See full program at:
mdpodium.com/SWG10

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

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

MDpodium

This program is sponsored by Ferring Pharmaceuticals Inc.

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

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.[1] 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.[1-5]

Disruption of the composition and/or diversity of the gut microbiome is known as *dysbiosis* (Figure 1).[6,7] 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.[6,8] Restoration of the gut microbiome is essential to rectify dysbiosis.[9] 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.[7,10-13]

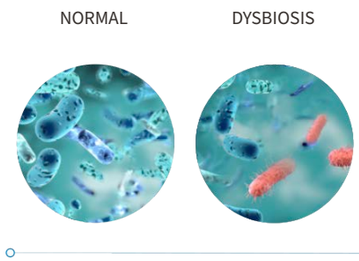
When this relationship between the gut and its healthy flora becomes imbalanced, the normal microbiome is disrupted. As a result, dysbiosis occurs, and the intestinal microenvironment becomes susceptible to pathogenic insult from bacteria like *C. diff*.[7]

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 clindamycin was so compelling that the disease was called 'clindamycin-associated colitis' before the etiology was discovered.[14] 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.[9]

Figure 1. Human Microbiota and Dysbiosis



When the relationship between the gut and its healthy flora becomes imbalanced, dysbiosis results **…leading to an intestinal microenvironment susceptible to pathogenic insult from opportunistic bacteria, such as *Clostridioides difficile* (*C. diff*)—capable of causing a wide spectrum of symptoms ranging from mild diarrhea to sepsis.[7]**

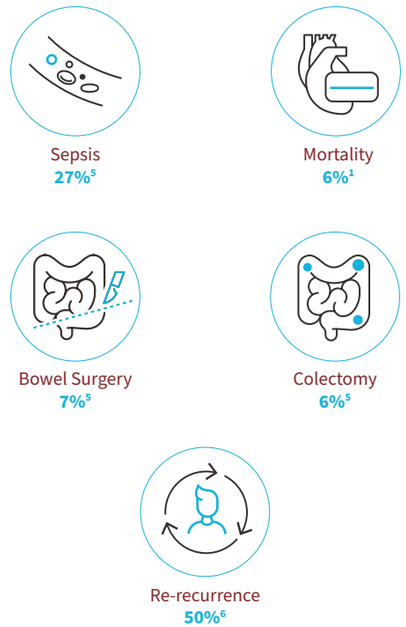
In addition, repeated courses of certain antibiotics to manage recurrent episodes of CDI can further erode the residual microbiome.[7] Evidence has shown that although antibiotics such as vancomycin are effective against *C. diff*, they can also disrupt protective flora.[15] Therefore, antibiotics with 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.[16]

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.[17] The 30-day mortality rate of CDI ranges from 5% to 15% after an initial episode.[17,18] In a recent report, patients (n=9) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and CDI had a 44% mortality rate.[19] 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).[20]

Figure 2. Significant Complications Exist With CDI

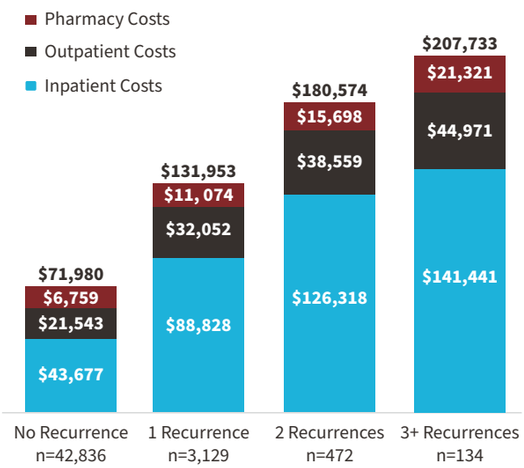


The Financial Burden of CDI and Subsequent Recurrences

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.[23] In a separate analysis, Rodrigues and colleagues noted that recurrent CDI (rCDI) is estimated to cost $2.8 billion annually.[24] Hospitals may lose between $5K and $13K per readmission.[25]

