

Transplantation of Intestinal Microbiota and its Clinical Application

Álvaro Zamudio Tiburcio^{1*}, Héctor Bermúdez Ruíz², María del Pilar Guevara Alvarado³, Hugo Ricardo Lezama Guzmán⁴, Elena Islas-Solares⁴ and Francisco Antonio Sosa-López⁴

¹Private Medical, Mexico City, Mexico

²Endoscopy Service, Hospital of Oncology, National Medical Center, XXI century, Mexican Social Security Institute, Mexico City, Mexico

³Anesthesiology Service, Magdalena de las Salinas Hospital (Dr. Victorio de la Fuente Narváez), Mexican Social Security Institute, Mexico City, Mexico

⁴Trinidad Hospital, Mexico City, Mexico

***Corresponding Author:** Alvaro Zamudio Tiburcio, General Surgery, Gastroenterology, Private Medical, Mexico City, Mexico.

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Abstract

The first intestinal microbiota transplantation (IMT) was performed in the 4th century, during the Dong-jin Chinese dynasty, physician Ge Hong described the oral administration of a suspension prepared from human feces in patients with food poisoning or severe diarrhea with good results. In the sixteenth century, during the Ming Dynasty, Li Shizhen described in the Chinese medicine book Ben Cao Gang Mu (Compendium of Materia Medica), the prescription of fecal suspensions (fermented or fresh) and dried feces for the treatment of abdominal diseases Who have diarrhea, fever, pain, vomiting and constipation. For aesthetic reasons, doctors labeled these preparations as “yellow soup.” The Italian physician Fabricius Aquapendente, in the seventeenth century, referred to IMT as a transfaunation and used it in veterinary medicine. In 1958, Eisman., *et al.* Published the first article in which four patients with pseudomembranous colitis were treated with IMT [1]. In the United States of America, in Europe and in Australia, the first cases directed to the management of severe diarrhea by *Clostridium difficile* have been reported 50 years ago [2,3]. Since then, numerous treatments against this aggressive bacterium have been performed, with excellent results and as the ultimate treatment, determinant of survival [4-6]. There are currently research centers where several hundred transplants have already been practiced in Australia at the Thomas Borody Clinic Probiotic Therapy Research Center (PTRC) specialists in the treatment of gastrointestinal conditions using Faecal Microbiota Transplantation The PTRC was founded by Professor and Dr. Thomas Borody, gastroenterologist and Director of the Center for Digestive Diseases ... or at Taymound Clinic in London (FMT Treatment and Gut Flora Experts), there is still concern about the potential transmission of infectious agents. There are hospitals that have their own stool banks like the Johns Hopkins in Baltimore, Maryland, within the University of the same name, the first in the United States dedicated specifically to research as well as the OpenBiome in Boston, located at 196 Avenue, Suite 1000 Medford MA 02155. Telephones: (617) 575-2201. Fax: (617) 575-2201. United States of America, has become the pioneer country in fecal transplants.

Keywords: Transplantation; Intestinal Microbiota; IMT

Introduction and Discussion

Research on the action and benefit of the intestinal microbiota in the world is progressing, diseases such as irritable bowel syndrome, inflammatory bowel disease and metabolic syndrome, are the focus of therapeutic care of researchers, has begun the era of management of the same with intestinal microbiota transplantation (IMT) [7,8]. Currently, other authors are reporting encouraging results with IMT in the treatment of other conditions, including: Idiopathic thrombocytopenic purpura, autoimmune diseases, allergies and neurological disorders [9].

Some more adventurous authors have performed IMT in such diverse conditions as anorexia nervosa, atherosclerosis, colon cancer, type 1 diabetes mellitus, celiac disease, multiple sclerosis, hyper or hypothyroidism, chronic fatigue syndrome, eosinophilia of the digestive system, disorders Neurodegenerative and developmental disorders, with diverse results, although in the majority of cases, with benefits, that have made the Transplant adopt new advocates and, more frequently, in the world [10-13].

