THE MICROBIOME IN CLINICAL TRIALS: OPPORTUNITIES & CHALLENGES

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UNDERSTANDING THE HUMAN MICROBIOME

The human microbiome is elaborate and dynamic. Composed of microbial cells in direct contact with the human body, the microbiome covers us inside and out like a cloud and plays a role in radically different areas of health, such as nutrition, early childhood development, hygiene, infectious diseases, and chronic health conditions.

Until just recently only about 20% of the bacteria in our body had ever been cultured, partly because there was really no pressing need to identify everything. Most of the time we live in harmony or symbiosis with these microbes, so medicine and microbiology had historically focused on those organisms that were identified to trigger disease and have the potential to quickly kill us. It is now better understood that other organisms, including some that have previously been thought to be innocent bystanders, have a more subtle way of interacting with us. New concepts on what is normal and what is not are advancing our understanding of microbes as not only part of a human but important in influencing our health and behaviors as humans. In turn, these microbes are influenced by our health and behavior, leading to a very complicated and interactive ecosystem. Based on its size, organization, and specialized functions, many now consider the microbiome as a distinct organ that carries out activities essential to our well-being.

Altering the microbiome to treat or decrease the risk of disease may be done more easily than finding therapeutics that rewrite the human genes that have been linked to a certain disease. As some have said, the microbiome is the only "organ" that can be replaced without surgery. Consequently, multiple clinical studies are underway that are testing single commensals, mixtures of defined species and subspecies, and cocktails of microbiota-derived molecules targeting specific microbial species or pathways that are enriched or absent in the disease state in an effort to treat or prevent a variety of diseases.

CLOSTRIDIUM DIFFICILE AND THE MICROBIOME

To illustrate the concept of how the microbiome may be altered to treat disease, we will use the example of Clostridium difficile and the gut microbiota. C. difficile may be present naturally in the gut in up to 5% of the population. It can be transmitted both person-to-person and person-to-fomite-to-person. Pathogenesis occurs when normal flora is destroyed or altered through a number of mechanisms. C. difficile can then overpopulate the gut leading to a cascade of events that can culminate in diarrhea, intestinal perforation, and even death. Treatment involves infection control procedures and removing the offending agent with anti-C. difficile antibiotics. These antibiotics are not always ideal as there are off-target effects and the rate of recurrence is oftentimes unacceptably high. Consequently, fecal microbiota transplant (FMT) has emerged as a potential therapeutic option through its ability to re-establish microbial diversity with beneficial gut flora.

While current research indicates that FMT results in restoration of gut microbial diversity and elimination of C. difficile infection (CDI), how this cures CDI (i.e. the mechanism of action) is not yet fully understood. The data show that the fecal microbiota community is more dynamic within patients without recurrence and decreases in diversity with subsequent episodes of recurrence. Recurrence has been reported to occur in 20% of patients after the initial infection, 40% after one recurrence, and >60% after a second recurrence with a stepwise and progressive loss of fecal microbial diversity.

Beyond just simply competing for intestinal real estate, researchers believe FMT works by blocking the essential functions of C. difficile. These functions include sporulation, spore germination, vegetative growth, adhesion to epithelial cells, and toxin production. This then restores the ecological balance and diversity of the gut microbiome, particularly in terms of the balanced production of bile acids and short chain fatty acids as well as subsequent changes in the innate and adaptive immune system of the patient.

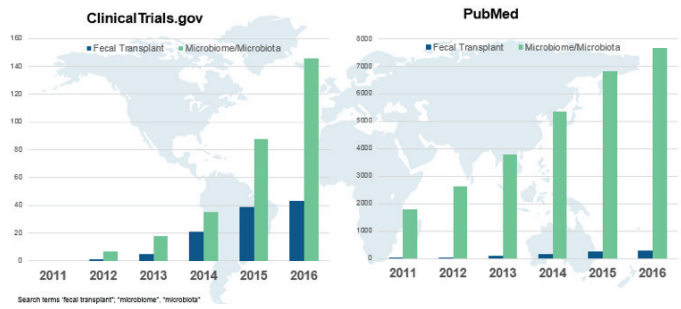
For severe cases of recurrent diarrhea caused by CDI, fecal transplant is efficacious in approximately 90% of affected patients. This model has served as the prime proof of principle that healthy gut microbiota can reproducibly correct a severe and specific microbial dysbiosis. While recurrent CDI is an obvious entry point to FMT, and microbiome research as a whole, it's hardly the end indication for most companies looking to develop products that impact the microbiome.

