

Special REPORT

Restoring the Full Diversity of the Gut Microbiome: Can It Break the Cycle of Recurrent *C. Difficile* Infection?

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Microbial communities play an important role in the maintenance of human health.¹⁻⁴ Microbes have evolved and adapted to the human host to our benefit.¹ These microorganisms that inhabit most of our body play important roles in our host defense, metabolism, and structural integrity.^{3,4} A technological revolution in molecular methods and informatics has reinvigorated our understanding of the symbiotic relationships that exist between these microbes, their genes, and the human genome.^{1,4} The human microbiota are a complex community of microorganisms living in the human body that includes bacteria, viruses, fungi, protozoa, and archaea.⁴⁻⁶ The genes of this collective are known as the microbiome.⁶ An estimated 500 to 1,000 species of bacteria exist in the human body,^{4,7,8} and subspecies, or unique genotypes, increase this number significantly and provide greater diversity.^{4,7} Overall, the human body contains about 100 trillion organisms, estimated to be 10¹¹ to 10¹² organisms per milliliter.⁹⁻¹³ The microbes found in the gut outnumber human cells several-fold, leading to the number of microbial genes exceeding human genes by more than 100 times.^{4,6}

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Each person possesses a unique microbial “fingerprint” or microbiome, which can evolve over time.^{3,6} Different microbes and their relative proportions influence health.³

The microbiota of the gastrointestinal tract guide the extraction and production of energy from ingested nutrients, promote development of the gut mucosa and its function, and stimulate the adaptive and innate immunity of the host.^{4,6} The microbiota in the healthy state are diverse and dynamic, responding and evolving with environmental challenges. These gut microbiota play a key role in extracting, synthesizing, and absorbing nutrients, generating metabolites, such as short-chain fatty acids,

vitamins, amino acids, lipids, and bile acids, which in turn also help stimulate and modify immunity.^{4,6}

Perturbation of the gut microbiome may lead to loss of diversity or function, a condition sometimes referred to as dysbiosis.^{1,6} A persistent reduction in microbial diversity may lead to adverse consequences for the host, including overgrowth of undesirable organisms or pathogens.^{1,4} Although most often associated with consumption of antimicrobials, diet, chemotherapy, pathogenic microorganisms and genetics also may adversely impact the microbiome (Figure 1).^{1,14-16}

