)	21.7 (19.0-24.4)	1.3 (0.7-2.0)
Health care–associated CDI, n (95% CI)	38,500 (32,100-44,800)	154,100 (140,700-167,400)	16,200 (13,300-19,200)
Estimated total: 226,400 cases	17.0%		7.1%
Incidence per 100,000 persons (95% CI)	12.0 (10.0-13.9)	47.9 (43.7-52.0)	5.0 (4.1-6.0)

CDI, *Clostridioides difficile* infection

Adapted from reference 62.

cases per 1,000 person-years (P=0.004).[65] The annual incidence of multiple recurrent CDI (mrCDI) increased by 188.8%, from 0.017 to 0.0309 cases per 1,000 person-years over the same period (P<0.001) (Figure 2).[65] This latter observation far exceeded the increase in initial CDI during the same period. This increase in mrCDI may be due to many factors, including the increased use of antibiotics associated with selecting for *C. difficile* and alterations of the microbiome resulting from long-term use of chronic proton pump inhibitors.[66] Additionally, some of the increase may be due to the emergence of the NAP1 strain of *C. difficile*, which is also a known risk factor for rCDI.[67] Ma et al established that risk factors associated with increased mrCDI included age, sex, exposure to antibiotics, and use of proton pump inhibitors as well as corticosteroids within 90 days of CDI (Table 2).[65]

Using a nationwide clinical database of 154 US hospitals over a 7-year period, Tabak et al demonstrated a 112% increase (P=0.0001) in community-onset community-acquired CDI and a 42% increase in community-onset health care–associated CDI, while hospital-onset disease showed a 33% increase (P=0.01).[68] Community-onset community-acquired CDI accounted for half of the total cases and proportionally increased from 45% to 56% during 2008-2015 (P<0.01).[68] The combined community-onset cases with or without a prior hospital stay accounted for 81% of all cases.[68]

Occurrences of CDI have been associated with an increased incidence of psychiatric conditions, with anxiety and depression being the most commonly reported in the Medicare population (Table 3).[69] The most concerning complication is sepsis, with almost one-third of rCDI cases being affected.[69] Sepsis carries a significant mortality burden with 22% of cases resulting in death.[70]

The impact of CDI on quality of life has only recently begun to be understood. Garey et al explored 3 different Health-Related Quality of Life (HRQoL) instruments to develop a 36-item survey tool.[71] This tool evaluated 3 major domains: physical, mental, and social with 4 associated subdomains.[71] Ultimately, the researchers developed the CDiff32 HRQoL questionnaire.[71] This scoring system revealed that overall, the lowest scores (meaning highest impact) occurred with social questions relating to relationships, such as "My C diff infection is affecting my closest relationships," "Because of my C diff infection, I have difficulty being around people I do not know," and "I feel that no one understands my C diff infection." The most impactful question related to general physical complaints was, "Has your C diff infection prevented you from leaving your house?"[71]

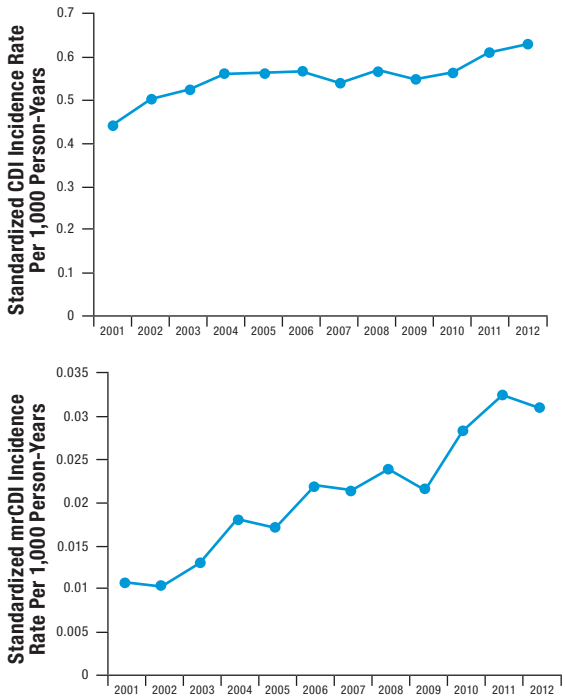
Barbut et al conducted an observational prospective study of 80 patients hospitalized for CDI to assess physical, social, and mental domains and found that patients with rCDI had lower mental scores than patients with an initial episode of CDI (P=0.0582).[72]

