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Ethical aspects of Fecal Microbiota Transplantation (FMT)

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Abstract. – The importance of human microbiota in preserving human organism healthy is nowadays well acknowledged. The alteration of the microbiota can be the consequence of a persistent use of antibiotics or immunosuppressive medications or abdominal irradiation or surgery, wrong diet, or can be caused by surgery or anatomical condition. These alterations can cause many infections and diseases that today can be treated with Fecal Microbiota Transplantation (FMT), also called Bacteriotherapy, that is the administration of a fecal solution from a donor into the intestinal tract of a recipient.

Although to date, FMT appears to be safe and without serious adverse effects, there are some ethical issues that are worthy to be investigated.

The aim of this article is to highlight these issues in order to give some notes for a better implementation of this particular clinical practice.

Key Words:
Fecal microbiota transplantation, Innovative therapeutic procedure, Ethics, Donor.

Introduction

The importance of human microbiota (formerly called gut or intestinal flora) in preserving human organism healthy is nowadays well acknowledged. There is enough evidence that a balanced composition of intestinal microbiota represents the basis of the wellbeing of human organism[1-3]. Scientific literature shows that our organism contains over 100 trillion of microbiota: some of them are essential for the human organism, others are harmful[4]. Moreover, microbiota can be subjected to many alterations that may change health condition. Anatomical or post-surgery or irradiation conditions may influence, in a pathological way, microbiota too. Microbiota can also easily be disrupted by use (especially a persistent use) of antibiotics, or for dietary intake, or malnutrition or advanced age[5].

Microbiota is located in the nose, mouth, skin, guts and genitals. Its composition varies according to the different sites where it lies but is dominated by bacteria (over 10^{14}, about 1.5 kg, more than 1000 species, with a predominance of anaerobes), and other microbes, such as fungi, parasites, viruses and archaea, many of which have not yet been cultured[6].

There is also consensus on the maternal influence on its composition according to which way babies are born – babies born vaginally compared to babies delivered by caesarian section[7] – playing an important role for the development of the immune system after birth. Studies have underlined that in the first case (babies born vaginally), the sterile intestinal tract of neonates is immediately colonized by maternal microbiota, while in the second one (by caesarian section) microbiota is mostly colonized by the environment.

Furthermore, microbioma, better defined as "the ecological community of commensal, symbiotic, and pathogenic microorganism that literally share our body space"[8] has been recognized to be different depending on each generation (genetic profile).

In order to deepen these features, in 2007 the American National Institute of Health (NIH) Roadmap for Biomedical research funded the Human Microbiome Project (HMP), to better understand how these unique microbial ecosystems

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that live in and on our bodies contribute to human health and disease. HMP includes projects on ethical, legal and social implications (ELSI) arisen from this field[9]. As stated within the Project description the goals were: (1) "To take advantage of new high-throughput technologies to characterize the human microbiome more fully by studying samples from multiple body sites from each of at least 250 "normal" volunteers; (2) To determine whether there are associations between changes in the microbiome and health/disease by studying several different medical conditions; and (3) To provide both a standardized data resource and new technological approaches to enable such studies to be undertaken broadly in the scientific community"[9]. A key goal of the HMP has been to characterize the human microbiome in healthy adults and develop a reference set of microbial genome sequences (the "Healthy Cohort Study")[10,11].

As noted by Slashinski et al[12] in citing Juengst and Huss[13], "Human microbiome research is considered part of a new phase of genomic research, aptly referred to as "*translational genomic research*" aimed to benefit both individual and societal health".

Gut microbiota can interact with the intestinal mucosa and influence intestinal permeability and is important for the absorption, distribution, metabolism, and excretion of nutrients[14] and can trigger (auto) immunity, playing indeed a paramount role in the systemic immunity not only of the local immune system[15,16].

The complex symbiotic relationship between gut microbiota and their host causes physiologic functions to be disrupted when microbial composition is altered. In fact, a variety of disorders and diseases, such as enteric infections[17], functional diseases of the gastrointestinal tract[18], inflammatory bowel disease (IBD)[19], colorectal cancer[20], liver diseases[21,22], and also non-gastrointestinal diseases such as obesity and metabolic syndrome[23,24], allergic diseases[25] and autism[26], are associated with alterations of gut microbiota.

Therefore manipulating the microbiota could (in some cases it is already possible) improve or prevent some pathologic conditions. Several interventions targeting the intestinal microbiota have been used to maintain and improve host health. These include antibiotics, probiotics, prebiotics, but the restoration of healthy gut microbiota by fecal microbiota transplantation (FMT) constitutes the most promising effective therapeutic option.