A recent analysis of the healthcare burden and costs of rCDI in the Medicare population demonstrated that patients ≥65 years with rCDI had higher all-cause hospitalizations, 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).[26,27]

Figure 3. Total, All-Cause, Direct Medical Costs During 12-Month Period After Initial CDI[11]



rCDI

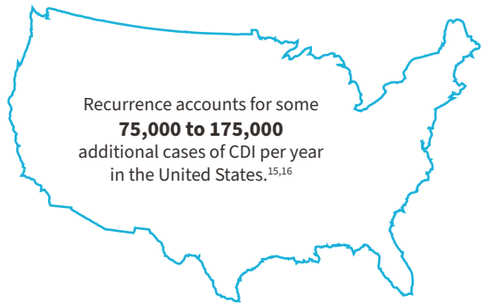
Sometimes, whether due to age, preexisting conditions, or treatments, the body cannot reestablish a microbial balance. This may start a vicious cycle of CDI and reinfection—impeding microbiome recovery, exacerbating morbidity, and creating a substantial economic burden.[28] CDI recurs in up to 25% to 35% of cases within 8 weeks after initial CDI diagnosis[17,29,30] and 35% of patients ≥65 years experienced ≥1 recurrence within 12 months.[26] Data indicate that recurrence accounts for some 75,000 to 175,000 additional cases of CDI per year in the US.[31] Furthermore, patients who have had a recurrence are at increased risk of additional CDI episodes (Figure 4).[31-33] Estimates of subsequent recurrences range from 38% to 60% in patients with a first recurrence.[29,30]

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, 33.1% with 2 rCDI, and 43.3% with ≥3 rCDI episodes.[34] These data are corroborated by Scott and colleagues who found a 27% sepsis rate among 268,762 patients with an index episode of CDI without recurrence and a 35.5% rate among those with one or more recurrence.[21]

rCDI: Hospital Readmission and ED Visits

In fact, 84% of patients with rCDI will be readmitted to the hospital within 12 months.[24] A study of patients with

Figure 4. CDI Recurrence



Furthermore, patients who have had a recurrence are at a higher risk of further CDI.[17]

CDI found that those with ≥3 recurrences had a mean of 5.8 inpatient visits and 4.6 emergency department visits per patient in a 12-month follow-up period.[27]

A retrospective cohort review of adults diagnosed with CDI between 1998 and 2013 in a hospital in Sherbrooke, Québec, Canada showed that 34% of patients with rCDI needed admission, 28% developed severe CDI, and 4% developed a complication.[29]

> **"It's my belief that rehospitalization of patients with CDI, whether for recurrent CDI or other complications, is an important and under-emphasized 'unmet need' in the management of CDI."**
> **--Stuart Johnson, MD, DTM&H, FIDSA**

In a real-world analysis of patients admitted to the hospital for recurrent CDI (430 hospitalizations), patients with fulminant disease had a 30-day CDI-related mortality of 21.3% and colectomy rate of 15.7%, and those with refractory severe or fulminant CDI had a 30-day mortality of 43.2% and colectomy rate of 31.8%.[35]

In addition, patients with CDI are increasingly susceptible to other infections with each recurrent episode, with sepsis occurring in 16.5% to 27.0% of those with no recurrence and in 35.9% to 43.3% of those with ≥3 recurrences within the 12 months after an initial CDI episode.[21,34] New diagnoses of depression has been shown in ~15% of patients on Medicare with CDI.[21]

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.[36]

Risk factors for rCDI 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.[37,38]

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.[39]

> **"Antibiotics and careful follow-up have been the mainstay of my approach to treating patients with recurrent CDI for many years. If an FDA-approved microbiome-based approach with reasonable assurance of safety becomes available, I will evolve my practice for sure."**
> **--Stuart Johnson, MD, DTM&H, FIDSA**