The IMT has generated a change in the treatment perspective of multiple diseases, Mark Smith refers to “We have more than 130 samples and ready to use”, who after graduating in Microbiology at the Massachusetts Institute of Technology has assembled OpenBiome, where feces, mixed with glycerol not to be damaged, stored cold. In exchange donors receive \$ 40 per deposition, and an extra \$ 50 if they offer their feces five days in a week, plus another \$ 40 for doing the test to rule Infections such as AIDS or hepatitis C [14]. “As in Spain we do not have these reservations, what will be done is to ask the family of the patient, parents and Brothers and sisters, to make the donation, “said Dr. Francisco Guarner, spokesman for the Spanish Association of Digestive Pathology.” Every day there is at least one article to this procedure. Themselves to obtain the substance of this magnificent method”.

The denominations that have been used for the Transplantation range from fecal enema, bacteriotherapy, fecal repopulation, fecal flora reconstitution, intestinal microbiota transfer, fecal transplantation, fecal infusion, Fecal microbiota transplantation - as is most frequently observed in Literature - because it is a true transplant. We call it Transplantation of intestinal microbiota, because it seems to us that the transplantation that is carried out is from this part, since there are other microbiotas in the human body [15].

Our group was the first to perform IMT in Mexico, in patients not carrying *Clostridium difficile*, as reported in the *Journal of Surgery and Surgeons*. Volume 86: No. 3. 2018. Microbiota.

Microbiota intestinal y microbioma

To understand the reason for the effectiveness and efficiency of IMT, it is necessary to know what the microbiota is, what the intestinal microbiota is and what the microbiome is. Microbiota is the set of micro-organisms that are frequently found in various parts of the body, in healthy individuals. It is made up of a multitude of bacteria, fungi and protozoa, as well as other microbes. They located in the skin, oropharynx, digestive tract, genitourinary apparatus and others, where the bacteria are scarce. Its composition includes viruses, fungi, protozoans, archaea and bacteria. Archaea are unicellular micro-organisms of prokaryotic morphology (without nucleus or internal membranous organelles), are different from bacteria. These microorganisms along with the rest of the microbiota are transcendent in the positive actions of intestinal microbiota transplantation [16].

The intestinal microbiota, previously known as normal intestinal flora, is the microbial ecosystem of the intestine, includes native species that permanently colonize the gastrointestinal tract and a variable group of living micro-organisms that are transiently in it. Native bacteria are acquired at birth and during the first year of life, while the bacteria in transit are acquired continuously through food, beverages or other sources [17]. Experimental data suggest that the intestinal microbiota exerts metabolic functions that contribute to the recovery of nutrients and energy from non-digestible substrates. In addition, microbial colonization is often essential for the normal development of the immune system, so it seems to influence the homeostasis of environmental antigenic burden and immune response, as in chronic inflammatory bowel disease, in which the immune system Reacts exaggeratedly against non-harmful microbial antigens [18]. The knowledge about the bacterial composition of the intestinal microbiota was based mainly on the information obtained by culture of stool samples or intestinal biopsies.

Conventional bacteriological analysis of fecal flora by isolation of strict anaerobic bacteria outnumber aerobes by a factor of at least 100 or 1000 anaerobic species per aerobic species. According the traditional methodology, the predominant genera are *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Clostridium*, *Lactobacillus*, *Fusobacterium* and various anaerobic cocci. However, researchers have always been aware that the information obtained by culturing is incomplete, because the techniques of anaerobic culture in the laboratory have many limitations and because more than 50% of the bacterial cells observed by microscopic examination of fecal samples do not are recovered in culture media [19].

The microbiome is defined to the set of genes of our commensal micro-organisms that form the microbiota, but nowadays both terms are used as synonyms [20]. Intestinal microbiotic transplantation. Clinical goodness.

Methodology

Our methodology has with 3 aspects: 1 The patient; 2 The laboratory and, 3 The Procedure.

The patient

Patients with *Clostridium difficile* diarrhea were ruled out, since in these patients (IMT) it has demonstrated its efficacy in 90%. The behavior of the patient during microbial transplantation was evaluated and the innocuousness of the procedure was demonstrated. Only in some cases did they present colic, diarrhea and nauseous state that they gave in spontaneously.

