Peggy Lillis Foundation
Fighting C. diff through Education and Advocacy

## Patient-led Listening Session: Clostridium difficile Infection

**March 10, 2023**

**Objective of Session:**

To provide the FDA staff with a comprehensive understanding of the challenges patients face in managing recurrent *C. diff* infections (rCDI). The epidemiology of rCDI has changed significantly in the past decade, moving from a largely healthcare facility-onset disease to where nearly half of the infections are community-onset. By emphasizing the socio-emotional and economic impacts of rCDI, we aim to illustrate the urgent need for new treatments. We will share the rCDI patient experience of people who have battled rCDI to provide a fuller picture of the unmet medical need with FDA to help inform its approval process.

**Summary of Topics Discussed:**
*Topic: Overview of Recurrent* C. diff *Infections (rCDI)*

*C. diff* infections present clinically as a watery, high-volume diarrhea. This is caused by the toxin-producing bacterium *Clostridioides difficile* (CDI or *C. diff*). The toxin causes the colonic epithelial cell to rapidly turnover causing diarrhea. If this bacterial infection is left unchecked, the colon becomes large and dilated, known as *toxic megacolon* which may lead to sepsis and death. Antibiotics are the primary treatment option for primary *C. diff*. For about 60 percent of patients, this initial treatment will resolve the CDI. However, because antibiotics disrupt the gut microbiome, first line treatment fails up to 40 percent of sufferers leaving them to experience refractory or recurrent *C. diff* infection (rCDI).

*C. diff* is the most common cause of infectious diarrhea in healthcare settings. Risk factors include being over 65 years of age, current or recent hospital admission, and current or recent antibiotic use. Taking antibiotics increases the risk for acquiring *C. diff* by 7-10 times. Since 2000, there has been a massive rise in *C. diff*, mainly due to new strains. These new strains are more virulent, resistant to certain antibiotics, and have developed new characteristics that have enabled them to spread more easily.

Patient experience with rCDI is extremely poor. rCDI often leads to extreme loneliness, isolation, collapse of social life, and fear of recurrence. In the SF-36 Quality of Life study, Primary *C. diff* scores in the 60s and rCDI scores in the 40s. When using the SF-36 Quality of Life scoring tool, scores can range from 0-100 with lower scores indicating a higher level of disability. This is significantly lower than severe multiple sclerosis (MS) or Parkinson's disease, showing how devastating this disease is on quality of life.

The current treatment algorithm for *C. diff* is to treat with antibiotics. The first episode of *C. diff* is treated with either vancomycin or fidaxomicin. rCDI can be treated with antibiotics, bezlotoxumab as an adjunctive therapy, or fecal microbiota transplant (FMT). FMT has been primarily provided over the last 5 years by a non-profit called OpenBiome with FDA enforcement

discretion. It is not covered by insurance and is financially out-of-reach for many patients. Pharmaceutical FMT type treatments are being developed although they still may be cost-prohibitive for many patients.

*Topic: rCDI Unmet Needs*

Patients with *C. diff* have a number of unmet prevention, diagnostic, and treatment needs. Prevention remains difficult as 60% of Americans have never heard of *C. diff*. Peggy Lillis Foundation was founded in 2010 following the death of Peggy Lillis and as a response to this lack of knowledge and awareness surrounding *C. diff*.

The main treatment for *C. diff* is antibiotics, specifically vancomycin or fidaxomicin. Vancomycin is a broad spectrum antibiotic and is more commonly used because it is less expensive. Fidaxomicin is the most recent new antibiotic for the treatment of *C. diff*, approved in 2011. It has a similar cure rate to vancomycin but lower rates of recurrence. It took over a decade for clinical guidelines to recommend it as a first line treatment. Ridinilazole was a promising novel antibiotic but failed to prove superiority to vancomycin during clinical trials, despite a lower recurrence rate.

Microbiome therapy is a relatively new treatment type for *C. diff*. Fecal microbiota transplant, or (FMT), is a process in which gut bacteria derived from fecal matter (stool), from a healthy donor are purified and placed in the gastrointestinal tract of a patient with rCDI. Enforcement discretion for FMT ended and the procedure now requires an investigational new drug (IND) application. The FDA approved REBYOTA™ (fecal microbiota, live-jslm), the first microbiome therapy for the prevention of rCDI in November 2022. SER109 is currently under consideration for approval.