Numerous illnesses have been associated with gut dysbiosis,

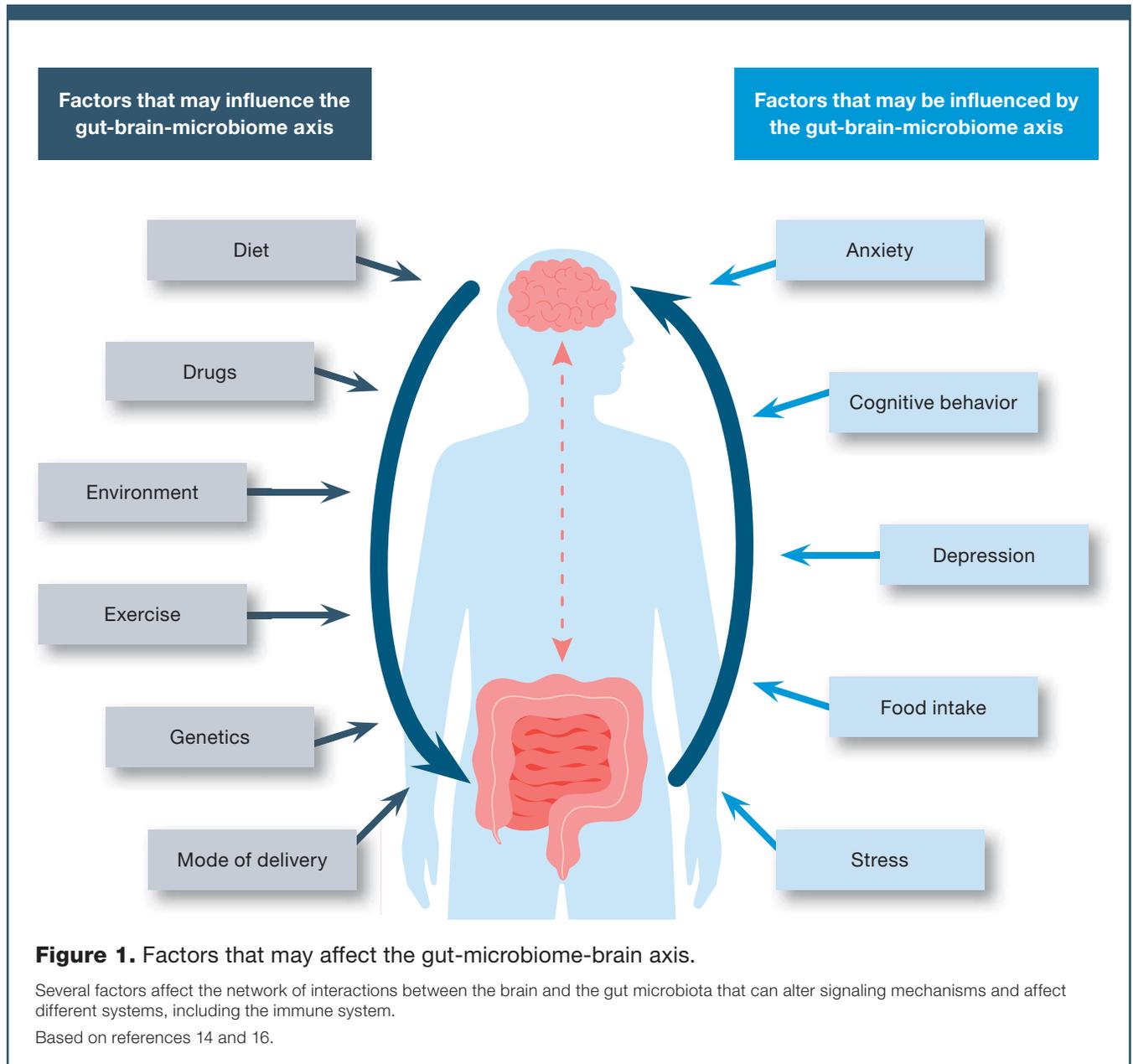


Figure 1. Factors that may affect the gut-microbiome-brain axis.

Several factors affect the network of interactions between the brain and the gut microbiota that can alter signaling mechanisms and affect different systems, including the immune system.

Based on references 14 and 16.

including neurologic disorders, such as Parkinson's disease, Alzheimer's disease, and autism; cardiometabolic conditions, such as obesity and diabetes; and pulmonary conditions, including cystic fibrosis and asthma.^{5,13,17-20} These may arise due to altered immune function or neuronal signaling triggered by the alterations in the gut microbiota.⁶ At present, we best understand the relationships of gut dysbiosis with digestive diseases, such as irritable bowel syndrome, Crohn's disease, and *Clostridioides difficile* infection (CDI) (Figure 2).^{1,5,20}

Alterations of the gut microbiota by antimicrobials, especially those with anti-anaerobic activity, may be associated with a loss of colonization resistance to toxigenic *Clostridioides difficile*.¹ Antimicrobial therapy for CDI, such as vancomycin or metronidazole, further disrupts the microbiota, which may lead to a cycle of recurrence.^{1,21-24}

The treatment of infections with broad-spectrum antibiotics, and long-term treatment with antimicrobials, may exacerbate dysbiosis and enhance the risk for recurrent CDI (rCDI).^{15,25-27} The inability of the host to rapidly restore gut microbial diversity may allow for recurrence of CDI, further environmental contamination with *C. difficile* spores, and enhanced opportunities for transmission, thus imposing a significant burden on patients and health care systems.^{25,26,28-30}

Rapid restoration of the microbial diversity appears to be associated with a reduction in the recurrence of CDI.^{11,31} The most rapid way to achieve the restoration of diversity is to instill a "healthy" diverse microbiota back into the gastrointestinal tract following the completion of an antimicrobial regimen.⁶ This procedure is known as fecal microbiota transplant (FMT).^{6,31} This Special Report provides a general overview of the role of the gut microbiome, the consequences of its perturbation in CDI and rCDI, and novel approaches to treating and preventing these infections.