STUDYING THE HUMAN MICROBIOME

Interest in the microbiome has surged in the past five years. The demonstration that fecal transplants are working in patients with C. difficile infection, and more recently in inflammatory bowel disease (IBD), lends credence to the hypothesis that restoration of a healthy microbiome can influence disease outcomes. These successes of the investigations into the microbiome have ushered in a new area of opportunity for drug development in personalized medicine. While investors, companies, and the media are currently infatuated with the microbiome, the science has not always lived up to the expectations. However, the scientific foundation is gradually being constructed and many new studies are now forthcoming.

Figure 1 shows the number of clinical trials and publications for fecal transplant and microbiome between 2011 and 2016 as reported on ClinicalTrials.gov and PubMed. Notice that the overall number of trials reported on ClinicalTrials.gov with "fecal transplant", "microbiome", or "microbiota" as a keyword has increased from 0 in 2011 to close to 200 in 2016. It is likely that these numbers are underreported due to the possibility of additional clinical trials running exclusively outside of the United States not being reported on the site. Likewise, the number of publications on PubMed where "fecal transplant", "microbiome", or "microbiota" are keywords has increased over 400% between 2011 and 2016.

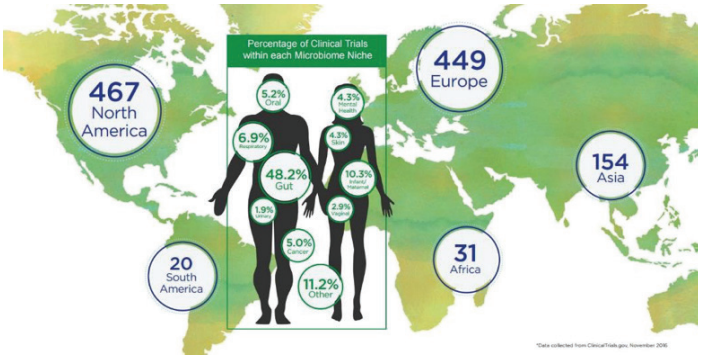
Figure 1: Interest in the Microbiome/Microbiota



Sources: ClinicaTrials.gov and PubMed.com

Figure 2 shows both the geographic distribution and anatomical focus of microbiome clinical trials. Most clinical trials still involve the gut, with the 'Other' category in second place and probiotic work in infant/maternal health in third. Despite the growing interest in the microbiome only a relatively small number of these trials and publications represent randomized, controlled trials. Even with this, the findings support the view that specific regimens targeting the human microbiome may hold potential for enhancing public health.

Figure 2: Microbiome Clinical Trials per Region

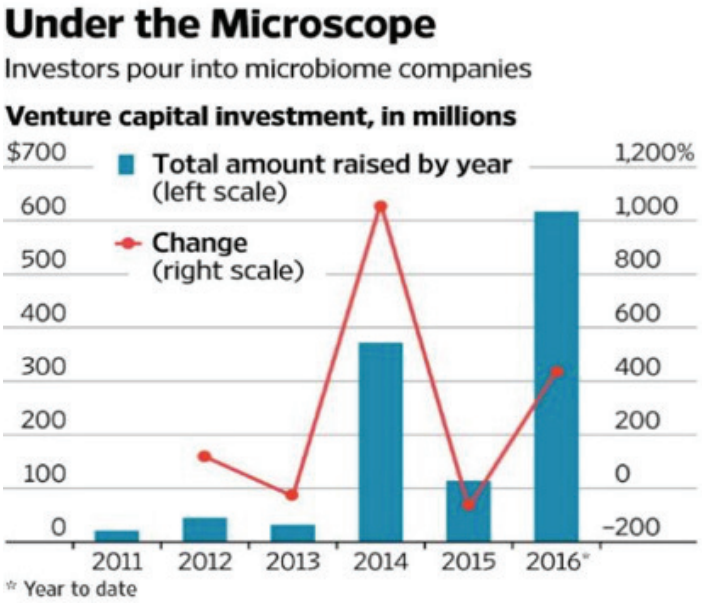


Source: Human Microbiome Congress 2017 – Data collected from Clinicaltrials.gov, November 2016

It is not only researchers who have demonstrated an increased interest in the microbiome. Investors are evaluating a host of businesses and potential partnerships ranging in size from small start-ups to global pharmaceutical companies. Multiple companies with therapeutics in clinical trials are in a race to market, many with their lead candidate targeting C. difficile, and with a wide variety of other applications in the queue. Venture-capital (VC) interest is mirroring this with VC investment in microbiome companies growing at a faster rate than overall VC funding.