*Since the Unmet Needs of rCDI Patient Listening Session, SER-109, now known as Vowst™, was approved by FDA in April 2023.*

Preventatives for primary *C. diff* infection are sparse. There has been no vaccine approved for preventing *C. diff*. Probiotics may be helpful in maintaining a healthy gut microbiome, but they are regulated as a dietary supplement. A diet that fosters a healthy and robust gut microbiome is the most helpful preventative, but there is low patient education around this topic.

There are many diagnostic tests for *C. diff* including PCR testing and toxin testing. However, the tests are seen as either too sensitive and diagnose people who are colonized. Or they are not sensitive enough and miss people who are experiencing an infection. This leaves many patients to be misdiagnosed, leaving them untreated for weeks or even months.

*Topic: Patient and Caregiver Perspectives*

1. **<u>Impactful Symptoms:</u> CDI patients and caregivers described a variety of physical symptoms that significantly impacted their daily life:**
    a. Severe, watery diarrhea is the primary symptom of *C. diff*. These bouts of diarrhea can occur 10-20 times per day. This near constant diarrhea leads to

additional symptoms such as dehydration and malnutrition. The diarrhea makes it impossible to lead a normal life, attend work, care for children, or even just leave one's home.

b. Severe fatigue occurs as a result of dehydration and malnutrition. It is also extremely difficult to rest when you are constantly in pain and using the toilet.
c. While patients are frequently told that abdominal pain is not a symptom of *C. diff*, all of the patients who spoke experienced severe pain and abdominal cramping.

2. **<u>Impactful Symptoms:</u> CDI patients and caregivers described the mental and emotional impact of their disease.**
    a. All of the patients described a significant level of embarrassment around their disease and symptoms. The unpredictable nature of *C. diff* symptoms made it difficult for patients to leave their home and go places where they may find themselves without immediate access to a bathroom. Diarrhea and incontinence were the symptoms most associated with this.
    b. The emotional toll of not being able to leave their homes, go to work, participate in social activities, engage with family and friends, or care for their children left patients with a severe sense of isolation. This emotional impact extended beyond the patients to affect caregivers, immediate family members, and friends.
    c. Fear was a common symptom mentioned among all patients: fear of being caught in public without immediate access to a bathroom, fear of spreading the infection to their loved ones, and fear of a recurrence of *C. diff*. Fear of recurrence has never ended for many of the patients, who are desperate to avoid future antibiotic treatment.
    *d.* Brain fog was a common symptom among patients. This was described in a variety of ways such as forgetfulness, inability to comprehend, and difficulty with recall.

3. **<u>Outcomes of Treatment</u>: CDI patients and caregivers described a variety of outcomes from varying treatments**
    a. Patients treated with vancomycin described a variety of side effects following treatment. While curing their *C. diff* infection, it often left patients with a depleted gut microbiome, irritable bowel syndrome, and other symptoms.

4. **<u>Patient/Caregiver Concerns:</u> CDI patients and caregivers described a variety of concerns with their disease.**
    a. The patients described a general lack of knowledge about *C. diff* symptoms and treatments from their general practitioners. One patient described a conversation with their provider after they received their diagnosis where they were told to "just Google it." Other patients described conversations where their symptoms were not taken seriously, or they were recommended outdated treatments. All patients found it difficult to find a secondary care provider experienced with *C. diff*, especially those who lived in rural areas.
    b. All patients found it difficult to find a specialist experienced with *C. diff*. Obtaining access to FMT was even more difficult. One patient was instructed to complete the procedure at home on their own. Several patients were instructed to locate

their own donors. Several patients described financial barriers in obtaining treatments.

c. Patients and caregivers felt that the distinction between recurrent infection and a failure of prescribed treatment to cure was not helpful and ultimately did not reflect their experience. Moreover, this was an issue that caused much frustration for patients and caregivers who were continually prescribed the same drug that they felt had never been successful at eliminating the infection.

**Question and Answer Segment**

*Industry Collaboration*

FDA asked if the *C. diff* patient community engages with industry. A patient advocate responded that Peggy Lillis Foundation specifically meets with professional societies and industry coalitions, as well as individual companies.

*Key Needs for Improving Patient Experience*

FDA asked if there was one thing, from the community's perspective, that would be most beneficial to improving the *C. diff* patient experience. Three patient advocates responded: awareness and empathy, in both the provider community and society at large, are key—as well as a more refined discussion around the terms 'recurrent' and 'refractory' infections when it comes to treatment successes and failures. One patient advocate also noted the lack of awareness and support across health systems and society at large for infectious diseases like *C. diff*, especially in comparison to chronic conditions (e.g., cancers, cardiovascular disease, diabetes, etc.).