The Gut Microbiota/Microbiome

The gut microbiota evolve with the host depending on age, environmental factors, and geography.³² The most prevalent phyla found in a healthy human gut are the *Bacteroidetes* and *Firmicutes*.³²⁻³⁴ These comprise more than 90% of bacteria in the healthy microbiome and consist of a diverse range of genera and species that may share ecological and metabolic niches.^{5,32} These microbes are predominantly anaerobes.³⁵ Less prevalent phyla include *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia*.³⁵

Bacteroidetes

Bacteroidetes are gram-negative bacteria with broad metabolic potential, with an ability to adapt and allow abundance and stability.^{1,4,33} Some *Bacteroidetes* have immunomodulatory effects and inhibit *C. difficile* spore germination by various cell wall components.³⁶ Among *Bacteroidetes*, *Bacterioides fragilis* is most understood and recognized as an essential contributor to the stability of the microbiome.³³

Firmicutes

Firmicutes are gram-positive bacteria with rigid cell walls,^{4,6,11} and are the most abundant bacteria found in the

gut, with *Clostridia* representing 95% of the phyla.^{11,32} Some of these organisms have demonstrated anti-inflammatory effects in studies of inflammatory bowel diseases^{37,38} and, in combination with other bacteria, provide physiologic support of the gut barrier.^{39,40} *Firmicutes* also include some pathogenic bacteria, such as *Bacillus anthracis*, which causes anthrax.⁴¹

Preserving Microbial Diversity

The healthy gut microbiota play a role in preventing bacterial invasion by maintaining intestinal epithelium integrity.^{8,42} They may prevent pathogenic colonization through competitive processes—nutrient metabolism, pH modification, peptide secretions, and effects on cell signaling pathways—known as colonization resistance.⁴⁰

Understanding the relationship between species in the microbiome is important. The diversity and richness is described as relative abundance.⁴³ A broad range of bacterial species constitutes a healthy microbiome. This relative abundance enables the healthy microbiome to withstand certain microbial stressors—a reflection of the community's resilience—until a tipping point is reached and the microbiome becomes dysbiotic.^{11,43} Depletion of *Bacteroidetes* and *Firmicutes* is associated with dysbiosis, causing disruption of the richness and diversity of the microbiome and enabling the proliferation of certain pathogenic microbes, such as *C. difficile*.^{1,6,11,21} Essentially, *C. difficile* is the invasive weed in the burned-out forest.

Pathogenesis and Clinical Presentation of CDI

C. difficile is a gram-positive, spore-forming anaerobic bacillus transmitted via its spore form through environmental contamination and from person to person via the fecal-oral route.^{27,44,45} CDI begins with the ingestion of *C. difficile* spores that germinate in the presence of specific primary bile acids in the gut, where the vegetative form then establishes colonization and releases toxins that interact with the colonic epithelial cells, leading to increased fluid secretion and inflammation.⁴⁶ As part of the life cycle, some vegetative cells will re-sporulate as a mechanism to ensure survival and further transmission.⁴⁷ In the healthy gut, primary bile acids are metabolized into secondary bile acids by certain microbes in the gut, which then inhibit the germination of spores and the growth of *C. difficile* vegetative cells.⁴⁶ The balance between primary and secondary bile acids that inhibits *C. difficile* is lost in dysbiosis, and this can lead to a cycle of recurrent infections.^{1,46}

