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THE POWER OF THE MICROBIOME:

Can It Be Unlocked to Break the Cycle of Recurrent
Clostridioides difficile Infection?

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THE BROAD CONSORTIUM OF BACTERIA WITHIN THE GUT MICROBIOME FUNCTIONS TO PROMOTE OVERALL HEALTH

The gut microbiome is composed of highly diverse microorganisms living in the human intestinal tract

Considered a distinct and essential organ within the human body, the gut microbiome contains 100 trillion microorganisms and consists of an estimated 500-1000 different species.¹⁻⁴ Common bacterial phyla in the gut^{1,5,6}:

- **Bacteroidetes** ← The most prevalent phyla within the gut microbiome
- **Firmicutes**
- Proteobacteria
- Actinobacteria
- Fusobacteria
- Verrucomicrobia

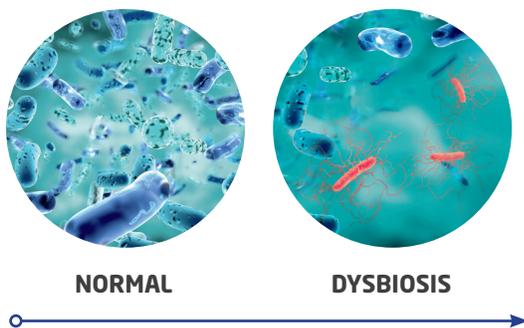
Dysbiosis of the gut microbiota is associated with a variety of diseases—with *Clostridioides difficile* infection (CDI) as the landmark⁷

Gut microbiota aid in digestion, protect against harmful microorganisms, and promote overall health.^{1,8} However, certain factors, such as frequent/uncontrolled use of antibiotic therapy, chemotherapy, and diet, can shift the balance of microbiota, causing dysbiosis.⁹ This disruption of the gut microbiome has been reported in patients with multiple health conditions, including CDI.⁷ *C. difficile* is a gram-positive, spore-forming bacterium that causes disease through the secretion of *Clostridioides* toxins.^{9,10}

Disruption of the gut microbiome leads to an environment suited for the proliferation of *C. difficile*^{11,12}

The gut microbiota generally play a role in colonization resistance by which the native organisms prevent pathogenic microbes from flourishing.^{11,12} Deficiencies in the most prevalent phyla—***Bacteroidetes* and *Firmicutes***—are particularly associated with *C. difficile* infection.^{3,6,13,14}

GRAPHIC 1



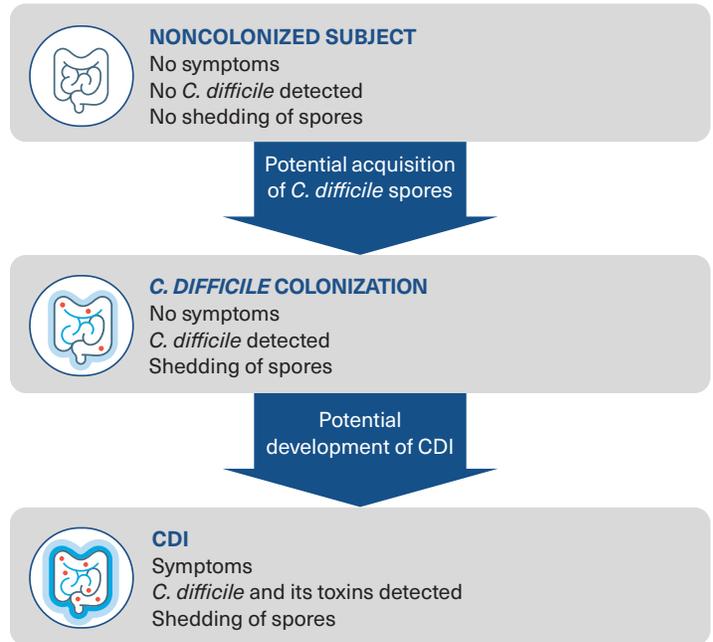
When the relative abundance (diversity and volume) of the microbiome becomes imbalanced, dysbiosis results...