Data from an international survey of HRQoL among patients either currently treated for CDI or with a past history but no current treatment for CDI demonstrated significantly worse HRQoL, greater impairment of daily activities, and reduced work productivity compared with patients who had no history of CDI.[73] These differences persisted after adjusting for age, sex, Charlson Comorbidity Index score, education, and country.[73] Respondents with current CDI reported diminished work productivity, with an absenteeism rate 2.5 times higher than that of respondents with no history of CDI.[73] For working respondents, productivity loss associated with current CDI is nearly double that of respondents without a CDI history.[73]

Epidemiology of rCDI

The Centers for Disease Control and Prevention (CDC) defines a recurrent episode as one in which a positive *C. difficile* stool specimen is documented between 2 and 8 weeks after the last positive specimen.[74] Although this definition of rCDI is commonly used to identify and characterize recurrence, especially in clinical trial settings, it is not uniformly used. Various studies use 4, 8, or 12 weeks as the period to determine recurrence, and some studies report recurrences over longer periods of time.[17]

Data show that after an initial episode of CDI, up to 35% of patients will experience recurrence.[17,19,46,75] Data indicate that in the United States, recurrence accounts for 75,000 to 175,000 additional cases of CDI per year.[76] Furthermore, of the patients who have had a recurrence, up to 65% will experience subsequent recurrence.[22,46,77,78] A vicious cycle of infection–reinfection



Age- and sex-standardized incidence rates per 1,000 person-years for CDI and mrCDI were computed using direct standardization with the 2007 OptumInsight population used as the reference.

Figure 2. Incidence of CDI and multiple recurrent CDI from 2001 to 2012.

CDI, *Clostridium difficile* infection; **mrCDI,** multiple recurrent *Clostridium difficile* infection

From *Annals of Internal Medicine*, Ma GK, et al. Increasing incidence of multiply recurrent Clostridium difficile infection in the United States: a cohort study. 2017;167(3):152-158.

impedes recovery, thereby exacerbating the substantial morbidity and economic impact associated with CDI.[79] For example, a retrospective, real-world analysis of 46,571 patients with CDI found that those with 3 or more recurrences had a mean of 5.8 inpatient visits and 4.6 emergency department visits per patient in a 12-month follow-up period.[80] On the clinical side, Medicare patients with CDI are increasingly susceptible to other infections, with each recurrent episode with sepsis occurring in up to 27% of those without recurrence and up to 35.9% of those with 3 or more recurrences in the 12 months after an initial CDI episode.[69] Additionally, new diagnoses of anxiety or depression occur in up to 18% of Medicare patients with CDI.[69]

A recent study of the Medicare system examined 268,762 patients with an index case of CDI, and of these, 175,554 (65.3%) did not experience a recurrence.[69] However, 14.2% had a single recurrence, 8.5% had 2 recurrences, and 12% had 3 or more events in the following year.[69] In the year prior to inclusion in the database, 84% of patients received an antibiotic and about half were taking gastric acid–suppressing medications.[69]

Treatments that reduce the rate of rCDI from an average of approximately 20% after an initial episode and about 50% after another CDI episode could translate to a substantial reduction in rCDI-related health care utilization, patient burden, and costs.[77,81]