Figure 3 shows the Wall Street Journal in 2016 reported that nearly $617 million was raised for microbiome companies in 2016. This is more than all of the microbiome VC investment from 2011 through 2015 combined, an increase of nearly 460%. These investments continue to grow due to excitement in findings from current studies with more than $1 billion total invested in microbiome start-ups currently.

Figure 3: Microbiome Study Investment

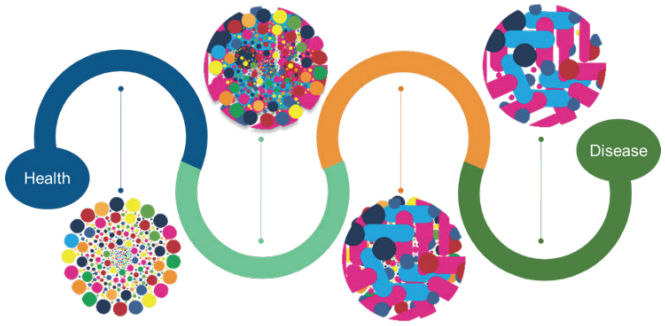


Source: Wall Street Journal. September 2016

STATES OF HEALTH AND THE MICROBIOME

There are unique issues that arise in how the microbiome changes and may be manipulated as a healthy state moves toward a disease state. Just as the states of health may not be binary and the establishment of disease may be quite flexible, so too may the states of the microbiome be quite flexible as one moves on the spectrum from health to disease as shown in Figure 4. However, this concept leads to additional questions. How ecologically stable is the microbiome during a patient's progression from health to disease? Where are the tipping points between microbes being symbiotic, benign, and characteristic of health to being more characteristic of disease? How exactly is the microbiome influenced by the state of health that we are currently in and how cooperative is it to change once we have started along this route?

Figure 4: Flexible State of Health



There have been many parallels drawn to the human microbiome based on lessons learned from other ecosystems. Within these ecosystems balance is secured by interactions, both competitive and cooperative, among members of the community. This balance then determines the overall health of the ecosystem. Similar to other ecological communities, a return to health and stability (in a microbiome perspective) is time sensitive and dynamic.

An early and dramatic intervention that restores the pre-disease ecological interactions may be more effective in returning the disease state back to a healthy state. Late in the course of disease, the same therapy may prove ineffective due to the fact that damage may have already been done or the resilience needed to heal may have been lost. In the case of a later intervention, whether the disease persists or not, is more determined by other non-intervention/non-controlled system factors, such as the immune system, other coinciding treatments, the environment, or the disease state itself. Additionally, the chance that unpredictable or negative effects (such as Adverse Events (AEs) or Serious Adverse Events (SAEs) in the context of a clinical trial) may occur through unsuspected networks may increase if the intervention is delivered later on down the path.

So, in fact, the pathway from health to disease and, hopefully, back to health may be quite circuitous with some of the most important outcomes, whether positive or negative, realized in the long-term. This brings in some long-term endpoints that would need to be considered in chronic diseases and long-term safety issues that are not yet completely realized. However, these are issues that may be expected with the premise that the microbiome is a determinant of chronic health and disease. The concept of promoting ecological balance (which is what many prebiotics, probiotics, and microbiome transplants claim to do) is not part of the disease paradigm that has governed regulation of health-related products in the United States for years.

Under the current disease paradigm, humans are healthy unless they have an illness that must be diagnosed and treated. This paradigm and the definitions that flow from it consequently bring interventions that impact the host microbiome under regulations that govern other drugs. A healthy, stable microbiome is one that balances the cooperative and competing networks of microbes. In disease states, this balance is off. The microbiota become compositionally unstable and less diverse compared to "normal". The trigger for this disruption may be either an endogenous or exogenous signal influencing the microbiota. These include changes in the host immune response, diurnal rhythms, the way in which a baby was born, diet, infections, antibiotics, and other drugs. When these triggers occur, opportunistic microbes are permitted to colonize and proliferate, with the spectrum of disease varying between asymptomatic carriage to a severe, complicated infection. To return to health the balance between the microbes needs to be restored.