...leading to an intestinal microenvironment susceptible to pathogenic insult from opportunistic bacteria, such as *C. difficile*—capable of causing a wide spectrum of symptoms ranging from mild diarrhea to sepsis.¹¹

GRAPHIC 2

C. difficile colonization vs infection: An important distinction

It is important to distinguish between *C. difficile* colonization and infection for proper diagnosis of CDI.¹⁵ Colonization is common and can promote the spread of *C. difficile* to the environment and to other individuals.^{15,16} It also complicates clinical diagnosis, since the organism can be detected but isn't necessarily causing disease.¹⁵ *C. difficile* colonization is not believed to be a direct precursor for CDI and therefore does not require treatment.¹⁶



To reduce the risk of misdiagnosis, diagnosing CDI starts with clinical symptoms, followed by toxin detection^{15,17}

The diagnosis of CDI is characterized by three or more watery, nonbloody stools per 24-hour period, diarrhea unexplained by an alternate cause, and a positive toxin assay or positive toxigenic culture of *C. difficile*.^{15,17} In addition to prompt diagnosis and treatment, another consideration for patients with CDI is the restoration of the gut microbiome, which is essential for rectifying dysbiosis.^{11,18,19} While this often occurs as a natural process, therapeutic intervention may also be required.

CDI MAY BE THE BEGINNING OF A VICIOUS CYCLE OF RECURRENCE

The incidence of recurrent CDI (rCDI) is rising, with each recurrence increasing the risk of subsequent infection

Data show that after an initial episode of CDI, up to 35% of patients will experience a recurrence.^{20,21} In the United States, recurrences account for approximately 75,000 to 175,000 additional cases of CDI per year.²² Furthermore, up to 60% of patients who have a recurrence will experience another one.²³ This troubling cycle highlights the importance of managing CDI risk factors where possible.

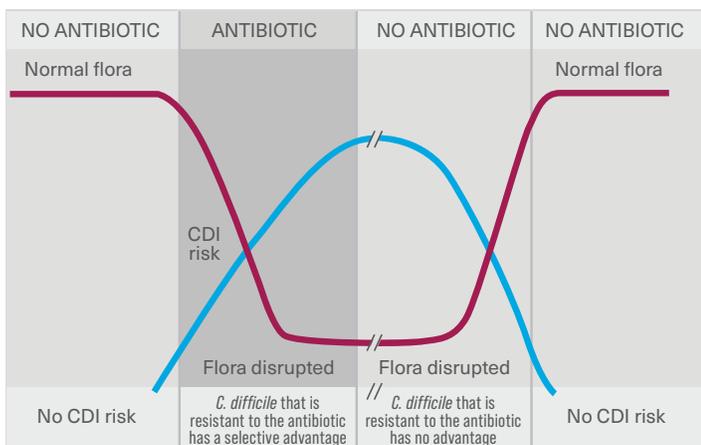
Unrelated post-CDI antimicrobial therapy is associated with increased odds of recurrence²⁴

After CDI treatment, patients receiving antimicrobial therapy for conditions unrelated to CDI have a greater risk of rCDI. In a retrospective review of all of CDI cases at a Veterans Affairs

medical center, patients receiving non-CDI-related antibiotics after CDI treatment were three times more likely to develop rCDI.²⁴

GRAPHIC 3

Effect of antibiotics on normal gut flora and risk of CDI¹⁰



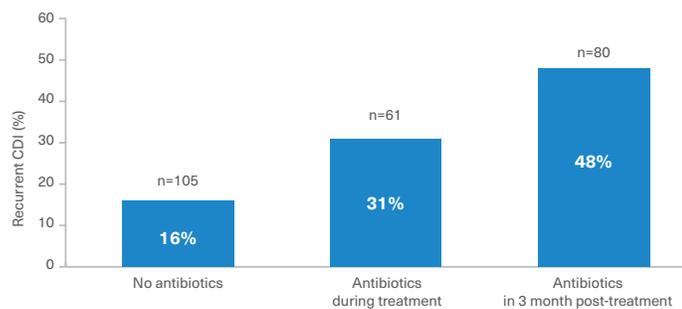
- Risk of CDI remains elevated for up to 3 months following completion of antibiotic therapy²⁵
- The data to support the use of probiotics to restore microbial balance in patients taking antibiotics are inconclusive²⁶