Fecal Microbiota transplantation

The characteristics above mentioned of microbiota have pointed out to the possibility of employing microbiota for transplantation. To be more specific, Fecal Microbiota Transplantation (FMT), also known as bacteriotherapy, represents a therapeutic alternative for patients suffering from some gastrointestinal conditions. At the beginning FMT was used exclusively for patients affected from recurrent *Clostridium difficile* infection (RCDI) not responsive to standard therapies and it proved to be effective in eradicating these bacteria[27,28]. More recently, other studies[29,1] have underlined the broadened application of this clinical treatment, which is proved to be effective against other infections and diseases, such as inflammatory bowel disease (IBD), irritable bowel syndrome, obesity and many others.

Administration of a fecal microbiota solution is performed via colonscopy, nasogastric tube and retention enema[30], or more recently, via oral capsules[31]. It seems safe, up to now, or with few transient adverse effects, such as fever or diarrhea, but the efficacy and safety profile of this intervention have not yet been fully evaluated in controlled clinical trials. Further limitations to the delivery of FMT can be mentioned: the lack of a consensus on the best protocol; the time stretch between stool's donation and stool's screening; safety concerns about the possibility to acquire diseases after stool infusion[32].

Main Ethical Issues

The ethical, Legal, and Social Issues (ELSI) of Human Microbiome Research

Since the beginning of the HMP it is has been recognized that human microbiome research, like other areas of genomics, raises ELSI issues that deserve careful considerations[33]. In fact, based on their experience of participation in the development and initiation of the HMP, Mc Guire et al[34] identified five major research ethics issues associated with conducting human microbiome research: informed consent and respect for autonomy; informing subjects of research-related results; data sharing and protection of privacy; invasiveness of sampling and minimizing risk; and diversity of subjects and justice. Subsequently, in an another work, to better understand the relevance of these issues to individuals involved in human microbiome research, McGuire et al[35] interviewed scientists and NIH employees involved in the HMP and in-

dividuals who were recruited to participate in the Healthy Cohort Study. These authors reported findings related to three major ELSI issues: informed consent, data sharing, and return of results. These data demonstrate that investigators and recruits were similarly sensitive to these three key ethical issues but the concerns they raised were largely not HMP-specific: complexity and length of informed consent document (ICD), the request to maximize the accessibility and utility of HMP data whit a sharing plan protecting individual privacy (some subjects in this study indicated they would like to be informed of new evidence of identifiably so they can re-evaluate their willingness to consent to public data release).

The Ethical Issues Related To FMT

It is important to emphasize that the FMT is an innovative therapeutic procedure certainly interesting and promising, but still in the test phase. Currently, in fact, at clinicaltrials.gov (access on March 13, 2015) 59 clinical trials have have registered to test FMT, including 21 for *Clostridium difficile* infection and 26 for bowel diseases, especially inflammatory. So, from the ethical point of view it is necessary to consider several aspects of this innovative therapeutic intervention that could be used in many areas of the clinic.

Before going into details, it could be interesting to pay attention to the fact that, initially, the Federal Drug Administration (FDA) classified human feces used for medical purpose as drugs. In other words, the procedure of fecal transplantation was considered as an experimental drug[36], therefore requiring drug-regulation policy. Only in a second time the opinion on this topic has changed and human feces have been classified as a human tissue, allowing physicians to perform fecal microbiota transplantation more easily and to deliver this new treatment to more patients[32].

Ethical aspects concerning FMT can be summarized as follows: (1) Donors' selection; (2) Safety concerns and *ratio* risk-benefit; (3) Informed consent.

Donors' Selection

Fecal microbiota transplantation presents unique challenges in recruiting healthy donors. Donor selection for FMT is more simpler than for other organs, because the immunologic matching between donor and recipient is not required but it is important to carefully screen and select donors to avoid causing a new disease in the recipient.

In March 2014, FDA announced a draft guidance for industry entitled "Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies"[37]. These guidelines aim to provide directions not only about the clinical aspect of stool transplantation, but, and even more, about the information to be given the patients undergoing such therapy. Particularly, the document underlines the importance to obtain adequate informed consent from the patient or his/her legally representative; it also envisages the stool to be obtained from a donor known to either the patient or the licensed health care provider treating the patient. Furthermore, it provides donor and stool to be 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/her patient.

The main reason to choose a "known" donor (family member, partner), instead of a "universal" donor, is to reduce the so-called "yuke factor", that is the repugnance of the patient toward receiving a fecal infusion and for the higher rate of resolution of the pathology to be treated[29,30]. But this choice is preferred also for the likelihood of low risk of transmitting an occult pathogen with the stool sample or other factors of susceptibility to disease[38]. In fact, some complications of bacteriotherapy are due to the transmission of pathogens contained in stool, such as bacteria, viruses, fungi and parasites. For these reasons, donor's stools are screened for ova and parasites (Giardia, Helicobacter and others), and donor's blood is screened for Hepatitis (A, B and C) and for HIV. Donors are excluded as such also if they have received antibiotics recently. Potential donors should be questioned about their travel history, sexual behaviour, previous operations, blood transfusions, and other factors that increase the risk of transmissible disease[39,40]. Donors are also screened for a family history of autoimmune and metabolic diseases as well as malignancies (in first- and second- degree family members). Once a donor is selected, blood and fecal samples must screened for pathogens[41].