Do not consider age or sex, only that the cases were more than 5 years of evolution, with minimum response to conventional treatment and which the patient seek another alternative, which offer improved and she was willing to continue any therapeutic medium-term, if necessary, to ensure the success of the procedure.

Various citations provided them so that they read them, accept the procedure, and made us all the questions that they need.

In any cases, we force or force to make decisions. All patients were convinced of the proposal and only did sign the document prior to the study (consent letter).

The laboratory

Pre-operative profile, not more than 30 days old.

Microbiology studies in blood and feces to the donor

In blood:

- a) Hav IgM serology, HBV HBsAg, AntiHBs IgM, Anti-HBc (Ig G and Ig M), HCV IgG (to rule out hepatitis)
- b) serology HIV types 1 and 2 (ELISA) (AIDS)
- c) studies for syphilis: VDRL (Venereal Disease Research Laboratory)
- d) others to consider: CMV, EBV, human leukemia, JC virus.

In feces:

- (a) glutamate dehydrogenase (GDH) and toxins A and B of *C. difficile*
- (b) bacterial culture and parasites exam
- (c) others to consider: *Giardia*, *Rotavirus*, *Norovirus*, *Listeria*, *Vibrio*, *E. coli*

O157, *Dientamoeba fragilis*, *Blastocystis hominis*, *Strongyloides stercoralis*, *Entamoeba histolytica*, *Helicobacter pylori*, *Schistosoma*, *Enterococci vancomycin resistant*, *Staphylococcus methicillin resistant*.

The Giver

Be less than 60 years, non-obese, diabetic, without intestinal surgeries and not taking antibiotics in the last 6 months.

Give a complete medical history. Be potentially healthy donor; request: *Entamoeba histolytica*; *Giardia lamblia*; *Blastocystis hominis*; *Dientamoeba fragilis*: stool culture. Antigen of Rotavirus and Adenovirus in feces (Adenovirus antigens of Rotavirus antigens). *Clostridium difficile* (toxin A and B). (VDRL). Profile of Hepatitis A, B and C. 1 and 2 human immunodeficiency virus antibodies. Presumptive test. Antibodies Anti-Cytomegalovirus IgG. Epstein-Barr antibodies IgG. Profile of immunoglobulins: immunoglobulin A, immunoglobulin and immunoglobulin M and immunoglobulin G.

The interrogation must include search: inflammatory bowel disease, colonic polyps, irritable bowel syndrome and consider the donor to exercise.

Clinical criteria of exclusion for the donor:

- a) virus infection of AIDS, Hepatitis B and C, or risk of transmission in the past 12 months.
- b) current communicable disease
- c) risk factors of Creutzfeld-Jakob disease (bad neurological with hereditary genetic forms produced by a protein called a prion (PrP). Hereditary and infectious cases are well documented.
- d) the last 6 months travel to countries with diarrhea disease or at high risk for Traveler's diarrhea.
- e) inflammatory bowel disease, irritable bowel syndrome, chronic constipation or chronic diarrhea syndrome.
- f) history of gastrointestinal malignancy or polyposis.
- g) use of antibiotics in the last 3 months.
- h) use of immunosuppressive medication: glucocorticoids, calcineurin inhibitors, biological agents. Use of anti-neoplastic treatment.
- i) obesity (BMI and gt; 30), metabolic syndrome, type 1 diabetes mellitus
- j) obesity (BMI and gt; 30), metabolic syndrome, type 2 diabetes mellitus
- k) syndromes of chronic pain (fibromyalgia, chronic fatigue syndrome).

Who can be a donor:

They may be relatives of the patients themselves, however, any person can donate Lee provided, I repeat, be properly studied and have met the requirements to be a donor, usually respond a questionnaire that used for blood donation (standard official Mexicana NOM-253-SSA1-2012, for the disposal of human blood and its components for therapeutic purposes).

The Procedure

Prepares the patient the colon when less 24 hours in advance based on liquid diet without dairy and Nectars, is given a laxative for the type of polyethylene glycol or a solution of dibasic sodium phosphate and phosphate sodium single phase.

Day of the TMF: the patient should be fasting for 6 to 8 hours, arrive with a adult companion and sign informed consent sheet.

