

The Giving Microbiome: Sharing the Health

Milena Pitashny MD D(ABMM)

Molecular Microbiology Diagnostic Laboratory, Barzilai Medical Center, Ashkelon, Israel

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With the discovery of penicillin and the further development of new antimicrobial agents over the last century, the medical community has proudly changed the course of previously fatal infectious diseases. Unfortunately, parallel to this progress we have also seen the advent of multiresistant organisms, the emergence of opportunistic infections, and the dysbiosis due to the blind killing of components now known as the “healthy microbiome.”

The Human Microbiome, defined as the community of microorganisms associated with the human body, comprises not only bacteria but also viruses, bacteriophages, fungi, protozoa and archaea [1]. A thriving microbiome is critical to human health, being the first encounter with pathogens in the mucosa, having direct interaction with the immune system, and participating actively in diverse metabolic processes. A disrupted microbiome is now recognized as associated with several conditions and diseases. Among all microbiomes, the gut microbiome has the highest density on planet earth and is notably influenced by diet, geography, gender, and disease states, among others [1].

For decades, pseudomembranous colitis has been classically linked to the use of antibiotics, but the precise nature of the cause was unclear. It is now known that the partial depletion of a healthy microbiome, or a state of dysbiosis consequent to antimicrobial exposure, offers *Clostridium difficile* (CD) an opportunity for growth and ultimately overgrowth [2]. Patients

with CD infection (CDI) receive further antibiotic treatment for the amelioration of symptoms, which ultimately leads to the development of resistant and hypervirulent strains of CD [2].

Fecal microbiota transplantation (FMT) is the transfer of a sample from an entire microbiome from the intestinal content of a healthy individual to a sick one, for therapeutic purposes. It is an ancient technique used by other cultures and since the last century has been used in the home for the treatment of certain conditions [3]. FMT and other forms of microbiota transplant (also known as bacteriotherapy) is not only limited to disrupted intestinal functions but has also been proposed as beneficial in diverse medical areas, such as metabolic disorders, neuropsychiatric conditions, autoimmune diseases, allergic disorders, and cancer [4].

Most significantly, the most remarkable therapeutic area of success for FMT is recurrent refractory CDI (RCDI). In 2013, a group in the Netherlands published the first randomized controlled study [5], followed by many others worldwide, that showed outstanding results: after performing FMT in patients with RCDI, a cure rate of about 90% was achieved. FMT leads to undetectable levels of CD by reconstituting the affected microbiome to a similar composition as that of a healthy donor [6].

In the current issue of *IMAJ* [7], Cohen and team summarize the success rates and side effects of FMT in 22 patients with RCDI who underwent the procedure in two tertiary Israeli medical centers (Tel Aviv Sourasky Medical Center in Tel Aviv and Shaare Zedek Medical Center in Jerusalem). The FMT protocol was different in each center, including the selection and recruitment of donors, preparation of fecal matter, and administration route of the filtrate. The researchers aimed to show, by

comparing patients' response to treatment and side effects, which approach showed superior results. Although demographically and in terms of severity, patients were not statistically different between the centers, 40% of patients at Shaare Zedek had severe disease as compared to 17% of the Sourasky patients. This may have been reflected in the choice of the treatment modality: 70% were treated as inpatients in the former while 60% were treated as outpatients in the latter. The different approaches of each center, i.e., mostly colonoscopy at Sourasky versus upper gastrointestinal (GI) delivery at Shaare Zedek, together with the different severity trends between groups suggest that the comparison may not accurately reflect whether one strategy is superior to the other. Both research groups showed response rates at day 7 of follow-up and symptom-free rates at 2 months of follow-up, which are consistent with the literature (~90%) [8].