Safety Concerns and Ratio Risk Benefit

To date, FMT appears to be safe. Most patients treated with FMT experience diarrhea on the day of infusion, and small percentage report belching and/or abdominal cramping or constipation[42,43].

Adverse events were reported for some patients (3 of 317): upper gastrointestinal tract bleeding, peritonitis, or enteritis[30,38]. In another case report[44], nasoduodenal FMT for Crohn's disease resulted in transient adverse effects, including fever and abdominal tenderness in 3 of 4 patients. However, these effects disappeared for all patients over the following 2 days.

Although the use of microbiota and specifically fecal microbiota transplantation have already been reported as generally safe in many scientific researches, more studies need to be done. Long-term follow up programs are in fact not yet available. To date, not so much can be said, for example, on a potential association between FMT and infection, inflammation, or gastrointestinal malignancies. So far, from the ethical standpoint, while we are waiting for results of clinical trials to better evaluate safety, we should use protocol with severe criteria for the screen of pathogens.

As regards the potential benefits, to date, most clinical experience has focused on the use of FMT in patients with relapsing or occasionally *Clostridium difficile* infection. Subsequently, FMT was used to treat patients with inflammatory bowel disease (IBD) with o without *Clostridium difficile* infection. For these diseases and conditions were obtained excellent results: FMT, in contrast with standard therapies, have eradicated the *Clostridium difficile* infection and replaced missing component of the microbiota[41]. Two systematic reviews concluded that FMT resolves recurrent *Clostridium difficile* infection in approximately 90% of patients[42]. According to the current guidelines for diagnosis, treatment, and prevention of *C. difficile*-associated disease, FMT can be considered in clinical practice after the second recurrence of the infection[45].

The use of FMT for inflammatory bowel diseases is represented only by small open-label trials, case series, or case reports, most of which have been published only as abstracts at conferences. Many of them have experienced FMT in patients with IBD and *Clostridium difficile* infection. Among different investigations, there is a large methodological variability, with regard to stool and patient preparation, number of infusions, route of delivery, and outcome evaluation[46]. Clinical results, in terms of symptom reduction, clinical remission, and suspension of IBD treatment, are promising but the evidence is weak.

Also the safety data of FMT in *Clostridium difficile* infection were not confirmed when FMT was used in patients with IBD. High fever and a temporary increase in C-reactive protein were the most reported adverse events related to the infusion of feces[47,48]. The uncertainty of available data on both efficacy and safety of FMT in IBD obligates to proceed with caution.

FMT has been proposed as a therapeutic option for irritable bowel syndrome (IBS) and other functional diseases of the gastrointestinal tract. In a case series of patients with IBS or IBD, FMT cured the disease or alleviated symptoms in 52% of subjects. In patients with chronic constipation, FMT led to the improvement in bloating, abdominal pain, and bowel frequency[29].

Later FMT was used to treat patients with other conditions such as metabolic syndromes and obesity. The application of FMT to the management of metabolic diseases has recently achieved preliminary but interesting results[49]. These findings indicate that the intestinal microbiota could actually cause obesity and insulin resistance.

FMT has shown efficacy in some neurological diseases, but data are still few and fragmentary. An improvement of neurological symptoms was resulted in 3 patients with multiple sclerosis who underwent FMT for chronic constipation[50], as well as in a patient with Parkinson disease[51] who received FMT for the same reason. In an uncontrolled study[52] of 60 patients with chronic fatigue syndrome and gastrointestinal dysfunction treated with FMT, 50% had resolved sleep deprivation, lethargy, or fatigue during a 15- to 20-year follow-up period.

Finally, in a patient with idiopathic thrombocytopenic purpura who underwent FMT for ulcerative colitis, a progressive but significant increase in platelet levels has been observed[53], testifying the potential benefits of FMT in immune disorders.

In conclusion, FMT seems to be a safe e promising treatment for recurrent *Clostridium difficile* infection. Well-designed randomized controlled trials are needed to establish the efficacy of FMT for other diseases.