Health and Economic Burden of rCDI

Recurrent CDI requiring rehospitalization imposes an increased health care burden in terms of 30-day readmission, length of stay, and mortality. Zilberberg et al studied diagnosis–related group reimbursement for these parameters in 39,274,132 discharges in the Healthcare Cost and Utilization Project (or HCUP) for California, Florida, Iowa, and New York.[82] Of the total, 385,682 were discharged with a CDI code (initial CDI hospitalization), and in the following 60 days, 99,175 (25.7%) were rehospitalized. Of the latter group, 36,504 (36.8%) were readmitted for CDI (rCDI); rCDI was the principal diagnosis in 14,005 patients (38.4%) and rCDI was the secondary diagnosis in 22,499 (61.6%).[82]

In a separate observational study of 55,504 eligible patients with a CDI, the average hospital length of stay was 8.0 days for an index episode and 9.3 days for an rCDI episode.[83] In 2016, the mean hospital stay for all conditions was 4.6 days, indicating that CDI places a higher burden on health care resource utilization than the average admission.[84] In a single-center study of 372 patients, 18.2% of patients with rCDI had an inpatient admission that required a stay in the ICU.[85]

Additionally, 6% of patients require surgical intervention, such as a colectomy.[86] Mortality has been shown to be 9% with CDI, and more serious manifestations such as fulminant or refractory CDI show mortality rates increased from 4.7% to 13.8%.[19,87]

The annual economic cost of all CDI in the United States is estimated at $5.4 billion, with $4.7 billion incurred in health care settings.[88] Specifically, rCDI is estimated to cost $2.8 billion annually (2016 dollars), accounting for almost half of all CDI costs.[86]

Most of the cost of CDI is attributed to inpatient treatment, regardless of whether the infection is community- or hospital-acquired.[53] The mean CDI-related cost is nearly $30,000 per patient per admission per episode of infection.[89,90] In a single-center study of 540 patients, the total hospitalization cost of treating an rCDI episode was 2.2 times that of treating primary CDI ($13,168 vs $28,218; $P<0.0001$).[91] In the 12 months after an initial CDI episode, the mean total, all-cause direct medical costs per patient ranged from almost $72,000 for those with no recurrence to $207,000 for those with 3 or more recurrences.[80]

Nelson et al analyzed the IQVIA database of CDI episodes requiring hospitalization from 2010 to 2017.[92] An index episode was observed in 46,571 cases. Of these cases, 3,129 (6.7%) had 1 rCDI, 472 (1.0%) had a secondary event, and 134 (0.3%) had 3 or more episodes.[92] Inpatient visits increased with the number of CDI episodes, as did emergency department visits.[92] All-cause costs after the index case were $71,980 for patients without rCDI, $131,953 for 1 rCDI, $180,574 for a secondary diagnosis of CDI, and $207,733 for 3 or more rCDI.[92] This significant financial burden of rCDI shows that minimizing the risk for rCDI is better not only for the patient but also economically.[92]

In an analysis of primary and secondary rCDI diagnoses, Zilberberg et al showed that the mean gap between hospital costs and diagnosis-related group reimbursements was greatest in secondary rCDI at $13,803 per admission, compared with patients initially hospitalized for rCDI at $4,881.[82] Additionally, the incidence of sepsis was significantly higher in the secondary rCDI group than in the primary rCDI group (39.2% vs 5.2%; $P<0.001$), as was the incidence of surgical or procedural intervention (2.42% vs 0.96%).[82] Rehospitalization following an index CDI admission is a common event and a