*Relationship Between Treatment Efficacy and Underlying Conditions*

FDA asked if Peggy Lillis Foundation has any data to suggest a relationship between treatment efficacy and underlying patient conditions. An organization executive and advocate responded that the organization does not collect any data with enough validity to make claims about treatment efficacy. A clinician added that he is not aware of any research to make efficacy claims based on such demographic characteristics.

*Willingness to Receive FMT at First or Second Recurrence*

FDA asked if patients would be amenable to FMT presented as an option after the first or second recurrence. Several patients responded with a resounding yes, and when asked if any objected, the answer was 'no.' Patients also stated that FMT was not discussed nearly enough, from their perspective, and often not until many treatments had failed and much time had passed. Patients, specifically those for whom FMT was a success, also noted their extreme gratitude for the option and how much better they felt after having received it.

*Changes in Availability of FMT*

FDA asked if there had been any change in the availability/discussion of FMT after the agency's first approval of an LBP/FMT therapy. A patient advocate and clinician both responded, saying

that it was too soon after the drug's approval and market launch to determine if physician awareness and patient education had improved/increased.

**FDA Divisions Represented:**

Office of the Commissioner (OC)

- OC/OCPP/PAS – Office of Clinical Policy and Programs/Patient Affairs Staff (organizer)
- OC – Office of the Commissioner
- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OCPP/OPT – Office of Clinical Policy and Programs/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) – 6 offices/divisions

- CBER/OCD – Office of the Center Director
- CBER/OCD/PS – Office of the Center Director/Policy Staff
- CBER/OVRR/DBPAP – Office of Vaccine Research and Review/Division of Bacteria, Parasitic and Allergenic Products
- CBER/OVRR/DBPAP/LMPCI – Office of Vaccine Research and Review/Division of Bacteria, Parasitic and Allergenic Products/Laboratory of Mucosal Pathogens and Cellular Immunology
- CBER/OVRR/DVRPA/CRB1 – Office of Vaccines Research and Review/Division of Vaccines & Related Products Applications/Clinical Review Branch 1
- CBER/OVRR/DVRPA/CRB2 – Office of Vaccines Research and Review/Division of Vaccines & Related Products Applications/Clinical Review Branch 2

Center for Devices and Radiological Health (CDRH) – 8 offices/divisions

- CDRH/OPEQ—Office of Product Evaluation and Quality
- CDRH/OPEQ/OHTI/DHTIA – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology I A
- CDRH/OPEQ/OHTI/DHTIB – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology I B
- CDRH/OPEQ/OHTIII -- Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIA -- Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III A
- CDRH/OPEQ/OHTIII/DHTIIIB -- Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III B
- CDRH/OPEQ/OHTIII/DHTIIIC – Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III C
- CDRH/OPEQ/OHTIV/DHTIVB - Office of Product Evaluation and Quality/Office of Health Technology IV/Division of Health Technology IV B

Center for Drug Evaluation and Research (CDER) – 8 offices/divisions

- CDER/OCD – Office of the Center of the Director
- CDER/OND/ODES/DCOA - Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON—Office of New Drugs/Office of Infectious Disease/Division of Anti-infectives
- CDER/OND/OII/DG – Office of New Drugs/Office of Immunology and Inflammation/Division of Gastroenterology
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/ Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBIII – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics III
- CDER/OTS/OB/DBIV - Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics IV
- CDER/OTS/OCP/DIDP – Office of Translational Sciences/Office of Clinical Pharmacology/Division of Infectious Disease Pharmacology

**Non-FDA Attendees**
Reagan-Udall Foundation for the FDA

**Participants Represented:**
1 clinician (gastroenterologist)
Patient Advocates

- 3 caregivers of *C. diff* patients
- 6 patients/survivors of *C. diff* infections
- 1 patient/survivor of *C. diff* and caregiver of a pediatric *C. diff* patient

**Partner Organization:**
Peggy Lillis Foundation: PLF is a 501(c)(3) nonprofit organization.

**Financial Interest Disclosure:**
Peggy Lillis Foundation receives funding from a variety of sources. None of the funds received were used for the purpose of organizing or participating in this session. None of the participants in this session are receiving compensation for attendance or participation.

**Disclaimer**
Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the Peggy Lillis Foundation's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of C. diff infections, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire C. diff patient

population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.