According to the results of this study [7], patients responded significantly earlier in the group that received mostly FMT through colonoscopy (Sourasky group) – up to 3 days vs. 5 days with upper GI administration at Shaare Zedek. The authors propose that the earlier response in the colonoscopy modality is based partly on the avoidance of the gastric hostile environment and better viability of the implant when instilled distally, although the less severe condition of patients in the Sourasky group may explain an earlier response as well. Accepted routes of administration are either duodenoscopy or nasoduodenal/nasojejunal tube in the upper GI approach, or through instillation via colonoscopy or retention enema in the lower GI approach [8]. The choice of administration route may be determined upfront as a standard procedure by a GI center performing the transplant routinely, i.e., colonoscopy, which appears to be the

case in the Sourasky group. The decision on the administration route may, on the other hand, depend on the patient's status: for outpatients an enema is probably the preferred route (less invasive), whereas for the patient who is bedridden or in a severe state and who already has a nasogastric or nasojejunal tube the upper GI route may be preferred. The latter was the main approach adopted by Shaare Zedek, which coincides with the higher severity in this group.

In general, short-term side effects of FMT are considered to be minor, especially when compared to the unpleasant CDI symptoms [8]. Nevertheless, in this article one patient showed a severe complication when the filtrate was administered via gastroscopy: aspiration of the stool filtrate with a fatal outcome [7]. Fatalities secondary to FMT have seldom been reported, and ultimately it is difficult to determine whether they are related to the procedure itself or to the severity of the disease [8]. To date no clinical studies have demonstrated the safety of FMT in the long-term [8]. Questions regarding the development of obesity by changing the composition of the gut microbiome, or the onset of autoimmune diseases by challenging the recipient's previously healthy immune system are gaping black holes in the existing literature.

Before the standardization of blood transfusions, the transference of blood was practiced directly from one individual to the other [9]. Today, no one would consider this an accepted practice. Fecal transplant or bacteriotherapy as a modern equivalent needs to be standardized as well. With the goal of helping patients, physicians have been using stool treatment in their improvised benches at their clinics using a kitchen blender. Medical centers must maintain careful regulation for processing and storing stool specimens. Donors must be screened for potential infectious pathogens at recognized and accredited laboratories, and additional types of screening implemented with the better understanding of the role of the human microbiome in physiological states. Questions such as the sexual behavior and diet of donors ought to be relevant to assure safety and good quality of the donated

material. A cross-match strategy might even be required in the future for certain conditions. The quality of the final product must be assured by professional laboratory teams taking into account the viability of the microorganisms, the optimal conditions for processing and storing, together with the strict observation of biosafety rules for the protection of both the laboratory staff and the recipient. As in many other fields of medicine, the oversight of a procedure (in this case FMT) is under dispute between several medical branches: the gastroenterologists who often recruit, treat and follow the patients, the microbiologists who have the facilities to screen and prepare the filtrate, and the infectious diseases specialists, who have to face the decision whether to treat with antibiotics and potentially destroy the patients' own healthy microbiome vs. treating, paradoxically, with the microbiome itself. Infectious diseases specialists are also challenged with the potential development of resistant strains, and, in the case of CDI, are responsible for reducing the spread of spores by infectious control measures. Hence, an interdisciplinary approach is crucial to take this field to another level. Metagenomic analysis of the composition of microbial communities in the healthy vs. the sick will only reach significance when approached with a multidisciplinary team prism.

What was once the future of bacteriotherapy is now very much with us. An encapsulated version of filtered fecal frozen material has already been tried [10], making the delivery an easy procedure. It won't be long before a map characteristic of each individual's microbiome will be digitally stored as a fingerprint, and the matching of "compatible" fingerprints will allow the replenishment of such amazing resources of metabolic processes that is the microbiome and without which we cannot survive. A new trend in laboratory medicine is the establishment of biorepositories or biobanks, centralized factories that aim to ensure the preservation of human products, mainly for research purposes, that are obtained with informed consent and recollected in optimal conditions in order

to assure the quality of the specimens. Stool banks are already being filled worldwide and are awaiting approval by regulatory entities to use banked stool for conditions other than CDI [11].

Following this trend, the storage of microbiomes from different parts of the body as a matching donor for certain conditions, not necessarily diseases, may hypothetically provide the solution for many medical problems without the use of medication. Utopically, the wealth of being healthy will become something we can share with others.

Correspondence

Dr. M. Pitashny

Head, Molecular Microbiology Diagnostic Laboratory, Barzilai Medical Center, Ashkelon 78306, Israel
email: milenapi@gmail.com

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