Intestinal Transplantation (ITx): "Who, when and how?"a general overview

Transplante de intestino: para quem, quando e como? uma visão geral

Anne Margot Roskott[1] , Flávio Henrique Galvão[2], Vicent B. Nieuwenhuijs[3]

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RESUMO: O transplante de órgãos se tornou parte importante da medicina moderna. O transplante de intestino (ITx) foi introduzido no final da década de 1960 como um procedimento heróico para tratar falência do intestino. O Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo foi um dos pioneiros mundiais neste procedimento. Com a evolução biotecnológica na medicina, o transplante de intestino emergiu na década de 1990 como a única e permanente opção terapêutica para pacientes com falência intestinal irreversível. Àquele tempo, os resultados clínicos eram, ainda, desapontadores, principalmente devido às altas taxas de infecção pós-operatória e rejeição do enxerto. Entretanto, houve um grande desenvolvimento do transplante intestinal e multivisceral graças à melhoria da terapia imunossupressora, ao refinamento das técnicas cirúrgicas e dos cuidados pós-transplantes. O objetivo deste estudo é oferecer um panorama sobre quando o ITx deve ser indicado e sobre como o procedimento deve ser realizado.

DESCRITORES: Intestinos/transplante. Nutrição parenteral. Intestinos/patologia.

INTRODUCTION

Organ transplantation has become a substantial part of modern medicine. Transplantation is a treatment option is case of organ failure such as the kidney, liver, heart, lung, pancreas and, recently also for intestinal failure.

Intestinal transplantation (ITx) was introduced in the late sixties as a heroic procedure to treat intestinal failure. The Clinic Hospital of University of Sao Paulo Medical School is one of the world's pioneer in this procedure. The legendary Professor Okumura performed in 1968 and 1969 the second and the third intestinal transplantation published in the medical literature, achieving one of the best survivals at that time; however, strong graft rejection and infection impaired the long term survival of this procedure[34-38].

Important advances in Total Parenteral Nutrition

1. Medical Doctor, Researcher and PhD student of University Medical Center of Groningen – Groningen University, the Netherlands.
2. Medical Doctor, Fellow of Pittsburg University, Surgeon of Liver Transplantation Team of Clinic Hospital of University of Sao Paulo Medical School.
3. Medical Doctor, PhD - Department of Surgery, Section Abdominal Surgery, Transplantation and Organ Donation of University Medical Center of Groningen – Groningen University, the Netherlands.

(TPN) successfully brought longer survival to intestinal failure patients and became the paramount treatment for this disease. Nevertheless, TPN promotes many inconveniences, such as inability to eat, catheter infections, metabolic and hydroelectrolytic alterations and dysfunction of other organs, mainly the liver.

With the biotechnological evolution in medicine, intestinal transplantation emerged in the 1990s as the only curative, permanent therapeutic option for patients with irreversible intestinal failure. At that time, the clinical results were also disappointing mainly due to the same high rates of post-operative infectious complications and graft rejection. However, the development of intestinal and multivisceral transplantation has been profound owing to the progress in immunosuppressive therapy, refinement of surgical techniques, and post-transplant care including immunological as well as anti-infectious monitoring[1,1,2,2]. This progress has accordingly caused substantial advancement in graft and patient survival (Table 1).

TABLE 1. Graft and patient survival after transplantation

Transplant type	Survival	1-year	3-year	5-year
Liver only (deceased donor only)	Graft survival	82.2%	73.2%	66.9%
	Patient survival	86.8%	79.1%	73.1%
Intestine only	Graft survival	73.8%	46.7%	37.6%
	Patient survival	85.7%	60.6%	53.5%
Liver/intestine	Graft survival	65.7%	49.7%	44.1%
	Patiënt survival	66.7%	56.6%	47.2%

Reprinted from Fryer JP. The current status of intestinal transplantation. Advances in Digestive Disease. Published by AGA Institute Press, 2007.

ITx has evolved from being considered an experimental procedure to become a clinically accepted therapy, now performed in over 73 centers worldwide, with over 2000 transplants to date.

The field of transplantation is not covered in the current medical curriculum despite a great interest and positive attitude of medical students towards organ donation and transplantation[1-3]. Therefore, especially the subject of intestinal transplantation which is a relatively novel transplant type - is generally unknown to the medical student and most specialists not directly involved in transplantation.

The aim of this paper is to give a general overview of intestinal transplantation.

This overview will address patient population and indications, types of intestinal transplant procedures, intestinal preservation, postoperative care (immunosuppression, control of infection and nutritional approach), and outcome (complications, rejection and survival). Finally, specific difficulties and future perspectives will be discussed.

