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Fecal Microbiota Transplantation for the Management of Digestive and Extradigestive Diseases

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Abstract

Gut microbiota is known to play a main role in human health and disease. Reconstitution of the physiologic gut microbiota represents a primary target in the treatment of diseases related to the impairment of gut microbiota composition. Fecal microbiota transplantation (FMT) is the infusion of feces from a healthy donor to a patient to cure a specific disease. Fecal microbiota transplantation has demonstrated undoubted efficacy in the management of recurrent *C. difficile* infection, and it is also considered a promising therapeutic avenue for other diseases associated with gut microbiota imbalance.

Over time, different procedural protocols of fecal microbiota transplantation have been experienced, and methodology has not yet been standardized up to now. Future efforts for the improvement of the therapeutic performance of the fecal microbiota transplantation will include, respectively, the definition of specific protocols for each disease, the application of brand new technique for the assessment of gut microbiota composition (e.g. metagenomics) to clinical practice, and the development of larger, well-designed, randomized controlled trials on this topic.

Introduction:

The role of gut microbiota in health and disease

An enormous number of microbes reside in the inner and in the outer part of our body. The majority of them is located into our gastrointestinal tract, forming the gut microbiota[1]. Gut microbiota is far from being a simple stockpile of microorganisms, and should be accounted as an adjunctive organ within the human body[2].

Gut microbiota composition is still unclear. Bacteria are the most common components of human gut microbiota. Bacteroidetes and Firmicutes are the most represented phyla[3,4]. Other constituents are Archaea, Viruses, Fungi and Protozoa[4].

The majority of the microbial community residing into our gut is not cultivable through standard microbiological techiques. The application of culture-independent diagnostic tools, including metagenomics, is giving a paramount improvement of our understanding of gut microbiota composition in health and disease[5].

Gut microbiota is involved in many relevant functions within the human organism, including the development and regulation of both local and systemic immunity, the modulation of several metabolic pathways, a barrier action against foreign agents passing throughout our intestine[6].

Several lines of evidence suggest that the impairment of gut microbiota homeostasis can lead to the development of many digestive and extradigestive diseases, including irritable bowel syndrome (IBS) and other functional gastrointestinal diseases[7], inflammatory bowel disease (IBD)[8], colon cancer[9], gastrointestinal infections[10], non-alcoholic fatty liver disease and other liver diseases[11,12], diabetes, obesity and metabolic syndrome[13,14], autism[15] and allergies[16]. In theory, the rebuilding of healthy gut microbiota is a sound approach for the management of gut microbiota-related diseases. Antibiotics, probiotics and prebiotics are currently the most popular therapeutic options at this regard. Probiotics, prebiotics and antibiotics represent at now the most diffused clinical approaches for the restitution of healthy microbiota. Fecal microbiota transplantation has demonstrated undoubted efficacy in the

management of recurrent *C. difficile* infection (CDI), and it is also considered a promising therapeutic avenue for other diseases associated with gut microbiota imbalance.

Fecal microbiota transplantation: the story so far

Fecal microbiota transplantation (FMT) is the infusion of feces from a healthy donor to a patient to cure a specific disease. The use of FMT in medical and veterinary field was sporadically reported since ancient times[17,18]. The first mainstream documentation of FMT in clinical practice dates back 1958, when Eiseman and his surgical equipe from Colorado successfully attempted stool enemas as rescue therapy for the management of few subjects with pseudomembranous colitis requiring surgery[19].

Since this first experience, several case series and case reports, and a single randomized controlled trial experiencing FMT for the management of recurrent CDI have been described in medical literature[20]. The consideration of FMT as a real organ transplant, instead of a simple infusion of feces, has provided the theoretical background to test FMT also in other gut microbiota-related diseases, with promising results[21,22].

