Quality & Safety Program

BIANNUAL REPORT
2019 | JULY – DECEMBER
Dear Partners,

I am pleased to share OpenBiome’s Biannual Safety and Quality Report for July 2019 through December 2019.

OpenBiome’s mission is to enable safe access to fecal microbiota transplantation (FMT) for treating recurrent Clostridioides difficile infections. As part of this effort, we publish these reports every six months to keep you informed of safety information related to our fecal microbiota preparations. The data aggregated here, which you have shared through Material Tracking Logs and Follow-Up Forms, allow us to maintain the quality of our service and update best practices in patient care. We are grateful for your ongoing partnership in maintaining patient safety.

As of December 31, 2019, we have shipped 53,461 FMT preparations to more than 1,250 healthcare facilities across the country. During this time, there were no reported infections or deaths definitely related to OpenBiome FMT material. Thank you for your participation in our continuous monitoring of safety and adverse events.

One of the most complex and critical aspects of operating stool banks is donor assessment, as there are currently no universal standards or requirements for screening and qualifying human stool donors. To share our experience as the largest universal stool bank in the United States and help advance patient safety, we published a research letter in the New England Journal of Medicine presenting our donor screening process. The publication highlights how our rigorous exclusion criteria, when applied to over 15,000 candidate donors, results in just a 2.5% qualification rate.

Of note, our screening process is designed to exclude candidates with certain antibiotic-resistant pathogens, risk factors associated with acquisition of such microbes, transmissible diseases, and potential microbiome-mediated conditions. We encourage you to review our full Quality and Safety Program at www.openbiome.org/safety and remind you to inform your patients of the potential benefits, risks, and alternative treatments to FMT. Please let us know if you have any questions regarding our Quality and Safety Program or the contents of this report. We are thankful for your continued input and look forward to serving patients alongside you in the years to come.

Sincerely,

Carolyn Edelstein
Executive Director
Dear Clinical Partners,

Thank you for working with us to increase safe access to fecal microbiota transplantation (FMT) for patients with recurrent *Clostridioides difficile*. This past August, because of your care and partnership, we were able to reach a significant milestone: the processing and shipping of our 50,000th FMT preparation.

Additionally, your participation in the Material Tracking Log and Follow-Up Form program has provided invaluable data on patient safety. This information is shared with regulators and helps us maintain the highest level of safety across our network.

From July 2019 through December 2019, we received 13 reports of serious adverse events (SAE) to OpenBiome. 10 were determined to be unrelated to FMT, and 3 were identified as possibly related to FMT. **No SAEs were determined to be definitely related to FMT material.** More detailed information on these cases is located on page 10.

On November 4th, I and several other OpenBiome team members attended an FDA meeting seeking input on the future of FMT regulation. During this hearing, I presented information on the safety and efficacy of OpenBiome material. This real-world data, information provided by practices like yours from across our clinical network, supported our position that patient access to FMT through enforcement discretion should continue as long as there is a lack of available, approved alternatives. I also highlighted the importance of rigorous donor screening, and the need for universal screening and safety standards that are applied to all microbiome-based products.

As the field of FMT and microbiome research continues to mature, I look forward to working with you to continually evaluate and update our stool banking practice. It has been an honor to partner with a community of physicians to maintain the best possible care for patients. Please do not hesitate to reach out to me with any questions or specific issues that you would like to see addressed in future reports. We greatly appreciate your feedback and your continued collaboration.

Dr. Majdi Osman, MD MPH
Clinical Program Directo
From July 1, 2019 through December 31, 2019, 13 adverse events were reported to OpenBiome by members of our clinical network. During this window, OpenBiome shipped a total of 4,967 treatments to clinical partners. Below, we have aggregated patient characteristics from reported adverse events and lessons learned from the subsequent investigations.