Exposure to antibiotics is a critical modifiable risk factor for CDI²⁷

The risk of CDI increases during antibiotic therapy. Symptoms may occur in the setting of antibiotic use, or up to one month afterward.¹⁷ Most cases occur within two weeks of antibiotic treatment.²⁸ In particular, antibiotic exposure during hospitalization is an important risk factor.²⁹

GRAPHIC 4

rCDI according to post-CDI antimicrobial exposure in the preceding 90 days^{24a}



^aRetrospective review of all CDI cases at a Veterans Affairs medical center from 2004-2006.

Although antibiotic therapy is the current standard of care for CDI, it does not address the underlying dysbiosis associated with high rates of rCDI.^{3,27,29} The restoration of a healthy gut microbiome is increasingly accepted as a promising treatment option, but available options are limited,^{11,18,19} creating an opportunity for therapeutic advances in the management of rCDI.

CDI: AN URGENT PUBLIC HEALTH THREAT

GRAPHIC 5

CDI affects approximately half a million people in the United States annually³⁰

CDI is potentially life-threatening and has been declared an urgent public health threat by the Centers for Disease Control and Prevention.³¹ Currently, it is the most common health care-associated infection in US hospitals.³⁰



~500,000 *C. difficile* infections/year in the United States³⁰



Leading cause of hospital-related infective diarrhea²⁹



Accounts for 15%-25% of all antibiotic-associated diarrhea episodes³²



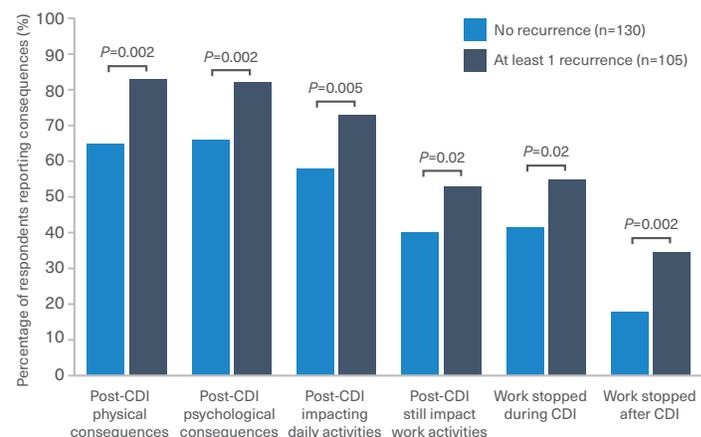
51% of CDI cases are health care-related³³

The impact of CDI and rCDI is significant

The physical and psychological effects of CDI and rCDI have a major impact on patients' quality of life. In an observational, cross-sectional study that surveyed 350 self-reported patients with CDI, a large majority admitted that daily activities were significantly impacted, and that the consequences of CDI were both physical and psychological. Even after the infection, more than half of the respondents noted that post-CDI symptoms remained—approximately 41% believed they would never get rid of them.³⁴

GRAPHIC 6

Reported consequences according to the recurrence status (yes/no), past CDI group³⁴



GRAPHIC 7

rCDI affects hospital quality metrics and reimbursement
In addition, rCDI is associated with a substantial economic burden.

