
Stuart Johnson, MD, DTM&H, FIDSA
Professor of Medicine, Loyola University Chicago Stritch School of Medicine
Staff Physician, Loyola University Medical Center
Maywood, IL

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**The Gut Microbiome and Dysbiosis**

The gut microbiome, the microbial community resident in the human intestinal tract, is increasingly recognized as an influencer of metabolism and immunity and a mediator of resistance to some pathogenic infections. It has been referred to as a distinct and essential organ within the human body, containing an estimated 500 to 1,000 species and 100 trillion organisms encoding 100-fold more unique genes than the human genome.

Disruption of the composition and/or diversity of the gut microbiome is known as dysbiosis (Figure 1). It has been shown that dysbiosis is associated with a range of different gastrointestinal (GI) and non-GI diseases, including neurologic, metabolic, liver, inflammatory, and infectious diseases. Restoration of the gut microbiome is essential to rectify dysbiosis. While this often occurs as a natural process, therapeutic intervention may also be required.

In the normal state, there is a symbiotic relationship between luminal bacteria and our human cells. They communicate and form long-lasting, interactive associations. These associations play a critical role in conservation of mucosal immune function, epithelial barrier integrity, motility, and nutrient absorption. When this relationship between the gut and its healthy flora becomes imbalanced, the normal microbiome is disrupted. As a result, dysbiosis occurs, and the intestinal microenvironment becomes susceptible to pathogenic insult from bacteria like *C. diff*.

**Dysbiosis and *Clostridioides difficile* Infection (CDI)**

Antibiotics have been intimately associated with CDI since the disease was first recognized. The association of pseudomembranous colitis with *Clostridioides difficile* was so compelling that the disease was called ‘clindamycin-associated colitis’ before the etiology was discovered. The effect of antibiotics on the gut microbiome and bile acid metabolism resulting in dysbiosis is now recognized as the major risk factor for CDI.

Dysbiosis can lead to CDI, and a lack of restoration and further disruption from antibiotics, as well as an inability to rid the body of *C. diff* lead to recurrent disease.

In addition, repeated courses of certain antibiotics to manage recurrent episodes of CDI can further erode the residual microbiome. Evidence has shown that although antibiotics such as vancomycin are effective against *C. diff*, they can also disrupt protective flora. Therefore, antibiotics with less disruptive effects may enable a longer recurrence-free period by virtue of their lower flora disrupting effects.

*C. diff* transmission resulting in disease in the healthcare setting is most likely a result of person-to-person spread through the fecal–oral route or, alternatively, direct exposure to the contaminated environment. As a result, the Infectious Diseases Society of America (IDSA) guidelines recommend multiple interventions to help prevent the spread of *C. diff*, including use of contact precautions for symptomatic patients.

**Burden of CDI in the United States**

CDI has become one of the most common healthcare-associated infections in the US, affecting approximately 450,000 people annually. The 30-day mortality rate of CDI ranges from 5% to 15% after an initial episode. In a recent report, patients (n=9) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and CDI had a 44% mortality rate. We can only speculate as to what degree CDI contributed to this overall mortality. One study of patients on Medicare with community-acquired CDI documented a 9% mortality rate during their inpatient stay, associated with an initial episode of CDI (Figure 2).

**The Financial Burden of CDI and Subsequent Recurrences**

The annual economic cost of all CDI in the US, according to 2014 data, is estimated at $5.4 billion, with $4.7 billion of the costs incurred in healthcare settings. In a separate analysis, Rodrigues and colleagues noted that recurrent CDI (rCDI) is estimated to cost $2.8 billion annually. Hospitals may lose between $9K and $13K per readmission.

A recent analysis of the healthcare burden and costs of rCDI in the Medicare population demonstrated that patients ≥65 years old with rCDI had a higher all-cause hospitalization costs, visits to the emergency department (ED), outpatient visits, and longer hospital stays than those without recurrence—all leading to higher overall healthcare costs (Figure 3).

**rCDI**

Sometimes, whether due to age, preexisting conditions, or treatments, the body cannot reestablish a microbial balance. This may start a vicious cycle of CDI and reinfection—impeeding microbiome recovery, exacerbating morbidity, and creating a substantial economic burden. CDI recurs in up to 25% to 35% of cases within 8 weeks after initial CDI diagnosis and 35% of patients ≥65 years experienced ≥1 recurrence within 12 months. Data indicate that recurrence accounts for some 75,000 to 175,000 additional cases of CDI per year in the US. Furthermore, patients who have had a recurrence are at increased risk of additional CDI episodes (Figure 4). Estimates of subsequent recurrences range from 38% to 60% in patients with a first recurrence.

In a 12-month follow-up of 46,571 patients with an index episode of CDI, sepsis occurred in 16.5% of patients with no rCDI, 27.3% with 1 rCDI, 32.1% with 2 rCDI, and 43.3% with ≥3 rCDI episodes. The recent cost of rCDI includes a 27% sepsis rate among 268,762 patients with an index episode of CDI without recurrence and a 35.3% rate among those with one or more recurrence.

**rCDI:** Hospital Readmission and ED Visits

In fact, 84% of patients with rCDI will be readmitted to the hospital within 12 months. A study of patients with...
A multicenter survey of patients currently treated for CDI or with a past history but no current treatment for CDI demonstrated significantly worse health-related quality of life (HRQoL), greater impairment on daily activities, and reduced work productivity, compared with patients who had no history of CDI. In addition, respondents with current CDI reported diminished work productivity, with an absenteeism rate 2.5 times higher than that for respondents with no history of CDI. Productivity loss among those attending work (ie, presenteeism) associated with current CDI is nearly double that of respondents with no CDI history. Risk factors for CDI are largely the same as those for an initial CDI episode, but also include the severity of previous CDI episode(s) and presence of a hypervirulent strain.

Antibiotics: The Standard of Care for CDI Is Also a Potential Risk Factor for Recurrence
Antibiotics have been the mainstay for treatment of CDI and recurrent CDI for decades and are effective for patients with recurrent CDI when given in tapered/pulsed regimens with careful patient follow-up.

A regulatory environment lacking standardization of product and administration methods has created a situation where a regulated, safe, and effective product is critically needed. In fact, as recently as April 2020, the FDA issued a warning of the potential risk of serious or life-threatening infections following investigational use of an FMT product.

The burden and impact of rCDI is significant and escalates with each event, and optimal management should address the cycle of recurrence. Readmission events have a major effect on the patient and healthcare system.

Ultimately, prospective studies are essential to ensure availability of a safe, effective, and standardized microbiota-based therapeutic that can restore the microbiome and break the vicious cycle of rCDI.

About Ferring
Ferring is committed to exploring the crucial link between the gut microbiome and the threat of CDIs. With the 2018 acquisition of Rebiotix, along with 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.

To learn more about the power of the microbiome and how it can be unlocked to treat disease, visit www.powerofmicrobiome.com.
References


The Power of the Microbiome: Unmet Needs in the Management of Clostridioides difficile Infection

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