A REGULATORY LOOK: PROBIOTICS OR DRUGS?

It is important to differentiate between a drug and a dietary supplement as we look at developing or expanding existing regulatory framework around these compounds. For FMT, while fecal matter is the raw material for the pills, the final product consists only of the spores necessary to treat the infection, which will have been extracted and purified. Like probiotic supplements, fecal transplant is a gut bacteria product. Unlike the supplements, by the time it's available it will have gone through the FDA wringer. There are other products under investigation that interface with the microbiome differently and bring in separate challenges and regulations.

Probiotics are microorganisms, either active microbes or in some cases their spores, which are introduced into the body for beneficial qualities. To help illustrate when a probiotic might be considered a dietary supplement versus a drug we will use the example of brewer's yeast.

Brewer's yeast, which is specifically Saccharomyces boulardii, has been advertised as a probiotic that has either real or perceived benefits for humans. From a regulatory perspective is it a drug or biologic, in the pharmaceutical sense, or is it truly a dietary supplement? The simple answer is in how it's being described or advertised and its intended use. If it is to be used by the general public, without reference to prevention, treatment, or disease mitigation, then a case could be made that the product is a dietary supplement. In this situation, a sponsor of a brewer's yeast product intended for the US market would likely only need to provide premarket notification following the advertising rules of the Federal Trade Commission (FTC) and the Food and Drug Administration (FDA). However, if one were to define this probiotic in the context of a prevention or treatment, such as for recurrent CDI, then premarket safety, efficacy, and approval would most certainly be required.

With this in mind, then, we need to look at how to appropriately evaluate safety and efficacy for a given product or preparation in a specific and well-defined patient population. Meaning, we need to start discussing ways at approaching regulatory and clinically meaningful endpoints. It is important to take into consideration that just because something is clinically interesting or meaningful does not necessarily mean it meets regulatory requirements. What may be appropriate for a single patient may not be able to be applied across a specific population. It is important to appropriately define endpoints as biomarkers, both novel and exploratory or recognized for a particular disease state, surrogate endpoints, or clinical outcomes. There needs to be a robust definition of the patient population and the endpoint if we're going to evaluate the probiotic properly.

TARGETING POPULATIONS AND INDICATIONS

Many of the studies where human commensals, microbes living in the human gut, and their products have been introduced to induce a health change have been performed under highly controlled conditions during defined stages of pathogenesis. Some of these have been in well-controlled animal experiments whereby extrapolations to humans have to be viewed with some caution. In addition, the relatively few controlled clinical trials in certain indications with various interventions affecting the microbiome have shown somewhat inconsistent effects and have been received with skepticism and caution.

Despite the fact that there's significant individual variation in the microbial collection and the fact that the microbial collection in each person is unique, the functional capacity of the gut microbiota is relatively consistent across healthy people. This core set of functions include pathways involved in metabolism, fermentation, methano-genesis, oxidative phosphorylation, and microbe cell wall biosynthesis. Consequently, it is possible to define an unhealthy (dysbiotic) group, but the dysbiotic population needs to be well-defined where the disruption of the microbiome has been directly linked to a disease, whereby not just a weak correlation but causality is established or strongly inferred, such as the example of C. difficile and CDI.

Primary endpoints of microbiome studies will be related to established and accepted clinical disease endpoints and will likely follow similar prior regulatory approval pathways for similar indications. Conversely, monitoring of effects on the microbiome for dose-response or as a secondary endpoint raises the question of development of biomarkers, the complexity and importance of appropriate sampling, assays, and measurements, and the need for data analysis plans.

These needs must be considered when identifying the most appropriate population. Patients will need to comply with clinic visits to permit monitoring the microbiome over time. In many indications, especially chronic diseases, the population needs to also be considered for its ability to provide long term follow-up.