It is essential to the administration of loperamide (an antidiarrheal in single dose) prior to the implementation of the transplantation, this, in order to reduce to the bowel movements, this leads to avoid that the patient evacuate immediately after the (IMT) and Miss part of it. Fully liquid (Microbiota) product is introduced into the gastrointestinal tract through colonoscopy, are deposited 500 cc in the colon being distributed in its whole length (ascending, transverse, and descending), also can be used as a probe nasogastric tube (Levin) or gauge jejunal feeding tube 12 or 14 French (3 Fr. = 1 mm) to pass it. Currently, there are pills or capsules of feces, less unpleasant than the colonoscopy alternative. The specialist must be expert, is performed under intravenous general anesthesia administered by a specialist anesthesiologist. Up to this point has been shown that the (IMT) carried out endoscopically (colonoscopy) has proved more effective (95%). Colonoscopy allows the administration of suspension throughout the entire colon and terminal ileum. Different ways to carry out the administration of the solution during colonoscopy, perhaps the most commonly used is gradual instillation every 5-10 cm have been raised.

After transplantation is left the patient at rest for one to two hours trying to avoid, also triggering the desire to evacuate to the move.

Used equipment: Enteroscope Olympus a balloon. 4 disposable sterile 50 ml plastic syringe.

Kidney of sterile aluminium
500 ml of intestinal Microbiota.

Microbiota for jejunal Administration:

In laminar flow mix 2 hours before transplantation 60 grams of feces with 500 milliliters of water.

We homogenize in a blender.

We filter the mixture through sterile gauze (3 layers), and deposit 500 ml aliquot into sterile plastic jar, covering at the end, with rubber stopper.

Put on the cap of the bottle hypodermic needle of the number 18, the same inside, 5 seconds and remove the needle, to remove the air produced.

Do not use the aliquot immediately can be refrigerated "Do not freeze". The vial must remain in vertical position.

This mixture is the microbiota.

Microbiota for Administration by Columbus. In laminar flow mix 2 hours before transplantation 180 grams of feces with 500 milliliters of water. The rest of the preparation was equal to the administration by jejunum.

Endoscopy jejunal-prior performing preoperative studies, applied 6 hours before transplantation enema with 45 mL of glycerol and loperamide 2 mg tablet; If the patient was not constipated.

Under General intravenous anesthesia.

The video endoscopes valuing the esophagus, stomach, and duodenum is carried out. Take biopsy for *Helicobacter pylori* usually in the antrum. In patients with inflammatory bowel disease, suspected malignant process or precise indication biopsies are taken and sent to histopathological study.

The enteroscope balloon is passed up to two centimeters after the angle of Treitz. 500 milliliters of microbiota administered in jejunum of the enteroscope balloon annex tube.

If necessary (high suspicion of relapse) must be naso-jejunal probe (up to 1 week) to be used for new transplant of intestinal microbiota.

Transplantation will conclude at the end of the administration of the microbiota. Loperamide 2 mg tablet is given.

Why we carry out the procedures in these regions?

The microbiota intestinal transplantation can be done through a naso-gastric tube, by endoscopy to the duodenum; by enema or colonoscopy.

We prefer the application via enteroscope, since is placed the microbiota in jejunum; There are 3 areas of tightness that prevent his return (lower esophageal sphincter, pylorus and clamp from the angle of Treitz), as well as report the literature more effectively by the high digestive tract [21].

The donor may be close relative or any healthy person. It is preferable that this based liquid diet for 3 days prior to transplant, so that feces present semi-liquid consistency and facilitate the procedure [22].

World experience: As mentioned above, the first experience of the microbiota transplant was to treat diarrhea, followed by management of severe diarrhea by *Clostridium difficile* more what has happened to the rest of the managed with this suffering methodology?

Let's experience the world with another type of ailments: One of the conditions is the recurrence of diarrhea by *Clostridium difficile* [23] has been observed that a second or sometimes until a third job of the microbiota transplant, has controlled this type of diarrhea, although, just a first attempt [24].

Diarrhea alone, either associated with the irritable bowel syndrome has also been considered in the conditions that have been treated with transplantation of intestinal microbiota, with varying results [25].