Experimental bases

The first reported small bowel transplantation was performed by Lillehei et al.[39] fifty year ago on dogs. In 1960, Starzl and Kaupp[40] described the first experimental observations of multivisceral transplantation, also on dogs. In 1972, Monchick and Russel[41]described the first microsurgical technique for intestinal transplantation on rats. Due to the genetic possibility, low cost and praticity, the rat became the best model to perform research on intestinal transplantation.

Experimental research was fundamental for the development of intestinal transplantation, including the evaluation of new immunosuppressant drugs. These studies reproduced and tried to control the main complications of intestinal transplantation, like the low period of graft preservation, graft rejection, graft-versus-host disease, and serious infections[40-58].

Experimental studies were conducted, showing that the strong rejection of the graft is due to high concentration of lymphoid tissue present in the intestine. After intestinal transplantation, a bidirectional flow of immunocompetent cells occurs between the recipient and the donor's organ. This exchange between donor and recipient cells is a phenomenon known as chimerism, leading to activation of potent immune complexes that cause not only strong graft rejection but also other complications, such as graft-versus-host disease and lymphoproliferative diseases[42-62].

The acute cellular rejection is frequently observed in intestinal transplantation and causes high morbidity and mortality due to the loss of integrity of the intestinal mucosa barrier, bacterial translocation and sepsis. Prevention, early identification and appropriate treatment are essential to control the morbidity of this procedure. Moreover, the strong immunosuppression

usually used to control rejection can cause various complications, such as susceptibility to infections, tumors and toxicity to various organs[42-62].

Using an experimental study with rats, they developed a new method of immunosuppression and immunomodulation to induce immune tolerance that lead to remarkable results. These patient with intestinal transplantation achieve better recovery, return to oral nutrition, improved quality of life and completely independence of total parenteral nutrition (TPN). The latest immunosuppression protocol lead to excellent results in intestinal transplantation, with significant reduction in the rate of rejection and other complications of immunosuppression. It is based on potent preoperative immunosuppression (induction) with high-dose antithymocyte globulin (ATG) or anti-CD 52 (CAMPATH), irradiation of the intestine, bone marrow infusion and continuous tacrolimus monotherapy. In clinical practice this model has been used without the irradiation and marrow infusion, and has seen encouraging results[60-65].

In the laboratory of Experimental research in transplantation of LIM 37 of FMUSP we are currently researching new trends on surgical techniques, xenografts, rejection and preservation of intestinal and multivisceral transplantation[42-49].

Patient population

Intestinal Failure (IF)

Intestinal failure (IF) is defined as the critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for maintenance in adults or growth in children[4]. Fortunately, IF is relatively rare. The incidence in Europe is 4-6/ million, and the prevalence 2-20/ million inhabitants. The natural history is variable and is largely influenced by the underlying disorder. The most common type of IF is secondary to short bowel syndrome (SBS) after extensive surgical resection of the small bowel for different reasons. SBS is generally defined as a remnant length of < 150-200 cm[5].

Functional intestinal diseases, like malabsorption or dysmotility disorders, can also result in IF. Causes of IF are multiple and differ between adults and children as displayed in Table 2. IF can be partial (patient is able to have some oral/ enteral intake) or total (patient fully depends on parenteral nutrition), and temporary (reversible) or permanent (irreversible).

TABLE 2. Causes of IF

Pediatric/ congenital	Adult/ acquired
• jejuno-ileal atresia	
• gastroschisis	• midgut volvulus
• necrotizing enterocolitis	• mesenteric vascular thrombosis/ ischemia
• midgut volvulus	• extensive surgical resection
• motility disorders	• inflammatory bowel disease
- Hirschsprung's disease	• abdominal trauma
- pseudo-obstruction	• chronic intestinal pseudo-obstruction
• inherited malabsorptive	• (desmoid) tumor
syndrome:	• radiation enteritis
- tufting enteropathy	
- microvillus inclusion disease	
- villus atrophy	

Total parenteral nutrition (TPN) and home parenteral nutrition (HPN)

Parenteral nutrition (PN) and home PN (HPN) is the mainstay of therapy independent of the cause of IF. Parenteral nutrition (PN) means feeding a person intravenously, bypassing the usual process of eating and digestion. The patient receives nutritional formulas containing salts, glucose, amino acids, lipids and added vitamins. It is called total parenteral nutrition (TPN) when no food is given by other routes in contrast to partial IF (patient is able to have some oral/ enteral intake). Alternatively, the degree of IF can be evaluated according to the amount of PN required for maintenance and/ or growth. PN dependence/ irreversibility is thought to be influenced by the length of remnant small bowel and the anatomy of the digestive circuit in SBS. Three types of SBS are distinguished: type 1; end-enterostomy without colon, type 2; jejuno-colic anastomosis with some colon in continuity, and type 3; jejuno-ileocolic anastomosis with full colon (Figure 1).