CHALLENGES WITH MICROBIOME STUDIES

While there are many novel insights from the evaluation of how the human microbiome influences health, the study of the gut microbiome in human health and disease remains loaded with challenges. We have already discussed that the microbiome is a complex and dynamic state affected by multiple influences. Not only do these influences increase the complexity of running a global study where the product under study is exposed to between subject variability, there are also major individual patient variabilities that affect the microbiome that must be considered. Changes in lifestyle, such as diet, age, socioeconomic status, and medication use, can lead to data reproducibility issues and statistically underpowered studies, where treatment groups run the risk of being significantly phenotypically, etiologically, and microbiologically different.

The diversity of the microbiome across individuals presents challenges for what defines a healthy or unhealthy (dysbiotic) microbiome and how to select subjects who would be most likely to benefit from a microbial intervention. It is likely impossible to exactly measure restoration of the microbiome for each individual given that their entry into the study, which is often at a disease state, will likely be the first opportunity that their microbiome has been studied. This highlights the need for clear and clinically meaningful human health endpoints that follow regulatory guidance.

Further challenges include sample collection and storage to enable clinical trial enrollment and to successfully achieve the endpoints. Differences in assays and measurements over time can add to the complexity of establishing both correlation and causality. Part of the issue is a lack of statistically powered longitudinal, interventional studies involving study participants with well-defined disease or at-risk conditions in order to explore causality.

Despite evidence linking dysbiosis of the gut microbiome with disease manifestations at sites distant from the gut, most studies have not explored mechanisms outside the affected site, nor have they considered the effect of the microbiome and its varied products on the multitude of molecular pathways potentially involved. Without rigorous testing and randomized clinical trials many will question whether imbalances of gut microbial communities are a consequence or a cause of chronic disease. What is cause and what is effect clearly has implications from an efficacy and a safety standpoint and understanding what correlates and what is causative has proven to be no simple task due to the volume of the background noise.

ADDRESSING THE NOISE

If there was ever an observational area subject to confounding, the microbiome is it! Clearly, a well-defined population is critical for a successful microbiome study. With as much heterogeneity, or noise, as is in the system, initial clinical trials that are looking to achieve regulatory approval will need to closely weigh the risk/benefit ratio for specific patient groups. Performing a risk assessment of how each of these subgroups may significantly add to the enrollment of the study and eventually benefit from the treatment, contributing to the overall efficacy, needs to be weighed against the safety signal that they may generate. Obviously, in a large, randomized clinical trial the risks that each of these groups generates, such as the number of AEs, SAEs, or laboratory abnormalities, will in theory be balanced between treatment groups such that there is no particular signal that is attributable to any single group or arm. However, for studies in earlier development or with smaller samples sizes, the risk for potential confounding, due to unequal distribution of a particular at-risk group to either arm, increases.

For example, in a relatively small phase 2 study looking at FMT for patients with recurrent CDI, patients who are at-risk for bacterial translocation through the gut (such as neutropenic or immunocompromised patients or patients with severe GI mucosal damage) may be excluded. However, if you are developing a product to decrease the risk of relapse of disease after allogeneic hematopoietic-cell transplantation, you are already including patients at-risk for graft vs host disease (GVHD), but you may consider excluding patients with IBD or put restrictions on timing of prior radiation or chemotherapy. Likewise, the potential for bacterial overgrowth in certain populations, such as diabetics with autonomic neuropathy and gastroparesis, may be a significant criterion to consider for exclusion in a recurrent CDI trial. This exclusion would then need to be thoughtfully managed to ensure balance between the arms of the trial looking at modulators of the microbiome in pre-diabetics or patients with type-2 diabetes.

Finally, as safety is the other part of the risk-benefit assessment, studies need to be designed to ensure that short-term safety monitoring (AEs/SAEs, safety labs, etc.) are properly collected and that the study is clearly designed to collect long-term safety data that continue to be a concern of the regulators. For instance, to address the potential for weight gain or loss after FMT, which has been reported anecdotally and corroborated with animal studies co-housing lean and obese mice, studies need to consider how weight and BMI will be captured and reported across multiple months. Deciding on whether to use a pre-illness historical weight or the weight from a calibrated scale on day 1 of a clinical trial as baseline is important. Additional decisions include how to follow this measurement overtime, do patients return to the clinic to use the same calibrated scale or is a patient reported outcome reasonable, and is the patient clothed? Finally, how the data is analyzed and a change in BMI determined must be decided on. These are just examples of some of the details that need to be considered.