There are countless articles that have been written in relation to the (IMT), especially in regards to diarrhea by *Clostridium difficile*.

Let’s look at the following list, where are those conditions that respond favorably to the (IMT). Fail to heal, more if they improve. These improvements range from 20 to 60%, depending on the condition that concerned.

Diseases That Can be Treated with Transplantation of Intestinal Microbiota (Fecal) [26]

- Food and respiratory allergies -Anorexia nervosa -Atherosclerosis (in review) -Systemic Autoimmunity
- Colon Cancer (in laboratory, animals) -*Clostridium Difficile* diarrhea -Fulminant colitis -Pseudomembranous colitis
- Chronic non-specific ulcerative colitis -Diabetes mellitus type 1
- Severe diarrhea by antibiotics -Non-reversible, severe diarrhea. -Atopic diseases (asthma and eczema) Celiac disease
- Cardiovascular diseases (in review) -Neurological diseases
- Multiple sclerosis -Constipation
- Hyper or hypothyroidism -Morbid obesity
- Idiopathic thrombocytopenic purpura -Irritable bowel syndrome
- Chronic fatigue syndrome -Metabolic syndrome -Bacterial overgrowth -Collagenous Sprue -Tropical Sprue
- Autoimmune disorders (rheumatoid arthritis, Dermatomyositis, Scleroderma, fibromyalgia, lupus erythematosus, osteoarthritis and osteoarthritis)
- Eosinophilic gastrointestinal disorders -Neurodegenerative disorders -Neuro-developmental disorders

Patient	Condition Main	Secondary Conditions
Case 1	Anxiety	Bronchial Asthma Irritable Bowel Syndrome, Diarrhea Variety
Case 2	Irritable Bowel Syndrome, Diarrhea Variety	Anxiety
Case 3	Anxiety	Irritable Bowel Syndrome, Mixed Variety
Case 4	Anxiety	Fibromyalgia Irritable Bowel Syndrome, Diarrhea Variety
Case 5	Intestinal Malabsorption, (Diarrhea)	Anxiety
Case 6	Anxiety	Metabolic Syndrome
Case 7	Irritable Bowel Syndrome, Diarrhea Variety	Anxiety Dyslipidemia Alcoholism High Blood Pressure
Case 8	Anxiety	Obesity Irritable Bowel Syndrome, Diarrhea Variety Diverticular Disease of the Colon Renal Lithiasis Uterine Fibroids

Case 9	Anxiety	Irritable Bowel Syndrome, Diarrhea Variety Neurodermatitis
Case 10	Irritable Bowel Syndrome, Diarrhea Variety	Anxiety

Table 1: Diseases which led to transplant of intestinal microbiota.

Patient	condition main	secondary conditions
Case 1	anxiety (6 years)	Bronchial asthma (3 years) Irritable bowel syndrome, diarrhea
Case 2	Irritable bowel syndrome, diarrhea variety (2 months)	variety (3 years) anxiety (5 years)
Case 3	anxiety (8 years)	Irritable bowel syndrome, mixed variety (4 years)
Case 4	anxiety (7 years)	Fibromyalgia (2 years) Irritable bowel syndrome, Diarrhea variety (3 years)
Case 5	Intestinal malabsorption, (diarrhea) (1 month)	anxiety (2 years)
Case 6	anxiety (4 years)	metabolic síndrome (5 years)
Case 7	Irritable bowel syndrome, Diarrhea variety (6 years)	anxiety (5 years) Dyslipidemia (20 years) Alcoholism (20 years) High blood pressure (10 years)
Case 8	anxiety (Year & half)	Obesity (5 years) Irritable bowel syndrome, diarrhea variety (Year & half) Diverticular disease of the colon (Year & half) Renal lithiasis (Year & half) Uterine fibroids (3 years)
Case 9	anxiety (5 years)	Irritable bowel syndrome, Diarrhea variety (5 years) Neurodermatitis (5 years)
Case 10	Irritable bowel syndrome, Diarrhea variety (5 years)	anxiety (8 years)

