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Intestinal Transplant: A Myth in México

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INTRODUCTION

Intestinal transplantation is the primary treatment option for eligible patients with severe gastrointestinal diseases, including inflammatory bowel diseases, acute mesenteric infarction, and refractory end-stage intestinal failure. In the United States of America, an average of 90 intestinal transplants have been performed per year since 2019. [1] Even with significant advances in surgical techniques and immunosuppression, up to 44% of intestinal transplant recipients still die within 5 to 10 years of intestinal transplantation. [2] Transplant types such as intestinal transplantation, combined liver-intestine transplantation, and multivisceral transplantation have been documented, which are like the standard of care for patients with irreversible intestinal failure. Alexis Carrel's pioneering work in experimental surgery, particularly in vascular surgery and organ transplantation, earned him the Nobel Prize in Medicine in 1912. [3] The first canine model of isolated intestinal transplantation is successfully reported in 1959. [4] In 1967, Lillehei performed the first human intestinal transplant, with vascular reconstruction, which was performed through the donor's mesenteric vessels anastomosed to the recipient's common iliac vessels, but the patient died shortly after. (12 hours after surgery). [5] In 1992, 5 cases of intestinal transplantation were performed, two adults and three children with a survival of up to 193 days. And then 16 patients survived 23 months. [6, 7]

In Mexico, intestinal transplantation has been carried out documented as successful, unpublished and anecdotally; however, no long-term survival has been reported, according to the references found and to date, no tangible results of this surgical procedure have been publicly evidenced, the real reason is unknown. [8, 9, 10]

The latest report by the World Health Organization's (WHO) Global Observatory on Donation and Transplantation (GODT) showed that 157,494 transplants were performed in 2022, meeting less than 10% of global needs. Among them, 170 were intestinal transplants (0.1%). And most of them are only made by England and the United States of America, in Latin America there are only a few countries that have carried it out sporadically such as Brazil (7 cases), Chile (3 cases), Mexico (2) and Argentina (1 case). [8, 9, 10, 11]

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It should be noted that solid organ transplantation in children is not easy, although it is a life-saving therapy, however, pediatric organ donation rates remain suboptimal; in Canada, response rates were 82% and 83% respectively for donated organs and transplant projects comprising 7 kidney programs. 3 heart, 2 lung, 2 liver and 1 intestine. [12] Simultaneous transplantation of these two liver and intestine organs is performed using grafts from a deceased donor; but there have been no such cases in Japan and the details of the procedure are still unclear. [13]

SHORT BOWEL SYNDROME

It is very complex to tacitly define the so-called short intestine, where the actual length of it is the guideline for its function, this will depend on many factors at the time of its counting or evaluation, since it is not exact or reliable, it is very subjective in terms of arithmetic or absolutely, being impossible or practically fatuous. Short bowel has been defined as those patients who have had an intestinal resection that leaves a short length, approximately 2 m or less of residual small intestine, and counting from the ligament of Treitz. [14, 15] The small intestine has three portions (duodenum, jejunum, and ileum, 4 to 5 centimeters wide and 6 to 7 meters long (the duodenum is 25 to 30 cm). The colon or large intestine is on average 10 centimeters wide, with a total length of 120 x 160 cm total. [16, 17]

In addition, intestinal length can vary from one subject to another due to the same constitution, the same weight, height, or being male or female, or the same age, or genetic or hereditary pathologies. [18]

Without also leaving aside that the dimensions of the small intestine and the large intestine can be altered by the following causes, with dilation or extension or elongation when there is a pathological condition or the combination of one or more of them such as: intestinal occlusion, [19] paralytic ileus, severe systemic malnutrition, a restrictive and/or specific diet, mesenteric ischemia, [20] metabolic or chronic-degenerative diseases, inflammatory bowel diseases, [21] cancer, [22, 23] etc.

