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Review Article

News in the Management of Intestinal Microbiota Transplantation

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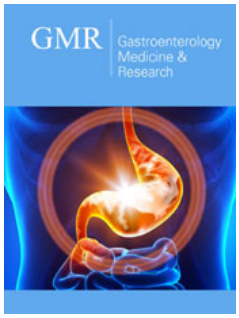

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Abstract

The history of 2000 years to date is reviewed, regarding intestinal microbiota transplants, or is it 3000? We carry out in-depth analysis on the importance of Intestinal Microbiota Transplantation, the importance of Stool Banks (Microbiota); current transplant procedure, including patient, laboratory, donor, and exclusion criteria; reinforcement, safety, limitations and complications; consensus and conditions that can be treated with Fecal Microbiota Transplantation. We develop the importance of transplantation in children and the elderly and conclude with a series of interesting topics.

History: The Intestinal Microbiota Transplant (IMT) or Fecal Microbiota Transplant (FMT) was carried out by Ge Hong, a Chinese alchemist, more than 1,700 years ago [1], although some point out that the treatment of diseases of the colon with fecal matter originated in India, a thousand years before, and that it was Charak Samhita, who in his book Uttara-Tantra, describes it. Although there are many doubts, in this regard [2]. The Intestinal Microbiota (IM) is called in the traditional Chinese medicine book Ben Cao Gang Mu, "yellow soup" [3]. The Italian doctor Girolamo Fabrizi d'Acquapendente, in the seventeenth century, professor of Williams Harvey, determines Transplantation as Transfaunation; word from English "Transfaunation": Transfer part or all of the symbiotic flora of the digestive tract [4].

Keywords: Intestinal Microbiota Transplant (IMT); Fecal Microbiota Transplant (FMT); Intestinal Microbiota (IM)

Introduction

The ingestion of fresh hot dromedary feces was suggested by Bedouins to German soldiers with dysentery, in World War II [5]. In 1958 Eisman, et al, a surgeon from Colorado, United States of America, treated patients with pseudomembranous colitis, with good results [6]. The bacterium called Clostridium difficile that produces pseudomembranous colitis was isolated in 1930 and was described until 1978 as the causative agent. That year it was isolated from the feces of a patient treated with Clindamycin [7]. The data is of enormous significance, as the IMT addresses the management of Recurrent Clostridium difficile Infection, representing an annual expenditure of $ 4.8 billion US dollars. The epidemiological burden of disease in 2011 in the United States of America included 29,000 deaths and 434,000 infections [8].

Stool banks (Microbiota)

[9-12]. Although Stool Banks are spreading in the world and especially in industrialized countries, we provide here a series of elements, in order to establish a Bank, in order to reduce the enormous problem of *C. difficile* and the possibility of treating other diseases. This is necessary, since the difficulty in obtaining donor stool suspensions has limited the management of IMT in specific cases of recurrent *C. difficile*, as well as other conditions; being able to operate at the institutional, regional or national level.

Some suggestions to install a Stool Bank (Microbiota)

A. The goal is to provide standardized and screened donor stool suspensions, allowing accessibility and safe use for patients.

B. Have at least one laminar flow cabinet to avoid cross contamination. -80°C freezer, for long-term storage, with alarm notification connected to ensure constant recording of storage temperature.

C. Have standardization, quality assurance and exclusive laboratory.

D. Comply with Good Manufacturing Practices.

E. Obtain a Quality Management System and information supervised by qualified personnel for coding, recording, monitoring and tracking of samples and recruiting donors.

F. Have a panel of experts to advise physicians on the clinical indication and eventual treatment with FMT.

G. All related serious adverse events should be recorded.

H. Donors will be healthy, unrelated anonymous volunteers. And they must live or work near the stool bank. They will be thoroughly screened before they can become a donor.

I. Potential donors are given an extensive questionnaire that addresses general health, risk factors for possible communicable diseases, and risk factors for disorders associated with disturbed microbiota. The age of the donors will not exceed 30 years and they will have a BMI that is not greater than 25kg/m^2

J. Active donors will undergo re-screening after at least 3 months.

K. Read and request a signature on the informed consent, both of the recipient and of the responsible family member.

L. If necessary, rely on Certified Laboratories.

M. Support the research and development of new therapies.

Process: It has to do with: the patient; the donor, the laboratory and the methodology [13]. Donating frozen feces has advantages over fresh material [14].

Patient: All patients are provided with various information in advance so that they understand the procedure and ask all the questions. If the patient is a minor, the information is provided to the responsible family member.

We do not force decisions, nor do we force. When the responsible family member and the patient agree, they sign two Letters of informed consent: Endoscopy and Anesthesiology. Preoperative, should not be older than 30 days, and are: Complete blood count. Prothrombin time, partial thromboplastin time. C-reactive protein. Globular sedimentation. Thyroid profile. Antibodies, anti-thyroid, if applicable. Lipidic profile. Transaminases. F. Alkaline. Bilirubins. Gamaglutamyltranspeptidase and general urine test.

Donor and laboratory [15]

If we show a potentially healthy donor, request:

Polymerase Chain Reaction (PCR). *Clostridium difficile*, Hepatitis A: immunoglobulin (IgM) and (IgG). Hepatitis B: Surface Antigen (HBsAg)

Hepatitis C: Antibodies. Antibodies to Human Immunodeficiency Virus (HIV) type 1 and 2 (ELISA). Treponema pallidus: rapid plasma reagin test (RPR; if Positive). Anti-Cytomegalovirus (IgG) Antibodies. Epstein-Barr antibodies (IgG)

Naso-Pharyngeal: Polymerase chain reaction (PCR). SARS-CoV-2. IgG antibodies against SARSCoV-2, depending on the stage.