While antibiotics are the standard of care for the treatment of CDI, their use is also a predominant risk factor for recurrence (Figure 5). Numerous studies have explored the rates of CDI recurrence, with reports of rCDI ranging from 20% to 35% following an index episode.[17,29] Antibiotic use has been shown to disrupt the ecology of the human microbiome and is associated with increased risk of deadly infections such as recurrent *C. diff*.[40] Disruption of microbiota increases the risk of *C. diff* by providing a niche for the infection to flourish.[16] Should the intestinal microbiota be disrupted by antibiotics, the effects mays be long lasting, and the risk of *C. diff* may increase during continued therapy. Longer exposure to multiple antibiotics and treatment with multiple antibiotics may increase the risk.[16]

Figure 5. Antibiotics: The Standard of Care for *C. Diff* Infection Is Also a Predominant Risk Factor for Recurrence[17]

While antibiotics are the standard of care for the treatment of CDI, their use is also a predominant risk factor for recurrence. Numerous studies have explored the rates of CDI recurrence, with reports of rCDI ranging from 20% to 35% following an index episode.

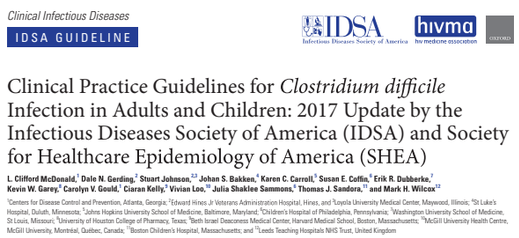
Restoration of the gut microbiome is increasingly viewed as a promising treatment option for recurrent *C. diff* infection.[41]

Current Therapeutic Options for Gut Microbiome Restoration Are Limited

The aim of microbiome restoration is to repopulate a diverse gut microbiota to treat disease. One historic approach for recurrent CDI has been fecal microbiota transplant (FMT).

The IDSA and Society for Healthcare Epidemiology of America (SHEA) issued revised clinical practice guidelines in 2017 (Figure 6). The recommendations include the use of antibiotics (vancomycin, fidaxomicin, metronidazole, and rifaximin) in all instances except for those who have failed antibiotic treatment for a second or subsequent recurrence, in which FMT can be considered.[16]

Figure 6. IDSA/SHEA Clinical Practice Guidelines for *C. Diff*


Clinical Infectious Diseases
IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

However, most studies assessing the benefits of FMT are retrospective case series or systematic reviews of contrasting sources of microbiota and limited safety data.[42-44] FMT products have been administered through varied formulations, dosages, and routes.[41,45]

A regulatory environment lacking standardization of product and administration methods has created a situation where a regulated, safe, and effective product is critically needed.[46] 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.[47,48]

A regulatory environment lacking standardization of product and administration methods has created a situation where a regulated, safe, and effective product is critically needed.[46]

The burden and impact of rCDI is significant and escalates with each event, and optimal management should address the cycle of recurrence.[33] Readmission events have a major effect on the patient and healthcare system.[25]

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 rCDIs. 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