We must not forget to mention the very high stomas, that is, jejunum, that some surgeons do in a wrongly scheduled surgery or because they have no other option in a trauma surgery or so-called emergency "damage control surgery", which leads to a short bowel syndrome in the patient. [24] In the pediatric population, causes of short bowel syndrome are gastroschisis, intestinal atresia, necrotizing enterocolitis, midgut volvulus, and Hirschsprung's bowel disease. [25] Patients with short bowel syndrome and not yet achieved intestinal adaptation, [26] will require artificial nutrition as the only vital option, but may present with several gastrointestinal disorders that interfere with digestive function, induce systemic inflammation, and influence physiological metabolic pathways, affecting energy and protein balance; with a refeeding syndrome that is considered a fatal condition, by fatal changes in fluids and electrolytes, resulting from metabolic and hormonal alterations that can occur in malnourished patients with artificial nutritional therapy. [27, 28]

In the most active European centers, intestinal transplantation is planned; it should be noted that, although it is a difficult procedure, it should be considered as a therapeutic option for children with total, definitive intestinal failure that is complicated when intestinal

rehabilitation fails, as the only and last option for life. Patients should be approached early by multidisciplinary teams from canters specializing in intestinal transplantation. [29]

Most countries in the world are not able to offer all the necessary steps to treat short bowel syndrome. Therefore, the development of cooperation networks between countries is necessary to ensure access to comprehensive treatment for the majority of patients on all continents of the world, but especially in low-income countries, since it requires complex multidisciplinary management, considerable resources and inputs of great economic value and in the very long term. [30]

GENERAL CONSIDERATIONS

Organ transplantation involves removing an organ from one person (the donor) and placing it in another (the recipient). This procedure is performed in patients with terminal organ failure, or by brain death or circulatory death; The process comprises five phases, which may overlap, and are listed below: [31, 32]

- "Phase I: Identification of potential organ donors and referral to an organ procurement organization.
- Phase II: Declaration of death and obtaining consent for organ donation.
- Phase III: Donor evaluation.
- Phase IV: Donor management.
- Phase V: Organ procurement."

Of the solid organ transplants, the intestinal transplant is the most complex, since it must be considered that in intestinal transplantation there is a massive number of lymphocytes present in the epithelial, subepithelial and lymphatic tissue of the entire small intestine, together with constant exposure to external antigens and the extensive commensal microbiota. which provide an active and intense immune environment in the tissue of the intestine. [33]

Acute cell rejection which is antibody-mediated rejection or chronic allograft failure and graft-versus-host disease; They are the main causes of graft loss and death in recipients, usually accompanied by infections that exacerbate inflammatory lesions in the allograft. [34]

The brain-dead donor is associated with hemodynamic, metabolic, and immunological dysregulation that could affect graft tissue quality, villi damage, and increased levels of fatty acid-transporting protein. [35] Acute rejection of intestinal transplantation is the leading cause of graft loss and an important predisposing factor to chronic rejection, occurring more frequently in isolated transplants and particularly with splenectomy. [36]

On the other hand, the need to have knowledge or the concern that should matter the most is that in the transplantation of a living donor it is the well-being and safety of the donor. To ensure this, only individuals with a low operative risk should be considered as possible quantities. In addition, HLA compatibility, ABO compatibility, and lymphocytotoxin cross-compatibility must be considered. [37]

Antibody-mediated transplanted small intestine graft rejection is of multiple and varied cause, which can be due to:

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1. donor-specific antibodies
2. acute tissue injury, with focal fibrin thrombin in the capillaries of the lamina propria, C4d deposition
3. anti-human leukocyte antigen antibodies
4. Other [38]

Chronic rejection occurs in 10-20% of small bowel transplants, with a lower number in transplants involving the liver. Unequivocally, the resection of the organ is the only thing that culminates this reaction. [39]

Graft-versus-host disease is the result of immune responses exerted by immune cells capable of the allograft to the recipient's organs, occurring in approximately 20 to 50% of patients after transplantation. In severe cases it is fatal, as already mentioned it is divided into acute and chronic. [40] Acute occurs during the first 100 days after transplantation or at any time by donor T cells and manifests in the skin, gastrointestinal system, and liver. Chronic disease, on the other hand, is a disease that occurs after the first 100 days of transplantation and is very similar to an autoimmune disease. [41]

The high immunogenic burden of intestinal transplantation and the unsatisfactory results of treatment with conventional immunosuppressive agents has initiated a fierce search for the fact of the viability of the graft for as long as possible. In addition, there is a risk of bacterial overgrowth of the small intestine that causes diarrhea and poses challenges in both diagnosis and treatment. [42]