Informed Consent

In a clinical trial the informed-consent process represents a key element expressing a fundamental ethical and medico-legal value: it is a voluntary agreement to participate in clinical trials based on the understanding of the objectives, risks and possible benefits of the research. Due to the nature of the research, the experimental field

is characterized by much more "grey-zones" than clinical praxis. The subject is asked to undergo clinical trial and to expose himself to situations – both therapeutic and non directly therapeutic for him – where balancing possible risks and benefits is not easy and where also the researchers do not have a full information. Furthermore, a greater care is asked whereas information about possible future risks is not yet available. Fecal microbiota transplantation seems to well adhere to such uncertainties. As it has been said, although bacteriotherapy has been showed to be generally safe, randomized studies evaluating clinical safety are still in their infancy; very little can be said about the transmission of occult pathogen.

Moreover, a specific attention should be given to the information schedule: the particular, and as it has been called "non elegant" aspect of the sample might facilitate anxiety. Patients should be well informed of what they are receiving.

From the donor's point of view, it is important to provide information about the procedure that he/she must undergo before becoming a donor (sample screening for parasites, bacteria and so on, and blood screening for HIV, and others).

Further Relevant Ethical Issues

Microbiota Fingerprint

Some researchers suggest that microbiome is unique to the individual[54]. If so, "microbiome technology may allow access to information such as past exposures, locations an individual has visited in the past"[4]. Said that, there could be also new intersections with the forensic use of DNA in so far this last one, employed to match a suspect to a crime scene sample, together with microbiome, would represent a further dowel enriching the toolkit of forensic science.

Recently Tridico et al[55] found out that hairs, in the specific pubic hairs, may provide data to "augment other forensic results and possibly provide association between victims of sexual assault and offender when other associative evidence is absent". As it can be understood, forensic investigation may benefice from the possibility that microbiota is unique to each individual. However, results extrapolated from interviews made by Hawkins and O'Doherty indicate that, at the present, in contrast to DNA, it is not possible to evaluate the stability of microbial fingerprints over the time[4].

Microbiota Commercialization

As it has been said, microbiota represents a key-element to maintain an organism healthy. At this aim, some authors[56] pointed out that the augmented use of dietary supplements has dramatically increased the market in this sector. The commercialization of dietary supplements to avoid microbiota imbalance poses several questions (both scientific and ethical). First of all, these authors report that the use of probiotics entails some safety-related considerations insofar studies have suggested an "unpredictable behaviour of both naturally occurring and genetic altered microorganisms, each of which have the potential to produces substances or gene-behaviours that are harmful to the body"[56]. From the ethical point of view, we have to make sure that people are aware and informed about these risks. Furthermore, although this could be thought as speculative, one should also contemplate the possibility of gaining money through the sell of a healthy microbiota, thanks to dietary supplements that avoid dysbiosis.

According to others[57], future research should also take into account the possibility, and above all the effects, of introducing novel kind of bacteria in the environment and in the human ecosystem.

Research Ethics Committees and FMT

As a part of clinical research, the Research Ethics Committees (RECs) are called to verify some key-elements of a clinical research protocol[58]. While contributing to more knowledge about human health of persons who are enrolled in clinical trials, RECs are invested of the responsibility of guaranteeing their safety and protection. They provide an opinion regarding the rights of the subjects in terms of their physical, psychological and moral integrity, the principle of fairness and equal opportunities and the rights of the people who can access to centres for assistance.

RECs may have an important role within FMT's in formulating more specific operating procedures.

Table I. Fecal micriobiota transplantation's ethical issues.

Main ethical issues
Donor's recruitment
Safety
Informed Consent
Other ethical issues
Microbiota fingerprint
Microbiota commercialization

Beyond the particular attention to the informational schedule, RECs should consider the following ethical suggestions when clinical trials are settled up. Suggestions are branched out according to concerns for patients and for donors.

Concerns for Patients:

1. Patients must be informed about the procedure they are undergoing, and above all they must be aware they are receiving stool donated from an healthy individual.

2. Patients must be informed about the lack of long term safety data.

Concerns for Donors:

1. Donors should be aware that to be effectively donors, their stool and blood will be screened for ova, parasite, HIV, HCV and others.

2. Donors must be informed that similarly to genetic research, microbiome screening can reveal the susceptibility to disease. So far they have the right to choose "to know" or "not to know" about them.

Conclusions

Microbiota represents a new challenge both for its scientific-clinical characteristics and ethical aspects. Although the very updated literature[59] confirms the positive safety/efficacy profile of the employ of health microbiota (so called Bacteriotherapy or FMT), from the ethical point of view it is to make sure that the information process has considered all the elements needed to make the agreement to participate in clinical trials effectively informed.

FMT represents in some ways a challenge for RECs. RECs are helpful in formulating more sharable procedure for this innovative therapeutic procedure. Furthermore, although the good expectation of FMT, RECs should demand long term follow-up to evaluate safety.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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