Table 2. Risk Factors Associated With Recurrent CDI

Patient Characteristic	Median aOR Per 10-Year Increase in Risk for Multiple Recurrent CDI vs Non–Multiple Recurrent CDI (95% CI)
Age, y	56.0 vs 49.0; aOR, 1.25 (1.21-1.29)
Female	63.8% vs 58.7%; aOR, 1.24 (1.11-1.38)
Exposure to antibiotics	72.3% vs 58.8%; aOR, 1.79 (1.59-2.01)
Use of proton pump inhibitors	24.6% vs 18.2%; aOR, 1.14 (1.01-1.29)
Corticosteroids within 90 days of CDI	18.3% vs 13.7%; aOR, 1.15 (1.00-1.32)
Chronic kidney disease	10.4% vs 5.6%; aOR, 1.49 (1.24-1.80)
Diagnosis in a nursing home	2.1% vs 0.6%; aOR, 1.99 (1.34-2.93)

aOR, adjusted odds ratio; **CDI,** *Clostridium difficile* infection

Based on reference 65.

substantial proportion of readmissions involved rCDI. Patients with a secondary rCDI tend to be more severely ill than primary rCDI patients, and incur a major deficit in all reimbursements in relation to expenditures.[82]

Clinical Management of CDI

Clinical practice guidelines for treatment of CDI are available as a joint statement from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).[46] These guidelines outline the use of antibiotics—vancomycin, fidaxomicin, and metronidazole—based on the severity of the disease (Table 4).[46,55] Originally published in 2010, the guidelines were revised in 2017, with the notable change that metronidazole was recommended for an initial episode of CDI in the earlier guidelines but was no longer a first-line recommended therapy in the 2017 edition, being replaced by fidaxomicin.[46,55] The revised guidelines also added fecal microbiota transplantation (FMT)—administering fecal material that contains distal gut microbiota from a healthy person to a patient with dysbiosis—as a recommended treatment for second or subsequent recurrence after appropriate antibiotic treatment has been administered, listing the strength of the recommendation/quality of evidence as strong/moderate compared with the other treatments in this category with weak/low evidence.[46,93] Although FMT was mentioned in the earlier guidelines, it was not recommended as a treatment at that time.[55]

Use of broad-spectrum antibiotics disrupts the bacterial composition of the gut, resulting in an environment for *C. difficile* to develop. Treatment with antibiotics such as vancomycin or metronidazole can kill the organism but spores can remain and the surrounding microbiota is altered from these antimicrobials, thus leading to an increased risk for rCDI.[94] Fidaxomicin has a narrower spectrum being more specific for CDI, therefore potentially causing less damage to the surrounding microbiome and is associated with lower recurrence rates.[46,75,94] The IDSA/SHEA guidelines recommend reducing the frequency and duration of antimicrobial therapy and the number of agents to reduce the risk for CDI.[46] Microbiota-based therapeutics could provide an opportunity to break the cycle of rCDI and improve the efficacy of treatment of CDI.

Management of rCDI

According to the 2017 IDSA/SHEA guidelines, treatment of rCDI should include vancomycin or fidaxomicin for a first recurrence. For more than 1 recurrence, treatment should include[46]:

- tapered and pulsed oral vancomycin (weak recommendation, low quality of evidence);
- standard vancomycin followed by rifaximin (weak recommendation, low quality of evidence);
- fidaxomicin (weak recommendation, low quality of evidence); or
- FMT for multiple recurrences with failed appropriate treatments (strong recommendation, moderate quality of evidence).

When the 2017 IDSA/SHEA guidelines were released, quite a few trials with open-label and retrospective study designs had been published, but several, better structured clinical trials evaluating FMT for rCDI were in progress. At that time, there were limited data from rigorous prospective randomized controlled trials. The inclusion of FMT in the updated guidelines reflects the growing body of evidence and expanding exploration of genomics and metagenomics of the microbiome, with emerging evidence suggesting microbiome-based therapeutics potentially offering a treatment path that can restore a patient's microbiome and treat rCDI (Figure 3).[95]

Table 3. Procedures and Complications Reported at 12-Month Follow-up of CDI Treatment