On the other hand, the importance of gastrointestinal health in maintaining overall health and preventing disease is not a new concept, as the significant role of the bacterial gut microbiome in mental health and neurodegenerative disorders has been understood and described within the framework of the microbiota-gut-brain axis. Impaired situation in a short bowel syndrome and/or after an intestinal transplant. [43] The small intestine harbors a central microbiota throughout, supplemented by specific taxa unique to segments of the tract. This dynamic environment in the small intestine is characterized by a less diverse and less densely populated microbiota compared to the colon. [44] Complex interactions between dietary nutrients, resident microorganisms, and the host then occur, positioning the microbiota as a crucial component of the microbiota-gut-brain axis. [45]

It should be taken into account or considered that patients with intestinal transplantation will continue for a certain time with artificial nutrition that can last up to 1.5 years, and some will even receive Teduglutide in combination. [46]

The enteric nervous system is composed of an extensive interconnected network of enteric neurons and glial cells that reside within the intestinal wall and regulate the numerous complex functions of the gastrointestinal tract, as they result in severe morbidity due to the major and severe alteration in intestinal motility. Current treatment for these conditions does not address the absence or loss of enteric neurons underlying their pathophysiology, but instead focuses on symptom management or surgical removal of affected intestinal segments only. [47] At the end of the day, intestinal transplant outcomes continue to be hampered by higher rejection rates than any other solid organ. However, maintenance immunosuppression regimens have

remained largely unchanged despite advances in therapies for induction, rejection treatment, and graft-versus-host disease. [48] Intestinal transplantation continues to be plagued by low survival rates and a high risk of allograft rejection, so extensive investigations are conducted into the roles of innate immune cells that are macrophages, natural killer cells, innate and adaptive lymphoid cells such as Th1, Th2, Th17, Tregs in inflammatory responses, in particular inflammatory bowel disease and graft-versus-host disease, and correlate these findings with intestinal allograft rejection, highlighting which effectors exacerbate or suppress intestinal rejection. [49]

One aspect of this panorama that is often not considered by the surgeon is that in patients with intestinal transplantation it is the appearance or temporal evolution of complications of a pediatric delirium related to the process, since at all ages it is associated with a poor prognosis, as reflected in a prolonged hospital stay. worse cognitive and functional outcomes and a higher mortality rate. [50]

SURGICAL CONSIDERATIONS

In free jejunal transfer, the ischemic tolerance time of the jejunum must be known, as it is crucial, ischemia tolerance in humans is unknown. In this research, time is exposed. jejunal flap ischemia, which ranged from 1 hour 24 minutes to 6 hours, with a mean of 197 ± 55.5 minutes; 4% have necrosis and 22% present with stenosis of the intestinal anastomosis, with two negative predictive factors such as age over 75 years and ischemia of the donated intestinal tissue that is greater than 3 hours. [51] Animal studies have suggested that the jejunum can tolerate ischemia for as little as 2 hours to up to 3 hours, with visceral anastomosis and posterior vascular anastomosis. The jejunal anastomosis goes first and then it is followed by a vascular anastomosis, the surgical procedure is more beneficial with an easier jejunal anastomosis to start, but it suffers from a longer jejunal ischemia time, corroborating that it can resist up to 4 hours without having any sequelae or consequence in the evolution of the patients. [52]

It should be considered that the most common reason was surgical complications, once the transplant was already performed (performed in Brazil). The spectrum of disease is widely variable from malabsorption of a single micronutrient to complete intestinal failure, depending on the remaining length of the small intestine, the anatomical portion of the intestine, and the function of the remaining intestine. [53]

Intestinal transplantation has a high morbidity rate (50%) but a significant proportion of patients who achieve nutritional autonomy (40%) has been quantified. The standard indication includes patients with a reasonable life expectancy. Recent advances can be deduced from the increase in the number of bowel transplants in adults: this is due to the continuous improvement in graft survival at 1 year worldwide (with no differences of 3 and 5 years). [53, 54] It has also been surgically mentioned that post-transplant inflammatory bowel disease occurs, which can occur after testosterone replacement therapy. Patients present with non-stenosing inflammatory disease, although one patient experienced fistulizing disease. (It must be considered a pathology typical of the same surgical technique, due to ischemia-spasm-vascular, stenosis-vascular of the anastomosis, or vascular-rupture, vascular-trauma and vascular-manipulation, with excessive-ischemia, cold and/or very prolonged hot ischemia, due to alteration of healing, malnutrition, anemia, technique, sutures, etc.) [55] The surgical