1. Gilbert JA, Blaser MJ, Caporaso JG, et al. Current understanding of the human microbiome. *Nat Med*. 2018;24(4):392-400.
2. Antharam VC, Li EC, Ishmael A, et al. Intestinal dysbiosis and depletion of butyrogenic bacteria in *Clostridium difficile* infection and nosocomial diarrhea. *J Clin Microbiol*. 2013;51:2884-2892.
3. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J*. 2017;474(11):1823-1836.
4. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. *Gut*. 2016;65(2):330-339.
5. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;464(7285):59-65.
6. Weiss GA, Hennet T. Mechanisms and consequences of intestinal dysbiosis. *Cell Mol Life Sci*. 2017;74(16): 2959-2977.
7. Bien J, Palagani V, Bozko P, et al. The intestinal microbiota dysbiosis and *Clostridium difficile* infection: is there a relationship with inflammatory bowel disease? *Ther Adv Gastroenterol*. 2013;6(1):53-68.
8. Wang B, Yao M, Lv L, Ling Z, Li L. The human microbiota in health and disease. *Engineering*. 2017;3(1):71-82.
9. Staley C, Khoruts A, Sadowsky MJ. Contemporary applications of fecal microbiota transplantation to treat intestinal diseases in humans. *Arch Med Res*. 2017;48(8):766-773.
10. Ley R, Hamady M, Lozupone C, et al. Evolution of mammals and their gut microbes. *Science*. 2008;320(5883):1647-1651.
11. Zoetendal E, Rajilic-Stojanovic M, de Vos W. High–throughput diversity and functionality analysis of the gastrointestinal tract microbiota. *Gut*. 2008;57(11):1605-1615.
12. Bäckhed F, Ley R, Sonnenburg J, Peterson D, Gordon J. Host–bacterial mutualism in the human intestine. *Science*. 2005;307(5717):1915-1920.
13. Mazmanian S, Liu C, Tzianabos A, Kasper D. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell*. 2005;122(1):107-118.
14. Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis: a prospective study. *Ann Intern Med.* 1974;81(4):429-433.
15. Abujamel T, Cadnum JL, Jury LA, et al. Defining the vulnerable period for re-establishment of *Clostridium difficile* colonization after treatment of *C. difficile* infection with oral vancomycin or metronidazole. *PLoS One*. 2013;8(10):e76269.
16. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):987-994.
17. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med*. 2015;372(9):825-834.
18. Freeman J, Bauer MP, Baines SD, et al. The changing epidemiology of *Clostridium difficile* infections. *Clin Microbiol Rev*. 2010;23(3):529-549.
19. Sandu A, Tillotson G, Polistico J, et al. *Clostridium difficile* in COVID-19 Patients, Detroit, Michigan, USA, March–April 2020. [published online May 22, 2020]. *Emerg Infect Dis*. 2020;26(9).
20. Collins CE, Ayturk MD, Flahive JM, et al. Epidemiology and outcomes of community-acquired *Clostridium difficile* infections in medicare beneficiaries. *J Am Coll Surg*. 2014;218(6):1141-1147.e1.
21. Scott TA, Unni S, Boules M, et al. Clinical burden of recurrent *Clostridium difficile* infection in the Medicare population. Presented at Digestive Disease Week; May 2-5, 2020; Washington, DC.
22. Riddle DJ, Dubberke ER. *Clostridium difficile* infection in the intensive care unit. *Infect Dis Clin North Am*. 2009;23(3): 727-743.
23. Desai K, Gupta SB, Dubberke ER, et al. Epidemiological and economic burden of *Clostridium difficile* in the United States: estimates from a modeling approach. *BMC Infect Dis*. 2016;16:303.
24. Rodrigues R, Barber GE, Ananthakrishnan AN. A comprehensive study of costs associated with recurrent *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2017;38(2):196-202.
25. Zilberberg MD, Nathanson BH, Marcella S, Hawkshead JJ, Shorr AF. Hospital readmission with *Clostridium difficile* infection as a secondary diagnosis is associated with worsened outcomes and greater revenue loss relative to principal diagnosis: a retrospective cohort study. *Medicine*. 2018;97(36):e12212.
26. Unni S, Scott TA, Boules M, et al. Healthcare burden of costs of recurrent *Clostridium difficile* infection in the Medicare population. Presented at AMCP 2020; April 21-24, 2020; Houston, Texas.