Fecal microbiota transplantation: procedural protocol

Donor selection

Differently from other organ transplants (such as liver or kidney transplant), fecal microbiota transplantation does not require any immune match between recipient and donor. However, a careful pre-procedural screening is mandatory to prevent dissemination of diseases from the donors to the recipients. Generally, donors are chosen among patients' relatives, partners or friends, to limit the "yuck factor", that is the revulsion of the recipient towards stool transfer. Higher resolution rates of recurrent CDI are obtained when stools derive from related donors[23]. As initial step, clinical history of candidates is collected, usually through questionnaire. At now, with regard to FMT for CDI, absolute or relative contraindications that exclude candidates from donating feces are represented by transmissible diseases (such as pulmonary infections), infection or recent exposure to viral hepatitis, syphilis, human immunodeficiency virus (HIV) infections; drug dependence, sexual promiscuity, jail history, recent tattoos, piercings, or travels to Countries characterized by endemic diarrheal diseases; risk factors for Creutzfeldt–Jakob disease, history of digestive cancers or polyps, IBD, IBS/functional gastrointestinal diseases, of other diseases potentially related to gut microbiota imbalance (metabolic syndrome, autoimmune and atopic illnesses), and of main abdominal surgical interventions; consumption of certain drugs (immunosuppressants, chemotherapic drugs, antibiotics) within the previous 3 months[24].

The second step includes blood and stool screening for, respectively: hepatitis A, B, C, HIV, syphilis; *C. difficile* toxin, stool culture, parasitologic exams.

This preliminary assessment seems to be suitable for the management of patients with CDI[25]. Nevertheless, when FMT is applied to other diseases such as IBD, donor's microbiota composition appears to influence deeply outcomes[26]. A thorough characterization of gut microbiota of donors and recipients will be probably included as a fundamental step in the donor selection process.

Preparation of recipients and fecal material

Generally, recipients undergo bowel preparation 24 hours before the transplant, to clean gut as best as possible. If stools are administered by upper route, patients usually take also proton-pump inhibitors to avoid microbiota destruction by gastric acid[24]. Before the transplant, feces are diluted in saline or water, and such solution is filtered, usually with water or saline, to eliminate rough residuals. The use of less than 50 g of stools usually brings to higher CDI relapse rates, whereas large (more than 500 ml) volumes of infusion are related to higher resolution rates, although without any statistical significance[23].

The fecal material should be administered within 6-8 hours from the donation[27,28]. Frozen feces have been used too, with similar results[29].

A single infusion of stools is usually able to heal *C. difficile* infection[30]. However, long-standing diseases (e.g. IBS, metabolic syndrome, IBD) may require multiple infusions to obtain comparable results.

Route of administration

Different routes have been experienced for the injection of feces during FMT: gastroscopy, nasogastric/nasojejunal tube, colonoscopy, enemas[31]. Upper route appears to get lower eradication rates than the lower one[30]. Cheapness and facility of administration represent the main advantages of enema. Nevertheless, colonoscopy has also a diagnostic value, allowing a better evaluation of the disease[32,33].

FMT through naso-jejunal tube has been tested in obese patients, with interesting results[34]. Also multiple approaches have been described[26]. Presumptively, one way of delivery is not better than others overall, but the choice of the more appropriate route of administration depends on features of patient and of the disease for which FMT is performed.

Fecal microbiota transplantation for the treatment of digestive and extradigestive diseases

C. difficile infection

Usually CDI develops after massive antibiotic treatment regimens, especially among fragile patients, in hospital setting occurs generally after antibiotic treatment and consequent impairment of physiologic gut microbiota composition, in particular in hospitalized fragile patients[24]. For this reason, it represents an exemplary model of gut microbiota-related diseases. To date, recurrent CDI is the main indication for FMT, with high rates (around 90%) of therapeutic success[24], and an excellent safety profile[30].

To date, in one randomized controlled trial, FMT showed significant efficacy over vancomycin in the eradication of recurrent CDI[35]. Current U.S. Guidelines suggest the use of FMT in clinical practice after the second recurrence of CDI[36].

Inflammatory Bowel Disease (IBD)

Alteration of gut microbiota is a main step in the development of IBD[37]. Lower diversity and higher instability, as well as a decrease of Firmicutes and Bacteroides and a growth of Enterobacteriaceae and Actinobacteria distinguish gut microbiota composition of IBD subjects[37].