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procedure of a living donor begins with a short incision in the midline to access the abdominal cavity, which explores the entire cavity and carefully measures the small intestine, which extends from the ligament of Treitz to the ileocecal valve. Subsequently, the cecum and terminal ileum are located and marked, approximately 30 cm proximal to the ileocecal junction. In the case of donor surgery, the goal is to harvest 200 cm of the distal ileum (160 cm in pediatric patients), ensuring the preservation of at least 20 cm of the distal ileum. [53]

What is the time of surgery? There is currently debate about the timing of enterectomy before intestinal transplantation. Some have argued against having patients undergo additional abdominal surgery and are in favor of performing the enterectomy simultaneously at the time of intestinal retransplantation. However, others have documented that the transplanted gut can act as a source of bacterial translocation and that enterectomy of the allograft prior to retransplantation can reduce the risk. [56]

It is evident that scientific medical publications will not be found in the medical literature on the surgical complications of intestinal transplantation; The fact that they do not have references does not mean that they do not exist, which is why they are described in animal experiments of small intestine transplantation; To cite an example, the various surgical complications, including hemorrhagic shock, intraoperative thrombosis, intestinal obstruction and twisting of blood vessels that resulted in intestinal necrosis and death. [57] In isolated small bowel transplantation, it includes the entire small intestine with or without a colon, which consists of removing the small intestine from the donor angle of Treitz to the terminal ileum, with the superior mesenteric artery and vein, to the portal vein. Arterialization of the graft can be done from the recipient's superior mesenteric artery or the infrarenal aorta. Restitution of distal intestinal transit was performed with an ileocolic latero-terminal anastomosis, 20 cm proximal to the end of the ileum, which is externalized by a terminal ileostomy, for monitoring of the graft with endoscopies and biopsies. [58, 59]

See Figure 1.

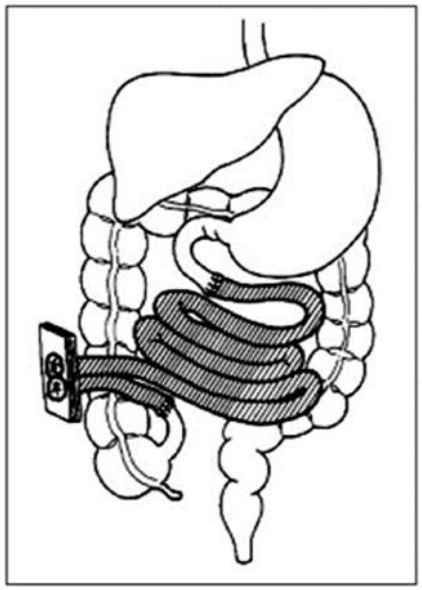

Figure 1: The mesenteric artery of the graft was anastomosed to the infrarenal aorta and the mesenteric vein to the recipient's infrared cava. It was optimally reperfused. Transit was

reconstituted using the small intestine in its entirety (approximately 6 m), performing proximal duodenoyejunal and distal ileoileal anastomosis. Ileostomy was left in the graft loop 15 cm from the distal anastomosis for endoscopic and histological control of the transplanted intestine. Image taken from reference: Buckel G. E., Ferrario B. M., Uribe M. M., et al. First intestinal transplant in Chile: Clinical case. Rev. méd. 2009; 137 (2): 259-263. [60].

Intestinal transplantation has been successfully employed in the treatment of patients with familial adenomatous polyposis and with unresectable intra-abdominal desmoid tumors, where there is no description of the technique or tactic for the restoration of the distal part of the intestinal graft, the strategy of including the ascending colon in the intestinal graft, regardless of the fact that intestinal continuity will be restored, It is based on the hypothesis that the presence of the colon and the preservation of the ileocecal valve could lead to more solid stools, thus reducing the risk of dehydration and local irritation, which due to space situations the transplant usually involves only the ascending portion of the colon. [61]