Treatment/Outcome	Index Case (N=175,554)	rCDI (n=38,163)	2 rCDI (n=22,898)	3 rCDI (n=32,147)
Bowel surgery[a]	11,952 (6.8%)	3,071 (8.1%)	1,758 (7.7%)	2,169 (6.8%)
Sepsis	47,382 (27.0%)	13,403 (35.1%)	8,183 (35.7%)	11,534 (35.9%)
Psychiatric condition[b]				
Anxiety	24,416 (13.9%)	5,972 (15.6%)	3,473 (15.2%)	4,645 (14.4%)
Delirium	19,919 (11.3%)	5,162 (13.5%)	2,943 (12.9%)	3,994 (12.4%)
Depression	26,891 (15.3%)	6,956 (18.2%)	3,869 (16.9%)	5,180 (16.1%)
PTSD	550 (0.3%)	122 (0.3%)	85 (0.4%)	96 (0.3%)

[a] Includes subtotal colectomy and diverting loop colectomy.

[b] Incident diagnosis with no prior claim for this condition in previous 12 months.

CDI, *Clostridioides difficile* infection; **PTSD,** post-traumatic stress disorder; **rCDI,** recurrent CDI

Based on reference 69.

Microbiota-Based Therapeutics: A Brief History From "Home-Brewed" Origins to Today

FMT was first described in the 4th century by Ge Hong as treatment for severe diarrhea, and in the 16th century, Li Shizhen treated gastrointestinal diseases using an oral fecal suspension.[96] Moreover, many animal parents supplement the diet of young animals with their feces, which ensures the developing animals get appropriate microbiota, particularly to obtain the bacteria that enable them to digest and absorb nutrients from vegetation in their environment that are part of their diet.[97]

In modern science, Eiseman et al reported the use of a fecal enema to treat pseudomembranous colitis in 1958.[98] Over the next 60 years, a litany of uses for "home-brewed" fecal or bacteriotherapy were reported.[98,99]

Clinical Considerations for FMT

There are several considerations in an FMT procedure, including donor selection; preparation of the fecal material; recipient preparation; delivery methods; and the safety of the procedure, which has been highlighted recently.[93,94,100]

The use of FMT for rCDI is becoming a component of managing rCDI using "home-grown" methods.[10,101] These rudimentary methods involve clinicians identifying donors, screening

Table 4. IDSA/SHEA Guidelines for Treatment of *Clostridium difficile* Infection

IDSA/SHEA Guideline Year	Disease Severity	Treatment Recommendations
2010	Mild/moderate	Metronidazole 500 mg 3 times daily by mouth for 10-14 d
	Severe	Vancomycin 125 mg 4 times daily by mouth for 10-14 d
	Severe/complicated	Vancomycin 500 mg 4 times daily by mouth or nasogastric tube, plus metronidazole 500 mg IV every 8 h; if complete ileus, consider adding rectal instillation of vancomycin
	First recurrence	Same as for initial episode
	Second or subsequent recurrence	Vancomycin in a tapered and/or pulsed regimen
2017	Non-severe	Vancomycin 125 mg 4 times daily by mouth for 10 d OR fidaxomicin 200 mg by mouth twice daily for 10 d; if vancomycin and fidaxomicin are unavailable, use metronidazole 500 mg by mouth 3 times daily for 10 d
	Severe	Vancomycin 125 mg 4 times daily by mouth for 10 d OR fidaxomicin 200 mg by mouth twice daily for 10 d
	Fulminant	Vancomycin 500 mg 4 times daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Metronidazole 500 mg IV every 8 h should be given, together with oral/rectal vancomycin, particularly with ileus
	First recurrence	If metronidazole was used for the first episode, use vancomycin 125 mg 4 times daily for 10 d, OR • If a standard regimen was used for the first episode (eg, 125 mg 4 times daily for 10-14 d, 2 times daily for a week, once daily for a week, and then every 2 or 3 d for up to 2-8 wk), use a prolonged vancomycin regimen that is tapered and pulsed, OR • If vancomycin was used for the first episode, use fidaxomicin 200 mg twice daily for 10 d
	Second or subsequent recurrence	Tapered and pulsed vancomycin regimen, OR • vancomycin 125 mg 4 times daily by mouth for 10 d followed by rifaximin 400 mg 3 times daily for 20 d, OR • fidaxomicin 200 mg twice daily for 10 d, OR • fecal microbiota transplantation

Based on references 46 and 55.