Feces:

1. Coproparasitoscopic, in series of 3.
2. Salmonella, Shigella and Campylobacter stool culture.
3. Helicobacter pylori antigen.
4. Rotavirus and Adenovirus antigen.
5. Vancomycin resistant enterococci.
6. Syaphylococcus methicillin resistant.
7. Carbapenem-resistant Enterobacteriaceae: screening culture.

Clinical exclusion criteria for the donor

[16-18] Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), chronic diarrhea or constipation. Atopias (eczema, asthma, eosinophilic pathologies of the gastrointestinal system). Fibromyalgia or chronic fatigue syndrome. Connective tissue diseases. History of gastrointestinal malignancy. Immunosuppressive drugs. Medicines against neoplasms. Obesity (BMI> 30), Type 1 Diabetes Mellitus. Type 2 Diabetes Mellitus. Metabolic syndrome. AIDS, Hepatitis B and C virus infection or risk of transmission in the last 12 months. Have been in prison; use illicit drugs, be an individual at high sexual risk, have tattoos, piercings, have traveled in the last 6 months to endemic countries with diarrheal diseases or high risk of traveler's diarrhea, have contagious disease or Creutzfel-Jacob disease. Generally, a single procedure, by naso-duodenal tube, panendoscopy, colonoscopy or capsules, is sufficient to obtain cure rates of 80% in recurrent *C. difficile* infection [19].

Reinforcement: We usually provide it through diet, probiotics (Lactobacillus), prebiotics (Fructooligosaccharides or Galactooligosaccharides) and symbiotics (Bifidobacterium or Lactobacillus with fructo-oligosaccharides), highlighting the management with symbiotics [20-22]. Consensus [23,24].

a. Excellent response to FMT in recurrent *C. difficile* disease has been demonstrated.

b. TMF has important value in IBS and inflammatory bowel disease, especially Chronic Nonspecific Ulcerative Colitis (UC).

c. There are promising effects of FMT in allergies,

autoimmune disorders, metabolic disorders, hematologic diseases, and tumors.

d. FMT in metabolic syndrome should be addressed only in research processes.

Treatable conditions

Allergies

Alzheimer's disease

Anxiety

Arterial hypertension

Arthritis

Asthma

Atopic dermatitis

Autism

Autoimmune liver disease

Autoimmune nephropathies

Cancer

Celiac Disease

Chronic constipation

Chronic Fatigue Syndrome

Chronic Nonspecific Ulcerative Colitis

Cognitive impairment

Depression

Diabetes mellitus type 2

Dyslipidemia

Fibromyalgia

Functional Digestive Disorders

Hashimoto's disease

Ideopathic Thrombocytopenic Purpura

Irritable bowel syndrome

Lactose intolerance

Metabolic syndrome

Multiple sclerosis

Neurodevelopmental Disorders

Nonalcoholic fatty liver

Obesity

Pouchitis

Pseudomembranous enterocolitis

Recurrent Clostridium difficile

Rheumatoid arthritis

Stem cells (transplant)

Systemic lupus erythematosus

Security: One of the most important aspects in the search for the security of the IMT is regulation, which should not be too strict, as it would discourage research [25]. IMT is considered safe if protocols are closely monitored, especially with regard to donors. In long-term follow-up, no significant abnormalities have been detected, which gives a further bonus for the practice and investigation of IMT [26]. On minimal occasions, there have been adverse outcomes, including deaths or transmission of bacteria resistant to antibiotics [27]. It is usually minimally risky, even in immunocompromised patients [28].

Limitations: Although limitations of the FMT have been intentionally sought, these are actually rare. Some authors refer those severe hepatic insufficiencies and some immune-deficient processes could be cited, but there are authors who point out that the second example is not a limitation [29,30].

Complications: In fecal microbiota transplantation, reported adverse events are minor and self-limited, appearing abdominal cramps, constipation, diarrhea, abdominal pain, flatulence and abdominal bloating [31].

IMT in children and the elderly. Undoubtedly, the criteria for determining the FMT are different at these ages; however, there are correlations that can be used to benefit such people. The increase in both recurrent infection by C. difficile, as well as the intestinal dysbiosis that generates countless diseases, have opened the enormous possibility that Fecal Microbiota Transplants have, both in children and in the elderly [32], although they are known differences between the microbiomes of these entities, especially between very young children and even older people [33].

Interconnections between children and the elderly

A. Recurrent infection with *C. difficile* requires management with FMT, as the traditional scheme fails [34].

B. Treatable conditions in children and older adults are increasing every day [35].

C. Considering that the best Donor is the child of approximately 6 years, with the inherent difficulties. It makes it a special candidate for treating the ailments of the elderly [36].

D. At both ages, the rational use of antibiotics should be a specific criterion [37].

E. Both transplanted children and older adults show new bacterial diversity [38].

Future

A. Regularize regulations to guarantee the well-being of patients [39].

B. The negative impacts are limited, while the improvement is substantial [40].

C. Monitor the altered microbiota, especially with antibiotics, before performing the FMT [41].

D. Seek the development of standardized, high capacity and specialized microbiota banks, as well as comprehensive management [42].

E. Although IMT is generally safe, we should not consider it risk-free [43].

F. Although IMT can be used in immunocompromised patients, we must be cautious in them [44].

Conclusion

A. Stimulate the development and strengthening of highly specialized Microbiota Banks.

B. The discussion has been opened whether the IMT is 2000 or 3000 years old.

C. Promote prospective studies with meta-analysis in conditions other than Recurrent Infection by C. difficile.

D. Support transplant patients on the ketogenic diet, if possible. Exercise according to its status, probiotics, prebiotics and symbiotics.

E. Deepen the analysis of phage therapy.

Conflicts of Interest

The authors declare that do NOT have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

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