27. Feuerstadt P, Stong L, Dahdal DN, Sacks N, Lang K, Nelson WW. Healthcare resource utilization and direct medical costs associated with index and recurrent Clostridioides difficile infection: a real-world data analysis. *J Med Econ*. 2020;23(6):603-609.
28. Fitzpatrick F, Barbut F. Breaking the cycle of recurrent *Clostridium difficile* infections. *Clin Microbiol Infect*. 2012; 18(suppl 6):2-4.
29. Sheitoyan-Pesant C, Abou Chakra CN, Pépin J, Marcil-Héguy A, Nault V, Valiquette L. Clinical and healthcare burden of multiple recurrences of Clostridium difficile infection. *Clin Infect Dis.* 2016;62(5):574-580.
30. Leong C, Zelenitsky S. Treatment strategies for recurrent *Clostridium difficile* infection. *Can J Hosp Pharm*. 2013; 66(6):361-368.
31. Burton HE, Mitchell SA, Watt M. A systematic literature review of economic evaluations of antibiotic treatments for *Clostridium difficile* infection. *Pharmacoeconomics*. 2017;35(11):1123-1140.
32. Shields K, Araujo-Castillo R V, Theethira TG, Alonso CD, Kelly CP. Recurrent *Clostridium difficile* infection: from colonization to cure. *Anaerobe*. 2015;34:59-73.
33. Vincent Y, Manji A, Gregory-Miller K, Lee C. A review of management of *Clostridium difficile* infection: primary recurrence. *Antibiotics (Basel).* 2015;4(4):411-423.
34. Stong L, Nelson WW, Feuerstadt P, et al. Clinical burden of recurrent *Clostridium difficile* infection: a real-world data analysis. Presented at ACG Annual Scientific Meeting; October 25-30, 2019; San Antonio, Texas.
35. Cheng YW, Phelps E, Nemes S, et al. Fecal microbiota transplant decreases mortality in patients with refractory severe or fulminant *Clostridium difficile* infection. *Clin Gastroenterol Hepatol*. 2020;18(10):2234-2243.
36. Heinrich K, Harnett J, Vietri J, Chambers R, Yu H, Zilberberg M. Impaired quality of life, work, and activities among adults with *Clostridium difficile* infection: a multinational survey. *Dig Dis Sci*. 2018;63(11):2864-2873.
37. Song JH, Kim YS. Recurrent *Clostridium difficile* infection: risk factors, treatment, and prevention. *Gut Liver*. 2019; 13(1):16-24.
38. Zilberberg MD, Reske K, Olsen M, Dubberke YY, Dubberke ER. Risk factors for recurrent *Clostridium difficile* infection (CDI) hospitalization among hospitalized patients with an initial CDI episode: a retrospective cohort study. *BMC Infect Dis*. 2014;14:306.
39. Sirbu BD, Soriano MM, Manzo C, Lum J, Gerding DN, Johnson S. Vancomycin taper and pulse regimen with careful follow-up for patients with recurrent Clostridium difficile infection. *Clin Infect Dis.* 2017;65(8):1396-1399.
40. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med*. 2016;8(1):39.
41. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368(5):407-415.
42. Drekonja D, Reich J, Gezahegn S, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: a systematic review. *Ann Intern Med*. 2015;162(9):630-638.
43. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol*. 2013;108(4):500-508.
44. Rossen NG, MacDonald JK, de Vries EM, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: a systematic review. *World J Gastroenterol*. 2015;21(17):5359-5371.
45. Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing *Clostridium difficile* infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. *Clin Infect Dis*. 2014;58(11):1515-1522.
46. Joseph J, Saha S, Greenberg-Worisek AJ. Fecal microbiota transplantation: an ambiguous translational pathway for a promising treatment. *Clin Transl Sci*. 2019;12(3):206-208.
47. Fecal microbiota for transplantation: safety alert - risk of serious adverse events likely due to transmission of pathogenic organisms. US Food & Drug Administration. March 12, 2020. Updated April 7, 2020. Accessed September 5, 2020. www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission
48. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med.* 2019;381(21):2043-2050.

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

This program is sponsored by Ferring Pharmaceuticals Inc.

US-MBIO-2000010

PeerDirect Publishing
Returned Mail Processing:
PO Box 3347
Champlain NY 12919-3347