Beyond restriction of the patient population, patient stratification will likely be required in early trials to ensure efficacy signals are not masked within a population that may or may not have a microbial community structure amenable to the microbial intervention, and to help balance the potential safety signals that may be seen. The issues (or noise) in studies evaluating the microbiome are compounded by a lack of stratification based on inherent characteristics of the disease or concomitant drug treatment. While stratification is important, there is a threshold where it no longer adds value. As in the case with many smaller early phase studies, if there are too many strata in relation to the target sample size, then some of the strata will be empty or sparse. This can be taken to the extreme such that each stratum consists of only one patient each, which in effect would yield similar results as simple randomization with no stratification at all. Studies should strategically keep the number of strata to a minimum for good effect. Revisiting the recurrent CDI studies example, successfully achieving the endpoint may be heavily influenced by, and at risk from, the number of prior recurrences, age, the infection ribotype, and a host of concomitant medications and procedures that are likely to accompany the management of this population. Clearly, there are more strata present than could be incorporated into even a large study.

There are, however, comorbidity indices and scoring systems that combine some of these factors and may be a consideration for stratification and randomization or, at a minimum, considered for collection of data for analysis. Examples include Horn's Index, Zar Score, and ATLAS. In Horn's Index, which was used in Merck with Bezlotuxumab, a qualified clinician rates the severity of the underlying disease, giving the patient a score of 1 (single mild illness), 2 (more severe illness but uncomplicated recovery expected), 3 (major illness or complications or multiple conditions requiring treatment) or 4 (catastrophic illness that may lead to death). A modified version of Horn's Index found that age and extremely severe underlying disease were strong independent risk factors for C. difficile diarrhea. Subsequently, a high Horn's Index score was shown to be a major risk factor for both primary and recurrent CDI (Kyne et al, 2002).

SAFETY AND POTENTIAL PATHOGENS

Clearly, many gaps, such as understanding what is "normal" and what is not, identifying all the dynamic influences that affect the microbiome, and connecting the inventory of various microbiome states to host functional states of health, still exist in the field and are potential challenges for regulatory development. Additionally, in the realm of biologics, such as fecal transplants, product safety is a particular concern.

There are still suspicions that transplantation carries the potential risk of transferring to recipients organisms that could become pathogenic based on certain host factors, or could transmit antimicrobial resistance to otherwise susceptible organisms. This has led to pre-clinical and clinical initiatives that are underway that are testing single commensals, mixtures of defined species and subspecies, and cocktails of microbiota-derived molecules targeting specific microbial species or pathways that are enriched in the disease state in an effort to treat or prevent the disorder under study.

Historically, there is reason for this suspicion. Jim was the name of a former milk wagon horse, who was used to produce serum containing diphtheria antitoxin. After having provided antitoxin for some time, Jim showed signs that he had actually contracted tetanus. Ultimately, there were at least 13 children whose deaths from tetanus were traced back to Jim's contaminated serum. It is likely that these contaminated sera could have easily been discovered if they had been tested prior to use. Ultimately, this incident, and a similar one involving contaminated smallpox vaccine, led to the passage of the Biologics Control Act of 1902, which established the Center for Biologics Evaluation and Research and later in 1906 the formation of the US Food and Drug Administration, or FDA.

Additionally, disease transmission by transplantation has long been recognized, including cases of rabies, Chagas, HIV, tuberculosis (TB), and lymphocytic choriomeningitis virus (LCMV). Furthermore, there are real, albeit unrealized, risks that transplanting fecal microbiota can spread infectious diseases such as HIV or hepatitis, as was seen in the 1970s and 1980s with thousands of people with hemophilia being infected with HIV from contaminated blood products. Even in the field of probiotics there are cases of seemingly healthy microbes turning rogue. In this case of translocation, microbes in our gut can cross the lining of the intestine and enter our bloodstream, causing a debilitating immune response and potentially sepsis. It's fascinating that the same microbes that we are talking about that can be beneficial allies may also be dangerous threats, with the difference in risk and benefit being only a few millimeters. As discussed this has been of particular concern in immunocompromised patients, but the available data have not supported this to be of a true concern.