- 

Up to 85% of all patients with rCDI were hospitalized in 12 months³⁵
- 

57% of patients with at least one CDI recurrence experienced ≥2 hospital admissions within 12 months³⁵
- 

Hospitalizations averaged 18 days for patients with rCDI³⁵
- 

84% of patients with rCDI are readmitted³⁶
- 

-\$3K to -\$29K gap exists in reimbursement per patient³⁷
- 

\$131K to \$207K comprised total cost of patient with rCDI³⁸

Transitions-of-care protocols are critical for the effective management of patients with CDI and rCDI

Many patients with CDI may require care across multiple health care settings.³⁹ Coordination of care among patients, caregivers, and members of the clinical team is essential for patients to³⁹:

- Be equipped with knowledge that will enable them to engage in self-care
- Recognize CDI symptoms should they recur
- Continue to receive appropriate treatment following discharge

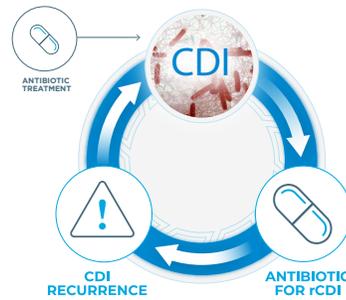
Effectively implemented transitions-of-care processes can reduce the risk for recurrence, hospital readmission, emergency department visits, and complications.³⁹

CURRENT THERAPEUTIC OPTIONS FOR GUT MICROBIOME RESTORATION ARE LIMITED

The aim of microbiome restoration is to repopulate a diverse gut microbiota to treat disease. For recurrent *C. difficile* infection, one historic approach has been fecal microbiota transplant (FMT).

GRAPHIC 8

Data suggest FMT is efficacious for the treatment of recurrent CDI and reestablishes biodiversity in the gut.^{40,41}



However, several limitations are found across clinical studies, diagnosis, and treatment.^{40,41}

There is variability across clinical trials—cure rates were lower in randomized controlled trials than in open-label studies (67.7% vs 82.7%, respectively; $P < .001$)^{40,41}

This inconsistency is due to considerable heterogeneity among randomized controlled trials, with marked differences in study structure, control groups, fecal transplant materials, and outcome assessments.⁴²

Also, most studies assessing the benefits of FMT are retrospective case series or systematic reviews of contrasting sources of microbiota and limited safety data.⁴³⁻⁴⁵

Likewise, the lack of product standardization and administration methods has created a situation where a regulated, safe, and effective product is critically needed.⁴⁶

- In fact, as recently as March 2020, the FDA issued a warning of the potential risk of serious or life-threatening infections following investigational use of an FMT product supplied by a US stool bank company⁴⁷

Patients ENROLLED IN CLINICAL TRIALS may not be a true reflection of patients seen in the real world

Strict inclusion and exclusion criteria in randomized controlled trials lead to inclusion of a small portion of patients from daily clinical practice, limiting generalizability of results to patients seen in clinical practice.⁴¹

CDI testing is inconsistent in clinical practice

There is no gold standard: sensitivity and specificity of current toxin tests for CDI are highly variable. Moreover, in the US, there is no consensus on best diagnostic testing for CDI.³³

- *C. difficile* colonization is common and can complicate diagnosis since its toxins can be detected but aren't necessarily causing disease¹⁵
- Patients can suffer and resolve an active infection, but harbor spores, putting them at risk for another potentially deadly infection¹⁵
- Colonization does not require treatment¹⁶

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

To learn more about the power of the microbiome, visit [medscape.com](https://www.medscape.com).

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A detailed illustration of a microbiome. It features a large, prominent red rod-shaped bacterium with numerous thin, red, hair-like flagella extending from its ends. Surrounding this central bacterium are various other smaller, colorful microorganisms in shades of blue, teal, and black, some appearing as spheres and others as elongated shapes. The background is a light, textured surface, possibly representing a mucosal lining.

WHAT IS THE POWER OF THE MICROBIOME?

...AND CAN IT BE UNLOCKED
TO TREAT DISEASE?

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US-MBIO-2100044

Ferring is committed to exploring the crucial link between the gut microbiome and the threat of recurrent *Clostridioides difficile* infections. With the 2018 acquisition of Rebiotix and several other alliances, Ferring is rapidly advancing its microbiome research, developing novel therapies to address significant unmet needs in deadly and debilitating diseases, and helping people live better lives.