IDSA, Infectious Diseases Society of America; **SHEA,** Society for Healthcare Epidemiology of America

their medical history and blood work/stool for various disease processes potentially transmitted with an FMT.[10,93] Although these processes were optimal in the past to deliver life-saving treatments to patients in need with no other options, comprehensive and structured universal screening has become more widely available through stool banks and pharmaceutical trials.[94] FMT is used for other gut-related conditions, such as inflammatory bowel disease.[10,93]

Donor selection is critical to avoid the transplantation of potential pathogens and other adverse events.[100] Stool samples must be thoroughly screened for potential transferable pathogens.[100] There are strict guidelines in the United States and Europe recommending the use of a donor questionnaire that lists inclusion and exclusion criteria.[100,102] It is only possible to screen for known infectious agents, but periodically new organisms are discovered such as HIV, hepatitis C virus, and SARS-CoV-2, so ongoing careful observation is advised. Equally important, chronic diseases, such as atherosclerosis, diabetes, obesity, and colon cancer, may be related to changes in the bowel flora.[100]

Another consideration of the transplant is whether there is a benefit to transplanting fresh stool passed on site of the FMT versus frozen stool that was donated at a different time and sometimes in a different location. Whether there is a difference in efficacy of fresh versus frozen fecal material preparation has been debated[100]; however, trials and meta-analyses have shown that frozen fecal material has similar efficacy as fresh material.[103]

Patients undergoing FMT require support and education before the procedure.[100] The recipient should not receive antibiotics within the 48 hours prior to the procedure.[100,102] FMT can be delivered via oral capsule, nasoenteric tube, enema,