While the most common of adverse events are transient, such as abdominal discomfort and bloating, many regulators are concerned that there is still relatively little long-term safety data. For example, there are theoretical hazards that FMT could change the microbiome to make people more susceptible to chronic conditions such as obesity or autoimmune disorders. FMT for CDI has been linked to relapses in IBD and to the development of several other serious diseases. There has also been a reported case of the development of obesity following FMT from an overweight donor, but further study is needed to truly understand the impacts of FMT beyond the GI tract.

BALANCING THE RISKS

Part of the risks of FMT can be mitigated by mandating rigorous screening of the donor. A thorough characterization of the investigational product may be one of the most important steps to helping to differentiate the product's role in a potential safety event of bacteremia from an unrelated infection to which the patient was at risk for non-FMT reasons. Additionally, sponsors need to ensure that the study sites are properly chosen and investigators understand the significance of organisms that may be cultured from various sites, especially urinary and respiratory samples, where colonization needs to be differentiated from infection. While the evidence supporting the role of any particular organism in a pathogenic process may seem obvious to those leading studies, it is not always as clear to all investigators and site coordinators in global studies. It becomes even less obvious in fields and indications beyond infectious diseases, such as diabetes, metabolic syndromes, or cancer.

Clearly rules are necessary and regulations need to be followed, but overly restrictive rules might encourage people to seek treatment outside the medical establishment. Instructions for do-it-yourself fecal transplants are available online; individuals have posted videos on YouTube with tens of thousands of views and written books advocating at-home procedures using stool from acquaintances or family members. There are even active blogs seeking advice about using their pets as donors. Indeed, the regulators understand the importance of ensuring a reasonable pathway is available for sponsors looking to develop products that address the microbiome and in our experience are eager to work with those developing products in the field. The concept of promoting balance, which is what many prebiotics, probiotics, and microbiome transplants claim to do, is not part of the disease paradigm that has governed regulation of health-related products in this country for years, but it's beginning to change.

REGULATIONS AND FDA ENFORCEMENT POLICIES

Since 2013, FMT has been recognized as a potentially viable treatment option for patients with recurrent CDI. It is important, however, that the boundaries are pushed and expanded in a safe and reasonably defined manner. From a regulatory perspective, the FDA has recognized the need to put out some guidance related to FMT that impacts both individual practitioners treating a single patient and potential sponsors of therapeutic FMT preparations or products. Between 2013 and 2016, several formal and informal guidance pieces have been made available. In March 2016, the FDA issued an enforcement policy regarding the need for investigational new drugs (INDs) for FMT (FDA, 2016). Specifically, this policy is to assure that patients with CDI not responding to standard therapies may have access to this treatment, while addressing and controlling the risks that centralized manufacturing in stool banks presents to subjects.

The enforcement discretion is evaluated based on three primary criteria:

1. The licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative for the use of FMT products. The consent should include, at a minimum, a statement that the use of FMT products to treat C. difficile is investigational and there was a discussion of the potential risks.
2. The FMT product is not obtained from a stool bank.
3. The stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product to treat his or her patient.

Furthermore, during the period of enforcement discretion, the FDA will continue to work with sponsors who intend to submit INDs for use of FMT to treat CDI not responding to standard therapies. As a final point, the FDA intends for this to be an interim policy, while the agency develops a comprehensive approach for the study and use of FMT products under IND.

CONCLUSION

Microbiome-based research presents a multitude of opportunities and challenges. It is an extremely exciting field with multiple successes. In order to increase the number of potentially successful clinical development projects in the microbiome space, it will be important to recognize standard drug development principles and global drug or biologic development requirements.

Understanding what normal flora is, what the confounders are, and what are clinically meaningful endpoints is an important step in developing a successful clinical development program for products affecting the microbiome. Additionally, a full evaluation of manufacturing processes and materials are critical in realizing the potential for microbiome platforms. Microbiome research is complicated as biologics-based manufacturing requirements greatly exceed those for the manufacture of dietary supplements. Intrinsic and extrinsic host parameters as well as dose and dosing regiments will have an impact on the safety and efficacy of a compound or preparation. Whether or not one size fits all in respect to regulatory concerns, manufacturing issues, dosing to balance pathogenicity and potency, and clinical trial design need to be adequately addressed in development programs. Ultimately, these questions will need to be answered by reaching agreement on risk versus benefit for our patients. We have not hit an apex of standard with microbiome clinical research to date, but due to the excitement from patients, practitioners, sponsors and regulatory agencies, success seems to be within view.

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