**Patient characteristics in suspected adverse events.** Four of the patients involved in adverse events were reported as having severe or fulminant CDI (30.8%, n=4). The most common treatment modalities were liquid preparations delivered via colonoscopy (84.6%, n=11) and capsules (15.4%, n=2). There were three deaths (23.0%, n=3) during the reporting period, all of which were determined to be unrelated to FMT. Reported adverse events are graded according to severity by NIH grading criteria (Figure 1).

**Adverse Event (AE) NIH Relatedness.** Based on information gathered through in-depth investigations with reporting partners, all cases were classified according to NIH Relatedness definitions. Ten of the reported AEs (76.9%) were determined to be not related to the FMT material and the remaining three AEs (23.1%) were identified as possibly related to the FMT material. **No reported AEs were determined to be definitely related to FMT material.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mild)</td>
<td>Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
</tr>
<tr>
<td>2 (Moderate)</td>
<td>Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
</tr>
<tr>
<td>3 (Severe)</td>
<td>Symptoms causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>4 (Pot. Life Threat)</td>
<td>Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, or persistent disability</td>
</tr>
<tr>
<td>5 (Death)</td>
<td>Death</td>
</tr>
</tbody>
</table>

1. Disease Adverse Event Grading Scale, National Institutes of Health
   - Grade 1. Mild: Symptoms causing no or minimal interference with usual social & functional activities
   - Grade 2. Moderate: Symptoms causing greater than minimal interference with usual social & functional activities
   - Grade 3. Severe: Symptoms causing inability to perform usual social & functional activities
   - Grade 4. Potentially Life Threatening: Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, or persistent disability
   - Grade 5. Death

2. Definitions of Relatedness, National Institutes of Health
   - Not Related: The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.
   - Possibly Related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
   - Definitely Related: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject’s clinical state.
KEY LESSON LEARNED
Considerations for Immunocompromised Patients

A limited but growing body of evidence supports the use of fecal transplants in patients who are immunocompromised. However, there are no randomized controlled trials exploring the use of FMT in severely immunocompromised patients. In this context, this review aims to highlight some key considerations for use of FMT in this patient population, as well as emphasize specific aspects for informed consent and monitoring of potential adverse events.

Characteristics of Patient Population

In general, patients who are immunocompromised—including those living with HIV infections, solid organ and hematopoietic stem cell transplants, undergoing myeloablative or immune therapy (such as chemotherapy), those with primary immunodeficiency syndromes, and individuals receiving immunosuppressant or immunomodulatory medications—comprise a high-risk population for Clostridioides difficile infection (CDI), and have increased rates of recurrence and CDI-associated complications. These patients are at greater risk of CDI-associated complications because of both general risk factors—such as more frequent antibiotic use and prolonged hospitalization—as well as disease-specific changes affecting the gut microbiome or immune response.

Clinical Data and Considerations

Limited data—mainly from retrospective analyses of single cohorts—suggest that FMT may be a suitable treatment for immunocompromised patients, and that immunocompromised and immunocompetent populations respond similarly to FMT for recurrent CDI.

Although these studies observed few adverse events, a recent case report describes serious adverse events directly related to FMT material that was transplanted into two immunocompromised patients. In this case, two patients treated with FMT material from a hospital-based stool bank that did not screen for multi-drug resistant organisms became infected with antibiotic-resistant E. coli transmitted through donor stool resulting in one death. These adverse events highlight the importance of rigorous donor screening, thorough patient follow up, and monitoring of adverse events.
Clinical Data and Considerations (continued):

Certain immunodeficiency states may confer greater risk of infection to fecal microbiota transplantation. For instance, individuals who have disruption to mucosal immunity, such as IgA deficiency, may be more likely to develop diarrheagenic disease. Similarly, patients who have breakdown of the gut mucosal barrier may have greater risk of bacterial translocation and subsequent bacteremia and sepsis. There is limited data available about the safety of FMT in specific immune deficiency states, so a high degree of caution should always be exercised.

