April 2022

Robert M. Califf M.D., MACC
Commissioner
Food & Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Dr. Califf,

We, the undersigned organizations, are writing to highlight the urgent and ongoing unmet need for patients suffering with recurrent *Clostridioides Difficile "C. diff"* infections (rCDI), and ask that FDA work with the community of C. diff survivors and caregivers to speed the approval of new treatments and preventatives as well as engage our community to better understand the rCDI patient experience.

As you may know, there are nearly 500,000 C. diff infections in the U.S. annually. Approximately 29,000 Americans infected with C. diff died within thirty days of their initial diagnosis with a higher mortality rate among Americans over the age of 65. Black Americans, while they have slightly lower rates of CDI, have worse outcomes with regard to length of stay, severity of disease, and mortality[1]. Further, one in five patients who are infected with C. diff will experience a recurrence of symptoms within two to eight weeks of their initial diagnosis.

The Peggy Lillis Foundation is working to build greater public awareness of the many challenges facing Americans who have been infected with rCDI including significant physical, emotional, and financial hardships. Current standard of care treatment does not meet the needs of patients with C. diff and worsen rCDI. No new treatment options have been approved for C. diff since 2011. And no first-line treatment has been approved to specifically address the significant unmet need for the approximately 100,000 Americans who battle a recurrent C. diff infection each year. For most of these patients, fecal microbiota transplant (FMT) is the treatment of last resort. FMT has been permitted by FDA through enforcement discretion, though accessibility and coverage has remained an issue. The COVID-19 pandemic has made FMT even more difficult to obtain.

Given the unclear treatment landscape, doctors treating patients who experience rCDI have broad discretion regarding treatment. Patients may receive multiple courses of vancomycin, or fidaxomicin. They may receive a tapered or pulse-tapered antibiotic course. While many doctors will refer patients for FMT following their second recurrence, others will wait for a third or fourth. Meanwhile, patients are left struggling with torturous symptoms, oftentimes including diarrhea 20-30 times per day, nausea, fever, and fatigue. In a 2020 paper published in the *Journal of Patient Reported Outcomes*[2], 70% of rCDI patients described physical pain, weakness, weight loss; 71% reported psychology distress including anxiety, depression and fear of transmitting C.

[1] Argamany et al. BMC Infectious Diseases (2016) 16:454 DOI 10.1186/s12879-016-1788-4
[2] Lurienne et al. Journal of Patient-Reported Outcomes (2020) 4:14 https://doi.org/10.1186/s41687-020-0179-1

diff spores; and 74% noted that rCDI impacted their daily activities from changing their eating habits to self-isolating to limiting travel from their homes for fear of soiling themselves.

The cycle of recurrent C. diff greatly increases patients' likelihood of developing sepsis and even dying. Forty-three percent of patients experiencing a third recurrence end up with sepsis[3]. rCDI also exacts a tremendous financial burden on patients and the healthcare system, with hospital length of stay and cost doubling for patients with rCDI versus a single occurrence[4].

Finally, rCDI has long lasting impacts on patients, 87% of whom fear it returning and 97% of whom fear taking antibiotics. These fears can compromise a person's health, their ability to work, care for themselves and others, and participate in daily activities.

The current state of affairs for rCDI sufferers is bleak, but there is hope. Several new treatments, both narrow spectrum antibiotic and microbiome-based therapies, have completed or are soon to complete Phase III clinical trials. The narrow spectrum antibiotics, which align with CDC and FDA's mandate for antimicrobial stewardship, mostly promise a reduced rate of recurrence while the microbiome therapies interrupt the cycle of recurrence by restoring balance to the patient's gut. While we do not endorse any specific treatments, we do find the number and variety in development to be promising.