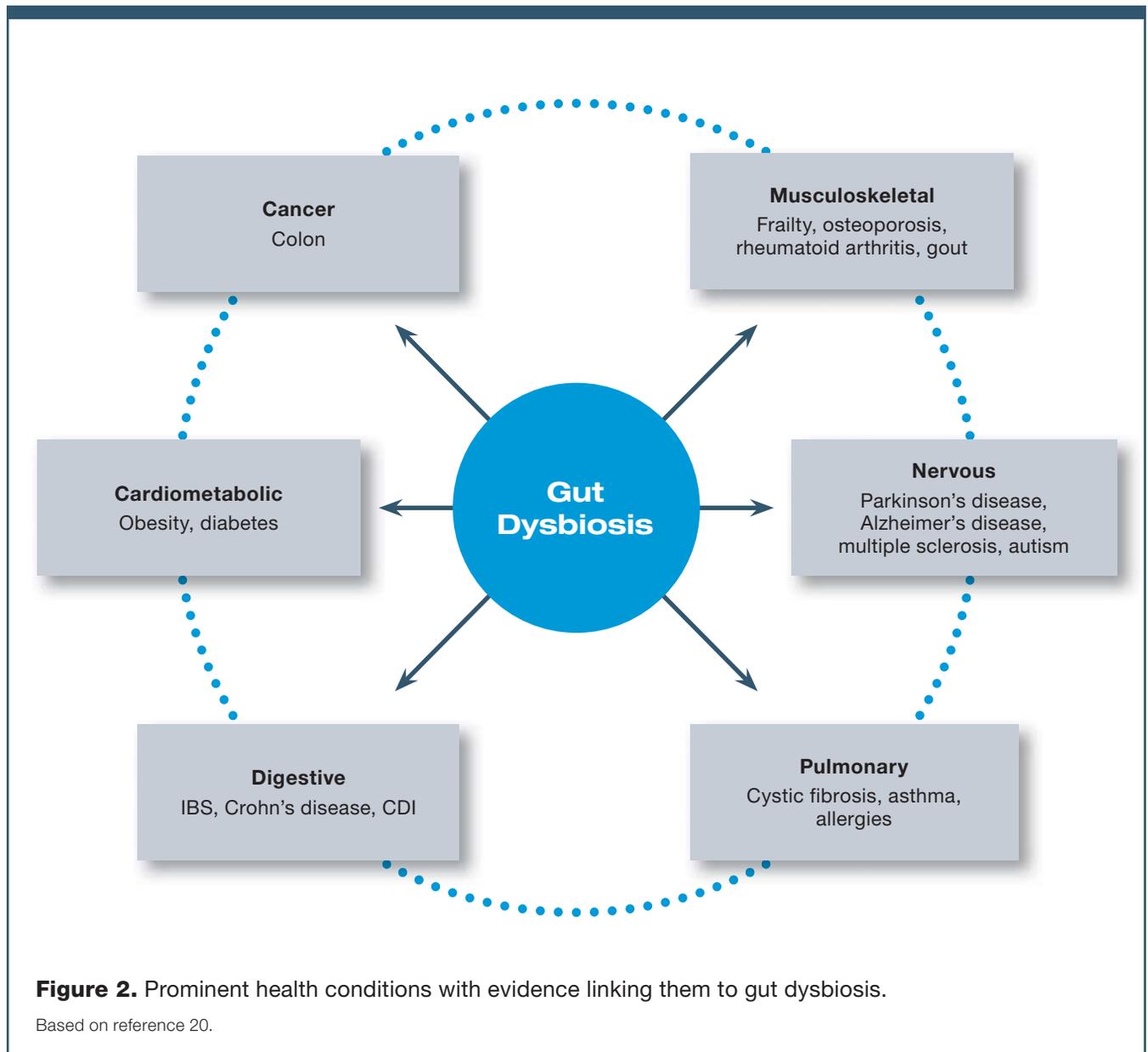
CDI can present in a range of illnesses, from mild diarrhea to fulminant colitis and septic shock.²⁷ The most common presentation is nonbloody diarrhea of 3 or more unformed bowel movements in 24 hours (Bristol Stool Scale, 6 or 7), sometimes associated with nausea, abdominal pain, and fever.^{27,44,48,49} Severe CDI may present with either diffuse or pseudomembranous colitis.^{27,44} Some features of severe disease include a markedly increased white blood cell count, decreased albumin, and increased serum creatinine.⁵⁰ These more severe cases can be associated with sepsis, toxic megacolon, bowel perforation, and renal failure.^{44,51-52}