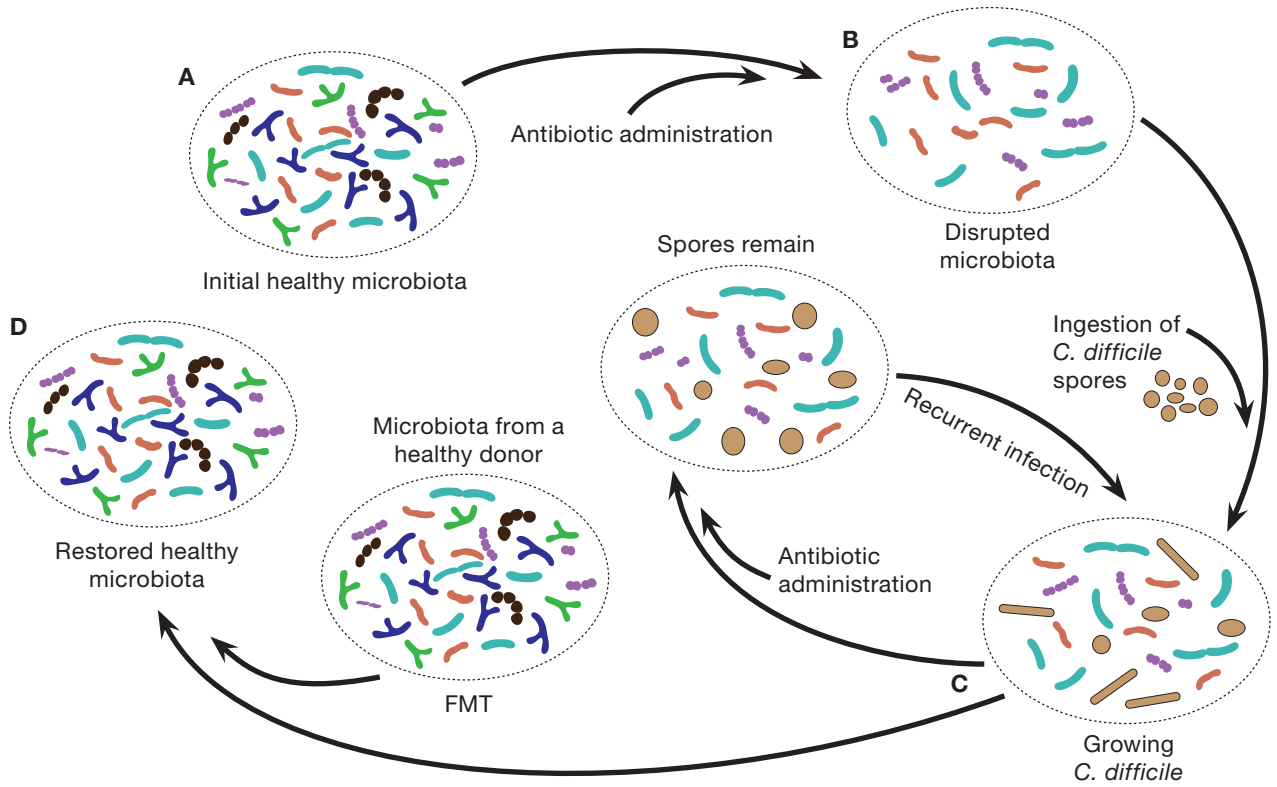


Figure 3. Fecal microbiota transplantation as an approach to microbiota restoration.

A. In an initial healthy gut, the microbial community typically contains different taxa, and features high taxonomic and functional diversity. Most of those taxa are benign. Some can even keep out pathogens such as *C. difficile*.

B. Use of antibiotics leads to low taxonomic diversity and to a disrupted gut microbiota, which allows colonization by *C. difficile*.

C. *C. difficile* spores are typically ingested following contact with contaminated biotic or abiotic surfaces, and then germinate in the gut to a vegetative cell-type and produce potent gut-damaging toxins during a late growth stage. This leads the development of CDI. Standard treatment of CDI involves prescription of antibiotics such as metronidazole or vancomycin. These antibiotics kill *C. difficile*, but spores can remain in the gut, leading to recurrent CDI.

D. Transplanting the fecal material from a healthy donor to the patient's gut can restore the healthy gut microbiota.

CDI, *Clostridioides difficile* infection; **FMT,** fecal microbiota transplantation

Reprinted from Xiao Y, et al. An ecological framework to understand the efficacy of fecal microbiota transplantation. *Nat Commun*. 2020;11(1):3329.

flexible sigmoidoscopy, or colonoscopy.[99,191] If a colonoscopy is the modality of choice, a standard bowel preparation is required as per any endoscopic procedure.[100] Ideally, the bowel should be free of contaminated fecal material to ensure the transplant has the best chance of a healthy graft.[100,102] Some centers that use flexible sigmoidoscopy or colonoscopy for the procedure give loperamide about 1 hour before the FMT to keep the new feces in the bowel for a longer time.[99,100]

The selection of a modality is center specific and based on clinical presentation. For patients with an inflamed colon, upper GI delivery routes (eg, esophagogastroduodenoscopy) are preferred; however, risks such as aspiration, discomfort while inserting the tube, or the inability to monitor the colon mucosa, must be considered.[100] Colonic administration via flexible sigmoidoscopy or colonoscopy is invasive, expensive, and carries the risk for colonic perforation.[100]