We believe that FDA needs to engage patients and caregivers to develop a robust understanding of the rCDI patient's experience. That will enable the agency to fully see the role various medicines could play in preventing primary CDI, reducing recurrence and interrupting recurrence as early as possible. Specifically, we would like the agency to consider:

- **What are the best endpoints for trials of treatments for CDI and rCDI?** The diagnosis of a C. diff infection is a clinical one; more akin to a diagnosis of AIDS than the laboratory detection of the HIV virus. There is no test for or cure. This has led to endpoints for some trials being set as less than a specific number of bowel movements per day. Unfortunately, many rCDI sufferers continue to experience at least some dysregulation of their GI tracts even after FMT[5]. This means they may experience days where they do have more bowel movements. Further, even a healthy person may experience one or two days of diarrhea in a 12-week period due to a variety of reasons, including stress, changes in medication, or eating an unusual food. Having such a narrow and potentially misleading endpoint, may risk keeping good treatments from patients.

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[3] Feuerstadt P, Boules M, Stong L, Dahdal DN, Sacks NC, Lang K, Nelson WW. Clinical complications in patients with primary and recurrent Clostridioides difficile infection: A real-world data analysis. SAGE Open Med. 2021 Jan 14;9:2050312120986733. doi: 10.1177/2050312120986733. PMID: 33505698; PMCID: PMC7812403.

[4] Shah DN, Aitken SL, Barragan LF, Bozorgui S, Goddu S, Navarro ME, Xie Y, DuPont HL, Garey KW. Economic burden of primary compared with recurrent Clostridium difficile infection in hospitalized patients: a prospective cohort study. J Hosp Infect. 2016 Jul;93(3):286-9. doi: 10.1016/j.jhin.2016.04.004. Epub 2016 Apr 20. PMID: 27209056.

[5] Wadhwa A, Al Nahhas MF, Dierkhising RA, et al. High risk of post-infectious irritable bowel syndrome in patients with Clostridium difficile infection. Aliment Pharmacol Ther. 2016;44(6):576-582. doi:10.1111/apt.13737

- **What are the socio-emotional impacts of rCDI? How does that change our perspective of the disease?** As noted above, rCDI is not simply a physical illness. It has at times profound economic, social and psychological impacts. And those impacts compound with each recurrence. We believe these factors must be weighed alongside the clinical data when considering new narrow spectrum and microbiome therapies for C. diff infections, perhaps through a patient-reported outcome scale.

- **What are the societal implications of using broad spectrum antibiotics where narrow spectrum ones are available? How do we "cost" that in a consumer-based healthcare system?** While we understand the agency is largely focused on patient benefit from and the safety of a particular medicine, its decisions from approval to labeling to communications can and have led to unintended societal consequences. Many infectious disease academics and policymakers argue that while our attention is focused on the SARS-COV-2 pandemic, another "silent" pandemic of antimicrobial resistant infections is occurring. One such pathogen is vancomycin-resistant enterococci (VRE). As noted by the Centers for Disease Control and Prevention (CDC), VRE develops in "people who have been previously treated with antibiotics, including vancomycin, for long periods of time", which mirrors the treatment of rCDI patients. Vancomycin is an important drug. Is it best used to combat C. diff when other, narrow spectrum options are available? What is the cost to the 20% of CDI patients who might be spared a recurrence? What is the cost to our society if VRE becomes widespread? This needs to be considered alongside the relative expense of newer antimicrobial and microbiome therapies.

We would welcome the opportunity to discuss these issues with the appropriate members of your team at your earliest convenience. We realize that these products will be entering the approval process shortly and believe that the considerations above should be addressed. Further, we think that the issue of antimicrobial resistance would be an excellent subject for a Patient Driven Drug Development meeting.

A member of our coalition, Peggy Lillis Foundation, is hosting its annual C. diff Advocacy Summit in DC on May 2, 2022. We urge the FDA to send appropriate staff to the meeting as it has at least once before.

We thank you for considering our perspective and look forward to a robust discussion of these issues.

Sincerely,

Alliance for Aging Research
Amputee Coalition
Antibiotic Resistance Action Center
Infectious Disease Society of America
NTM Info & Research
OpenBiome
Partnership to Fight Infectious Disease
Peggy Lillis Foundation
Sepsis Alliance