Before administering FMT, which is classified by the FDA as an investigational drug, doctors are required to obtain informed consent from patients. This process includes a discussion reviewing the known risks associated with FMT (including risk of infectious disease transmission and potential for developing a microbiome-mediated disease) and whether alternative treatments are more suitable. A template for obtaining informed consent can be requested at info@openbiome.org. OpenBiome representatives are also available to answer questions by email at info@openbiome.org or phone (617-575-2201) from 9AM-5PM, Monday through Friday.

References
Common, mild adverse reactions after FMT delivery:

Mild, self-limiting symptoms may occur after FMT and should be clearly discussed with patients during informed consent. Based on the peer-reviewed literature, potential expected non-serious adverse reactions that can be anticipated after FMT are:

- Transient diarrhea
- Transient abdominal cramps or discomfort
- Nausea
- Constipation
- Excess flatulence

In addition to the above, mild fever, bloating, vomiting, and borborygmus have been reported to occur after FMT. Expected mild adverse reactions do not require reporting to OpenBiome.

Managing treatment failure:

CDI recurrence or non-response have been known to occur in approximately 10-20% of patients post-FMT. In events where CDI recurrence or non-response is suspected (e.g. development of or continued diarrhea, abdominal pain, etc.), a full work-up should be conducted to rule out other infectious etiologies. Non-infectious etiologies should also be considered (e.g. post-infectious IBS). Cases where CDI recurrence or non-response has been confirmed do not require reporting to OpenBiome.

Serious adverse events that warrant reporting:

While there have not been any definitely related serious adverse events attributable to FMT material, should a serious adverse event (SAE) occur within a reasonable timeframe post-FMT where relatedness of the FMT material cannot be definitively ruled out, these SAEs should be reported to OpenBiome. Examples of such SAEs include:

- Post-FMT new onset of infectious diarrhea
- Post-FMT new onset of sepsis
- Allergy or anaphylaxis

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There is a theoretical risk of developing disease that may be related to donor gut microbiota. These include obesity, metabolic syndrome, cardiovascular disease, autoimmune conditions, allergic/atopic disorders, neurologic disorders, psychiatric conditions and malignancy. People with these and similar conditions are excluded from donating stool to OpenBiome. However, if an FMT recipient appears to be experiencing a new onset of any of these diseases and FMT is suspected, this should be reported.

In addition to the above, any SAEs as defined by the FDA (21 CFR 312.32(c)(1)(i)) where there is uncertainty in the relationship between the event and the FMT, must be reported to OpenBiome.

Adverse events should be reported to OpenBiome through the online portal (www.openbiome.org/adverse-events). Clinicians may contact the Safety Team directly (617-575-2201 ext. 9) to discuss whether an SAE requires reporting.
SUMMARY OF ADVERSE EVENTS
JULY-DECEMBER 2019

All adverse events reported to OpenBiome that were possibly related to FMT and investigated between July 1, 2019 and December 31, 2019 are summarized in the table below. Clinicians who are interested in learning more about specific adverse events reported to OpenBiome are welcome to request a copy of the detailed case narratives by contacting safety@openbiome.org.

<table>
<thead>
<tr>
<th>Summary</th>
<th>CDI type</th>
<th>Severity (NIH grade)</th>
<th>Relatedness (NIH definition)</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteropathogenic <em>E. coli</em></td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 1. Mild</td>
<td>Possibly related</td>
<td>39F with combined IgA &amp; IgG deficiency</td>
</tr>
<tr>
<td>Fever</td>
<td>Recurrent CDI, Mild</td>
<td>Grade 1. Mild</td>
<td>Possibly related</td>
<td>13M with inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td>Enteropathogenic <em>E. coli</em></td>
<td>Recurrent CDI, Unknown Severity</td>
<td>Grade 3. Severe</td>
<td>Possibly related</td>
<td>65M with known comorbidities</td>
</tr>
</tbody>
</table>