Efficacy

In randomized trials of FMT for CDI and rCDI, efficacy rates of 62% to 76% have been reported with a single FMT.[104-106] Real-world analysis after a single FMT confirmed the efficacy, with an effectiveness rate of 71.5%.[107] Efficacy rates as high as 90% have been reported after multiple FMTs.[106,108] A meta-analysis of 13 studies (N=610) reported that 439 patients experienced a clinical cure rate of 76.1% after 1 FMT and 89% after multiple FMTs.[106] A randomized controlled trial of 20 patients with rCDI found that FMT was more effective than vancomycin (remission rate, 90% vs 26%; $P<0.0001$) in resolving these infections.[108] A systematic review of 37 studies with meta-analysis of FMT in recurrent and refractory CDI found that a clinical resolution of 92% (95% CI, 89%-94%) was observed across all studies.[109] Notably, a significant difference was observed between lower gastrointestinal (95%; 95% CI, 92%-97%) and upper gastrointestinal (88%; 95% CI, 82%-94%) delivery of FMT.[108] No difference was found between fresh and frozen FMT (92%; 95% CI, 89%-95% vs 93%; 95% CI, 87%-97%).[108]

A real-world database analysis showed that although initial FMT treatment is effective in the majority of patients, only a small proportion of patients undergo FMT as rCDI treatment.[107] A recent study reported that currently, no more than 1% of patients are receiving FMT to treat CDI.[69]

Adverse Events

Recently, there have been adverse events related to FMT that prompted warnings from the FDA. Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*), one of whom died.[110] FMT used in these 2 patients were prepared from stool obtained from the same donor from a stool bank.[110] It is important to consider that neither of these patients had *C. difficile* and received FMT for encephalopathy and prevention of graft-versus-host disease. The donor stool and resulting FMT were not tested for ESBL-producing, gram-negative organisms prior to use.[110] After these adverse events occurred, stored preparations of FMT from this stool donor were tested and found to be positive for ESBL-producing *E. coli* identical to the organisms isolated from the 2 patients. It is important to note that these transplants were stool bank in origin and not a clinical trial conducted by a pharmaceutical company.

Recently, the FDA issued safety warnings pertaining to the screening of stool donations for COVID-19 and SARS-CoV-2.[111] Although there have been no reported cases, this development emphasizes the need for updating screening procedures for all known pathogens, whether bacterial or viral.[111]

A New Chapter for Microbiome-Based Therapeutics

Presently, there are numerous companies studying various microbiome-based preparations for the management of CDI. These products include consortia of bacterial species or collected, screened, donated material that are delivered via enema or oral routes of administration.

Without an FDA-approved microbiome-based therapeutic, a regulatory environment lacking standardization of product and administration methods has created a situation in which a regulated, safe, and effective product is critically needed.

Further research is essential to ensure availability of safe, effective, and standardized microbiome-based therapies that can help—along with antibiotic treatment—to restore the microbiome and break the cycle of rCDI.

Conclusion

The incidence of CDI continues to be a great concern in the community setting, and lack of antibiotic stewardship programs coupled with suboptimal transitions of care from the hospital setting are ongoing challenges. New antibiotics and therapies for CDI have been approved in the past decade, but rCDI continues to present a major challenge. Recurrence becomes more frequent as the patient experiences repeated infections, and contributes to a growing personal, economic, and societal burden. Due to the cyclical infectious process of CDI, a biological approach, such as a microbiome-based therapy, in addition to antimicrobial therapy, may reduce the impact of disease-mediated change to restore the microbiome.

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Disclosure: Dr Chopra reported that she is a consultant to and on the speakers bureau of Cepheid. She also is the Data and Safety Monitoring Board chair for Rebiotix, Inc. Dr Feuerstadt reported that he has received grant/research support as a principal investigator from Adare Pharmaceuticals, Finch Therapeutics, Ironwood Pharmaceuticals, Pfizer, Inc, Rebiotix, Inc, and Vedanta Biosciences. He is a consultant to Ferring Pharmaceuticals and Roche Diagnostics, and is on the speakers bureau for Merck and Company. Dr Garey reported that he has received grant/research support from Acurx Pharmaceuticals, Merck, Paretek Pharmaceuticals, Summit Therapeutics, Tetraphase, and Vedanta Biosciences.

SR207 DECEMBER 2020 US-MBIO-2000027