Epidemiology of CDI and Recurrent CDI

In the United States, nearly a half-million individuals are infected with *C. difficile*, with about 30,000 deaths reported annually.^{28,29,53} The primary reservoir of these infections is health care settings, but community-acquired infections now account for almost 50% of all cases of CDI.²⁸ Although the overall incidence of CDI has declined slightly in the past few years, the incidence of rCDI has increased significantly and is identified as a major public health challenge.^{25,26,53-55}

Recurrence of CDI is a continuous challenge, with up to 35% of primary infections recurring within 8 weeks and

subsequent recurrence occurring in an additional 40% to 60% of these patients.^{25,26,53,54} Data indicate that in the United States, recurrence accounts for 75,000 to 175,000 additional cases of CDI per year.⁵⁶ Ma et al studied the incidence of CDI using a database of about 39 million insured individuals and found the annual incidence of CDI increased by 42.7%, while the incidence of multiple rCDI (mrCDI) increased by 188.8%.⁵⁷ The study identified several risk factors for the increase in mrCDI, including age, sex, and exposure to antibiotics and proton pump inhibitor use, as well as use of corticosteroids within 90 days of CDI.⁵⁷



Health Burden of CDI and Recurrent CDI

CDI not only affects the gastrointestinal tract, but is associated with a significant reduction in overall health and quality of life. People with CDI experience mental health conditions, including anxiety (13.9%), depression (15.3%), post-traumatic stress disorder (0.3%), and heart failure (43%).^{55,58} The mortality rate among individuals with CDI is reported at 6.4% within 30 days of diagnosis.⁵³ One of the most significant complications is sepsis, affecting 27% of those with CDI.⁵⁸ The rate of sepsis increases significantly with each episode of rCDI. In a 12-month period, 16.5% of patients with no recurrence presented with sepsis, but this increased to 27.3% with only 1 recurrent episode of CDI and continued to increase with each subsequent episode (up to 43.3%).⁵⁹ Sepsis also carries a significant mortality burden, with 22% of cases resulting in death.⁶⁰

Patients with fulminant CDI may require surgeries, such as a total colectomy or an ileostomy.⁵⁹ Recurrent episodes may increase the need for surgical intervention, from 4.6% with no recurrence to 7.3% after the first episode of recurrence.⁵⁹ Although colectomy may be lifesaving, surgery for CDI carries a significant risk for mortality.⁵⁹ More than 75% of patients undergoing a colectomy for CDI suffer colectomy-related morbidities within 30 days of the procedure.⁵⁹ Furthermore, the in-hospital mortality rate following colectomy for CDI ranges from 36% to 80%.⁵⁹ The postoperative complications underscore the burden of CDI, particularly those with mrCDI.⁵⁹

Anyone who has suffered from rCDI can describe the negative impact on their daily life. Studies show a greater impairment of daily activities and reduced work productivity than for individuals without a CDI history.⁶¹ These effects of CDI are not limited, as 30.6% of patients with prior CDI report a lasting impact on their life, long after the infection has resolved.⁶² A survey of 420 individuals with current or past CDI showed that 56.6% of those with past CDI still experienced CDI-related symptoms.⁶² People with past CDI also reported chronic conditions, such as depression (91.3%), to be exacerbated or more severe.⁶² Furthermore, 87.2% of the survey respondents feared disease recurrence.⁶²

Economic Burden of Recurrent CDI

The annual economic cost of all CDI cases in the United States is estimated to be \$5.4 billion.⁶³ The main contributors to these expenses are direct medical costs, including inpatient costs with \$4.7 billion incurred in the health care setting.⁶³ In terms of the individual financial strain associated with CDI, one study reported out-of-pocket expenses to be \$4,355 and \$8,695 for current and past CDI, respectively.⁶² As a recurring infection, CDI requires rehospitalization and an increase in health resources; consequently, the associated costs increase significantly.