On the other hand, the absolute and relative contraindications of intestinal transplantation are listed. The absolute ones are oncological disease, HIV infection, heart failure or severe pulmonary pathology, uncontrolled sepsis, neurodegenerative diseases and systemic autoimmune diseases or severe immunological disease. Relative laparotomies are older than 60 years, low nutritional status, and the number of previous laparotomies. [59] There are defined endoscopic criteria for detecting graft rejection, as well as a protocol for endoscopic surveillance of graft at the same time for biopsies performed after intestinal transplantation, at 5 days, then weekly for 1 month, then every 2 weeks for the next 2 months, and monthly for the next 6-12 months. [62] After intestinal transplantation, surveillance ileal mucosal biopsies provide a unique opportunity to map the dynamic establishment of recipient intestinal lymphocyte populations under immunosuppressed conditions, and it is still unknown how intestinal B-cell populations and B-cell receptor repertoires are established and maintained over time in humans. [63]

The different types of intestinal transplant surgical technique:

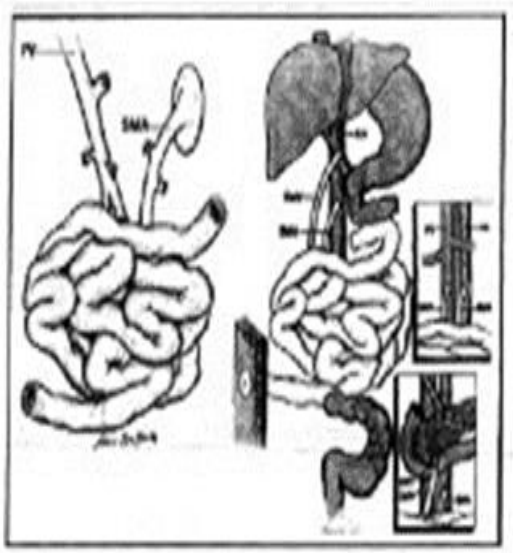

Figure 2: Isolated intestinal transplantation.

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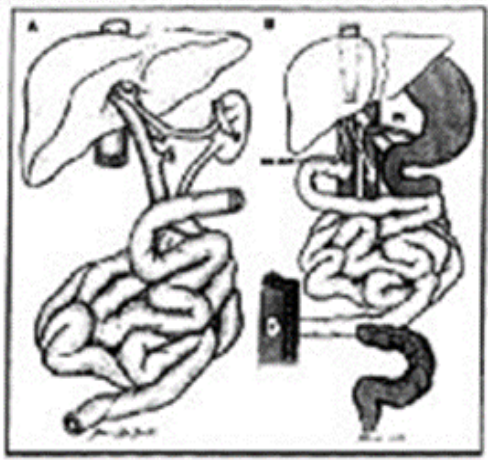

Figure 3: Hepatic and intestinal transplantation.

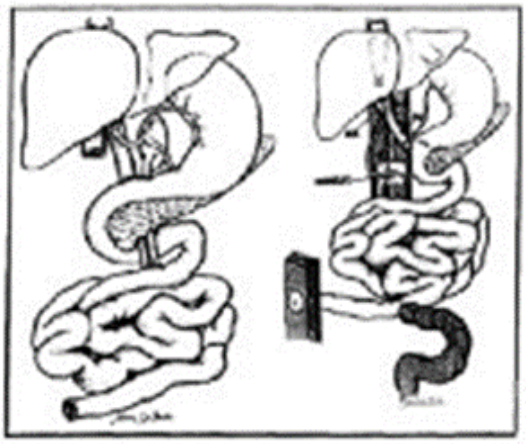

Figure 4: Complete multivisceral transplant: liver, stomach, duodenum, pancreas, small intestine, with or without colon.

Figure 5: Modified multivisceral transplant: without the liver.

Images figures 2 to 5 taken from the reference: Padillo J., Álamo J.M., Suárez G., et al. Intestinal and multivisceral transplantation. Rapd online. 2014; 37(6): 326-332. [64].

RESPECTS

The different present and future strategies in intestinal transplantation.