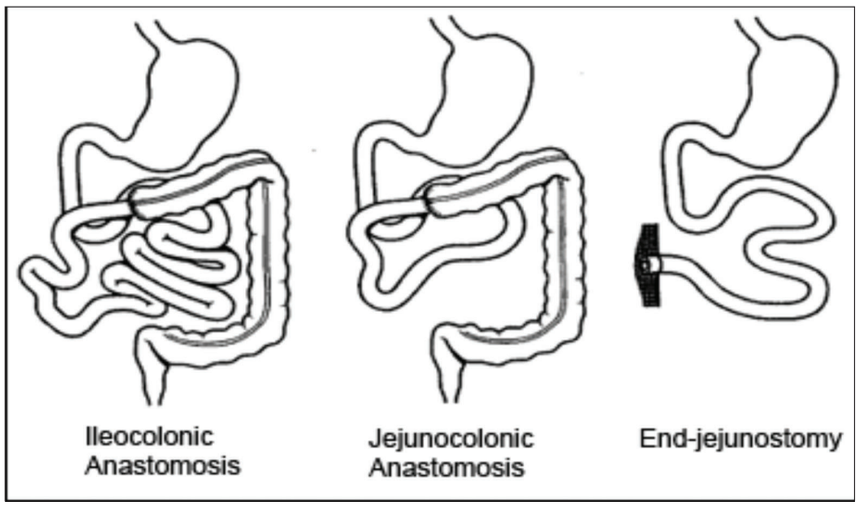

FIGURE 1. Types of short bowel syndrome. From Feldman: Sleisenger & Fordtran's gastrointestinal and liver disease. 7th ed. 2002. Figure 92-1, page 1808

The length of remnant small bowel and preservation of the ileocaecal valve and colon improves oral water-mineral and energy balances. The anatomy of remnant digestive circuit therefore highly predicts reversibility of IF. Independence from PN can be achieved with > 40 cm in type 3 SBS, > 60 cm in type 2 and at least 120 cm in type 1 SBS. More factors are being identified predicting reversibility and survival in IF. Clearly, in patients with a functional cause of IF the condition is irreversible. For example in (pediatric) patients with total intestinal aganglionosis, and in most patients with (mucosal) functional disease. Furthermore, abdominal wall defects are more likely to cause permanent IF.

In general, 3 and 5 year survival prognosis for IF patients treated with TPN are 86% and 75%, respectively. Survival is mainly influenced by the underlying disease. Desmoid tumor in familiary adenomatous polyposis (FAP), functional disorders, SBS with short remnant intestine (type 1 with < 50 cm remnant), mesenterial infarction and age (neonates < 1jr of age and higher age) and intestinal failure associated liver disease (IFALD) have a negative impact on patient survival.

The introduction of intravenous feeding and TPN in the 1960s generated a life saving treatment option for patients with IF. TPN allowed long term survival for the first time in patients with massive intestinal loss. Unfortunately, long-term TPN causes various serious complications. The permanent need for a central venous access catheter (CVC) for TPN administration exposes the patient to the risk of infection and/ or loss of access. The major parenteral nutrition related complications are blood stream infection (septicaemia), venous thrombosis, metabolic disorders (e.g. hyperglycaemia and/ or fluid and electrolyte dysbalance) bone disease, and parenteral nutrition associated liver disease (PNALD) as a consequence of the unphysiological nature of IV feeding [6].

It must be clear that the dependency on PN - the inability to eat, the practical aspects and it's associated complications - must have great impact on physical, psychosocial and social aspects of life and thereby can reduce the quality of life, as experienced by these patients[7].

Indications for ITx

HPN is still considered the primary treatment for chronic IF based on the comparison of relative safety and efficacy of both treatment options; HPN and ITx. Survival rates for PN therapy are superior to survival rates after transplantation.

International indication criteria have been established, but truly, practice differs among centers and individual 'patient case' exceptions are being made.

The US Center for Medicare and Medical Services has approved payment for ITx when HPN failure occurs, in view of life-threatening complications related to HPN[8].

Failure of HPN is defined by:

a) Impending (total bilirubine > 3-6 mg/dL, progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of parenteral nutrition/ IF associated liver disease (IFALD);

b) Central venous catheter (CVC)-related

thrombosis of ≥ 2 central veins;

c) Frequent central line sepsis: ≥ 2 episodes/ year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungemia; septic shock or acute respiratory distress syndrome;

d) Frequent episodes of severe dehydration despite intravenous fluid in addition to HPN.