Inpatient admissions and emergency department visits are most frequent for people with the highest number of rCDI episodes.²⁹ A study observed that 84% of patients with rCDI will be hospitalized within 12 months, with hospital stays

averaging 18 days for patients with rCDI.^{30,55} Additionally, 57% of patients with at least 1 rCDI have 2 hospital admissions or more within 12 months.⁵⁵

The financial burden of rCDI in the United States is \$2.8 billion annually (ie, approximately 50% of all CDI costs).³⁰ The total mean cost per patient for rCDI is \$34,104.³⁰ The total, all-cause, and direct medical costs during a 12-month period after an initial CDI range from \$131,000 (1 recurrent episode) to more than \$200,000 for patients with 3 or more episodes of CDI.²⁹ Furthermore, data from a commercial claims analysis showed an approximately \$3,000 to \$29,000 gap in reimbursement per patient with CDI.⁶⁴ Because patients with mrCDI experience greater severity of illness than those with an initial CDI, they incur a significant deficit in reimbursement.⁶⁴

Current and Emerging Treatment Options

The current standard of care for managing CDI is to treat with an antimicrobial that targets the vegetative form of the organisms.^{22,26,65} Unfortunately, although more targeted than broad-spectrum antimicrobials, CDI antibiotics continue to cause disruption of the gut microbiota.^{22,26,65} In addition, repeated antimicrobial therapy can select for drug-resistant organisms and maintain the cyclical pattern of CDI and rCDI.^{21,22,26,30}

Newer therapeutics are designed to be more narrowly targeted in order to cause less disturbance to the gut microbiota; however, they do not address the preexisting dysbiosis fueling recurrent infection. The 2021 update to the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America's clinical practice guidelines outlines new recommendations for the management of CDI in adults with a focus on reducing recurrence.⁶⁶ These guidelines emphasize more targeted therapy for CDI and the first episode of rCDI, and note the advantages of fidaxomicin over vancomycin and metronidazole.⁶⁶ The guidelines also describe the role of bezlotoxumab, a monoclonal antibody against *C. difficile* toxin B as an adjunct to antibiotic treatment in rCDI within 6 months of the initial infection.⁶⁶

The other emerging strategy for managing rCDI is the use of microbial restoration therapies, such as FMT.²² The instillation of a diverse fecal sample into the dysbiotic host's GI tract may help to reestablish the microbial diversity needed to ward off further episodes of CDI.^{21,22,27} FMT can be delivered via rectal administration (including enema and colonoscopy), oral capsules, a nasoenteric tube, or flexible sigmoidoscopy.^{67,68}

Several studies have shown FMT to be efficacious in treating rCDI and restoring the biodiversity of the gut.^{31,69} When selecting FMT to treat rCDI, it is important to consider the limitations in the published studies. In a systematic review and meta-analysis of 13 open-label and randomized trials, researchers reported that according to inclusion and exclusion criteria of the studies, enrolled patients may not reflect the broad range of patients seen in the real world.⁷⁰ Current evidence shows variability in clinical cure rates across randomized clinical trials and open-label studies.⁷⁰ Open-label studies showed higher clinical cure rates than randomized studies (82.7% vs 67.7%; $P < 0.001$).^{70,71} Additionally, lack of

agreement in the diagnostic methods used to enroll patients in the studies is often overlooked, contributing to the variability in outcomes.^{28,66}

Biologically derived microbiome-based therapeutics, such as FMT, require oversight to ensure short- and long-term safety. In March 2020, the FDA issued a warning on the potential risk for serious or life-threatening infections following the investigational use of an FMT product supplied by a US stool bank company.⁷² Concerns regarding lack of standardization, assurance of safety, and quality have led to a pathway for the development of products under FDA guidance. These products are currently completing clinical trials and

may provide the opportunity for treatment of rCDI with safe and effective rectal, oral, or enterically administered products.

Conclusion

Disruptions in the gut microbiota may enable the proliferation of pathogens causing diseases such as CDI.^{1,21} Anti-microbial therapy with vancomycin or fidaxomicin remains the standard of care for the treatment of CDI. However, our recognition that gut dysbiosis may be a driving force in the recurrence of CDI has led to a new pathway of discovery and potential new therapeutics that focus on the restoration of microbial health.^{22,26,65}

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