At now, only few, uncontrolled experiences of FMT for IBD have been described. The majority of them tested FMT in IBD subjects with concomitant CDI. Available reports display a high methodological diversity, in terms of procedural protocol and outcomes[38], with alternate results. Recently, the assessment of gut microbiota composition before and after FMT has been performed through metagenomics techniques[26,39]. Improvement of Mayo score was associated to a sustained modulation of the repicient's microbiota toward the donor's one[26]. Although FMT showed to be safe in CDI, several adverse events, such as high fever, transient relapse of the disease or bacteremia, have been reported in patients with IBD[29,39,40,41,42].

Functional gastrointestinal diseases

Gut microbiota has been suggested to play a role in the pathogenesis of IBS through several pathways, such as the impairment of gut barrier, modulation of gut-brain axis and other neuro-enteric avenues[43]. Moreover, a decrease of Roseburia – *E. rectale* group bacteria (butyrate producers), and an increase of sulphate-reducing bacteria have reported[44].

In a mixed cohort of subjects with IBD or IBS, FMT cured the disease or alleviated symptoms in 52% of cases[45]. Furthermore, FMT improved symptoms in 45 subjects suffering from chronic constipation[46].

Obesity and metabolic diseases

Several lines of evidence support the role of gut microbiota impairment in the development of obesity. A Reduction of Bacteroidetes and augmentation of Firmicutes have been reported in obese mice. As shown in several mouse models, gut microbiota can seize energy from dietary intake, and also non adsorbable polysaccharides can be fragmented by microbiota-derived lytic enzymes[47].

After transfer of conventional mice-derived gut microbiota, an increase of insulin resistance and bodily fat percentage despite food limitation has been described in germ-free rats. Moreover, when gut microbiota of conventionally grown mice is transferred in germ-free ones, an increase in insulin resistance and in body fat content occur in the latter, despite dietary restriction; gut microbiota promotes hepatic lipogenesis and the absorption of monosaccharides, counteracting the action of Fasting-induced adipocyte factor (Fiaf), an inhibitor of lipoprotein lipase[48]. Furthermore, expression of microbial genes related to metabolism of metabolism-related microbial genes, as well as gut microbiota composition have been shown to be different between lean and obese twins[49].

Obesity and insulin resistance are characterized by persistent low-grade inflammation[50]. Augmentation of Gram-negative bacteria promote the maintenance of low-grade inflammation by the upregulation of lipopolysaccharide (LPS) absorption[51,52].

In a small randomized controlled trial, insulin sensitivity and number of bacteria related to butyrate production were significantly increased in 18 subjects suffering from metabolic syndrome[34].

Immune and neurological disorders

Mouse models suggest a relationship between neurological disorders and gut microbiota alterations[53,54]. The relief of symptoms in multiple

sclerosis[55] and Parkison's disease[56] after FMT has been reported, but data are weak and fragmented.

Moreover, FMT was tested in 34 patients with chronic fatigue syndrome (CFS), with sustained improvement of symptoms in 14 of them 57.

FMT has shown some efficacy also in immune disorders. An improvement in platelet counts has been described in a patients with immune thrombocytopenic purpura (ITP) undergoing FMT for ulcerative colitis[58].

Conclusions

Gut microbiota plays a main position in our health as well in the development of several diseases. The amelioration of our understanding of gut microbiota composition and functions is leading us to the discovery of new therapeutic avenues for the management of gut microbiota-related diseases. FMT brings a sustained modulation of gut microbiota, and has shown incontestable efficacy on recurrent CDI, as well as promising results on metabolic diseases. However, data are already few and fragmentary. Moreover, a satisfactory safety profile has not been reached in all patients.

The development of a standardized protocol for each disease, as well as a thorough assessment of gut microbiota composition of donors and recipients will probably improve outcomes, allowing the spreading of FMT in clinical practice.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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