Tacrolimus is a calcineurin inhibitor and inhibits T-cell activation (its mechanism of action is unknown to date), which revolutionized intestinal transplantation by taking the procedure from experimental to lifesaving, with 1-year patient and graft survival rates of 69%. [65] With its immunosuppressive effect and narrow therapeutic range, blood concentrations of FK506 should be monitored, which is essential to avoid nephrotoxicity from this drug. [66] In addition, tacrolimus and corticosteroids are the most used immunosuppressive therapy in the treatment of food allergies with a highly variable incidence ranging from 3.3% to 54.3%, as consistent immunological monitoring, such as skin testing and IgE level assessments, are essential for the early detection and treatment of allergies in these patients. [67] On the other hand, this immunosuppressant, which is commonly administered after solid organ transplantation, is characterized by a narrow therapeutic window and high variability in exposure, requiring personalized dosing. [68, 69]

Another way to address intestinal transplant rejection is the so-called mixed chimerism, which allows it to be long-lasting and with immune tolerance without toxicity, in this research the recipients did not show clinical or histological signs of rejection and chimerism did not vary. These results demonstrate the potential value of generating its long-lasting effects in achieving bowel transplant tolerance. [70]

Advances in microcatheter technologies and vascular imaging modalities have allowed access to any part of the intestine through its blood supply, including areas that are difficult to reach endoscopically. Therapeutic administration has been facilitated by endovascular techniques or at the segmental level. Treatment with infliximab and high-dose IV methylprednisolone yielded a modest endoscopic and histopathological response, however, an angiography during the same anesthesia identified arterial supply to the ileocecal region, after which intra-arterial methylprednisolone was administered, achieving a marked improvement in ulceration and histopathology that showed resolution of cryptitis and regenerative changes in enterocytes. [71]

A growing incidence of antibiotic resistance in terms of therapeutic options has been pointed out, especially in immunosuppressed patients, such as in transplant patients; where the imbalance of the microbiota caused by the use of antibiotics and low host immunity favors intestinal overpopulation with pathogenic species, leading to an increase in bacterial translocation and susceptibility to serious systemic infections. [72]

Acute graft-versus-host disease, which is a fatal complication in organs with abundant lymphoid tissue such as the liver and intestines, where it was successfully managed with ruxolitinib, describing a potential treatment approach, which in addition to drug therapy including 5-aminosalicylates, steroids, and azathioprine; biological therapy was added that was combined with the different drugs mentioned above, With the use of vedolizumab, infliximab, and adalimumab, with some adjustment of immune suppression. [71, 73] The efficacy and safety of vedolizumab combined with basiliximab as second-line therapy result in a greater therapeutic response and longer overall survival in patients with acute graft-versus-host disease. [74]

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Another more recent option, which although still limited in use and consistent treatment protocols lacking, is extracorporeal photopheresis, as well as extracellular vesicles derived from mesenchymal stem cells that have been used to treat refractory rejection after intestinal transplantation as embryonic stem cells present new opportunities to address graft rejection and inflammation in intestinal transplant recipients. [75] On the other hand, a final possibility is to be able to perform an intestinal retransplantation when there is an acute rejection during the first year of the primary intestinal graft, which is the most frequent, or in its absence a chronic rejection; since it is planned to perform a new surgical procedure that is already of low incidence and that few centers report a significant experience. [56]

It should be noted that intestinal graft bioengineering that focuses on developing functional and/or viable intestinal tissue as an advance in regenerative medicine with cellular elements, biomaterials and biochemical signals to obtain a tissue that recapitulates the native human intestine, has become a possible cutting-edge solution that promises to revolutionize patient care. [76] And together with regenerative cell therapy of enteric neuropathies, it is a promising treatment option that directly addresses the fundamental problem and, together with the transplanted nerve fibers, interacts and travels exclusively along and within the muscularis propria. [46, 77]

CONCLUSION

Intestinal transplantation is actually a viable, unique and recommendable option; however, the ideal conditions must be met for its correct implementation. Unfortunately, in Mexico the limitations are extreme with a total absence of health policies in this area (lack of administrative vision of decision-makers), the lack of competencies and integration (organization) of multidisciplinary teams, the meagre and irrational use of economic resources allocated to the health sector, as well as the immeasurable lack of material and human inputs (lack of administrative competence); all this is recalcitrated to become a myth, since it is a fact of not truly carrying out a large-scale intestinal transplant project in Mexico.

Conflict of Interest

The authors stated that they had no potential conflicts of interest regarding the research, authorship, and/or publication of this article

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