Table 2: Main disease and chronicity

Patient	Condition Main	Secondary Conditions
Case 1	Anxiety (improvement of the 57.14%)	Bronchial asthma (ceded spasm) Irritable bowel syndrome, diarrhea variety (improvement of the 33.33%)
Case 2	Irritable bowel syndrome, diarrhea variety (improvement of 71.43)	anxiety (50% improvement)
Case 3	Anxiety (improvement of the 57.14%)	Irritable bowel syndrome, mixed variety (80% improvement)
Case 4	Anxiety (75% improvement)	Fibromyalgia (gave) Irritable bowel syndrome, variety diarrhea (100% improvement)
Case 5	(100% improvement) Intestinal malabsorption syndrome	Anxiety (improvement of the 33.33%)
Case 6	Anxiety (improvement of 62.5%)	Metabolic syndrome (under 1 k and 2 sizes)
Case 7	Syndrome of Irritable Bowel syndrome, variety, Diarrhea (50% improvement)	Anxiety (50% improvement) Dyslipidemia (20% improvement) Alcoholism (30% improvement) High blood pressure (not improved)
Case 8	Anxiety (60% improvement)	Obesity (20% improvement) Irritable bowel syndrome, variety, diarrhea (40% improvement) Diverticular disease of the colon (no improvement) Renal lithiasis (no improvement) Uterine fibroids (no improvement)
Case 9	Anxiety (90% improvement)	Irritable bowel syndrome, variety diarrhea (60% improvement) Neurodermatitis (80% improvement)
Case 10	Irritable bowel syndrome, variety, diarrhea (50% improvement)	Anxiety (60% improvement)

Table 3: Results of intestinal microbiota transplantation.

Conclusions

They were 7 men and 3 women, with ages ranging from 35 to 83, with a main condition, and 5 patients with 1 co-morbidity; 4 patients with Comorbidities 2 and 1 patient with Comorbidities, added 4.

All cases improved his primary condition, with rates that were 50 to 100%. 6 patients were enrolled with anxiety of different levels; 4 with 1 and irritable bowel syndrome with intestinal malabsorption.

Within the co-morbidities improvement occurred in 5 patients with irritable bowel syndrome; 4 with anxiety; and 1 with bronchial asthma, fibromyalgia, metabolic syndrome, Dyslipidemia, alcoholism, obesity; While there was no improvement in patients with diverticular disease of the colon, kidney lithiasis, and uterine fibroids.

Three cases favorably surprised us. The first to give up the bronchial spasm (asthma), completely at the end of the transplantation, the second not introducing a woman no symptoms 6 months later. "Even gave me flu, told us" and the 3rd. To give anxiety 2 days after the (IMT) and give full neuro-dermatitis, fifteen days after the transplant.

There were three patients who attended with diarrhea post-transplant. 2, 4 and 5 bowel movements per day, respectively, which surrendered with probiotics in 3, 4, and 7 days. One of the patients added antiparasitic.

Personal suggestions

The priority in the IMT is the selection of an excellent donor, who carried out all the necessary studies, avoiding transmit some disease.

To select the recipient, should try to use all her therapeutic existing methodology, before undertaking (IMT).

We prefer to use the jejunal tract or colon, for the reasons already stated. The amount of microbiota to transplant believe must be at least 500 milliliters. The IMT is a safe procedure and complications occur, tend to be reversible.

Not expect total healing, although the response is magnificent, corrections tend to be between 40 to 70% improvement. The literature reports that in some patients, two or more transplants, are required to enhance their clinical status. In our cases has no need, only a transplant, to date, in which we have been 2 years of follow-up.

The literature also reports that there is reversal of the (IMT) usually a year. We have not noticed this circumstance.

The results of improvement manifested by patients have fluctuated between 2 days to 2 weeks from the date in which the transplant was made.

Our case is not very high, because it is quite expensive (IMT), given the basis of laboratory studies conducted to the giver.

Future of transplantation of microbiota

In the future will have to consolidate this procedure and to place it in their fair dimension, we'll include new conditions and they will be some of those who are considered likely, to be treated, currently.

The methodology is cheaper and we observe tablets, capsules, syrups, liquids for enemas, containing the specific bacteria or bacteria specific determinants of sufferings and carried out a revolution to learn more of the genome and the therapeutic effects of different products.

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