The American Society of Transplantation position paper on pediatric ITx also considers patients with a high risk of death or with high morbidity related to their underlying intestinal failure as candidates for ITx[9]. High risk of death attributable to the underlying disease is defined by: a. Desmoids tumors associated with familial adenomatous polyposis (FAP) b. Congenital mucosal disorders (eg, microvillus atrophy, intestinal epithelial dysplasia) c. Ultra short bowel syndrome (gastrostomy, duodenostomy, residual small bowel < 10 cm in infants and < 20 cm in adults).

High morbidity IF or low acceptance HPN is defined by: a. Intestinal failure with high morbidity (frequent hospitalization, narcotic dependency) or inability to function (eg. pseudo-obstruction, high output stoma); b. Patient's unwillingness to accept long-term HPN (eg. young patients).

Contraindications for ITx are clearly defined[10]. Absolute contraindications are: a. Non-resectable malignancy (local or metastatic); b. Severe immunological deficiencies; c. Advanced cardiopulmonary disease; d. Advanced neurologic dysfunction; e. Sepsis with multisystem organ failure; f. Major psychiatric illness; g. Demonstrated patient noncom-pliance; h. Insufficient vascular patency for central venous access for ≤ 6 months after ITx.

Relative contraindications are: a. Age older than 65 years; b. History of cancer in the past 5 years; c. Physical debilitation; d. Lack of family support.

A prospective study (11) comparing survival in candidates (±ITx) and non-candidates based on these criteria as presented above (US Medicare and American Society of Transplantation) confirmed HPN as the primary therapeutic option for irreversible IF, and supported the appropriateness/ potential life-saving role of timely ITx for patients with HPN failure.

The low prevalence of ITx (10% in candidates, 20% all patients on HPN for irreversible IF) reflects a generally reserved attitude toward ITx[11].

Referral and screening

Since IF and long-term PN treatment is a complex and relatively rare disease condition, the care for IF patients should be multidisciplinary and specialized. Most countries have (several) intestinal failure centers. These centers have an IF program run by dedicated health professionals from different disciplines. Ideally such a team coordinates IF care and includes physicians, (pediatric) surgeons, (pediatric) gastroenterologists, microbiologists, nutrition specialist nurses, dieticians and pharmacists.

Local primary care givers managing IF patients should have a close link with these specialized IF centers. Early collaboration should be initiated for any IF patient whose PN requirements are more than 50% for at least 3 months after initiating PN. Intestinal failure centers, in their turn, should have close contact and an active collaboration with intestinal transplant centers for timely referral before a patient's condition has deteriorated.

The importance of timing and early referral is becoming more evident. Still, there are many unanswered questions about children and adults with IF and optimal timing of ITx is still unknown. Therefore, international recommendations state that intestinal failure databases should be established that can support multicenter studies and lead to the adoption of universally accepted standards of patient care with the goal of improving outcomes in all long-term IF patients including those requiring ITx[10;12].

Types of intestinal transplant procedures

The small intestine (including jejunum and ileum) is the defining part of any intestinal transplant type. Intestinal failure patients with the indication for ITx without irreversible parenteral nutrition/ IF associated liver disease (IFALD) are candidates for an isolated (intestine-only) intestinal transplantation (Figure 2a). However, long-term parenteral nutrition has frequently caused substantial degrees of IFALD and is part of the indication for ITx or has developed after the patient has been placed on the waiting list for an isolated ITx. In these patients a combined liver-intestine transplant (LITx, figure 2b) must be performed. Clinically this decision remains a difficult one, as the exact criteria when to include a liver (for what degree of IFALD) remain controversial and vary between transplant centers. The fact that non-cirrhotic liver injury appears to be reversible after ITx on the one hand, and on the other hand a chance that preserved liver function may deteriorate following isolated ITx makes this decision even more complicated.

A combined LITx can be accomplished with a composite allograft or with organs separately from the same donor. The pancreatic head and the duodenum are always included in LITx to facilitate en-bloc engraftment and to obviate biliairy reconstruction, particularly in children (this is the "so called" Nebraska variant).

In addition to isolated ITx and combined LITx, a multivisceral transplant (Figure 2c) represents a third type. Multivisceral transplantation includes transplantation of grafts of other abdominal viscera along with the liver and the intestinal graft. This may include the stomach, pancreas, spleen, and/ or colon. This procedure is usually reserved for patients with additional organ system failure (e.g. pancreatic insufficiency, diabetes, kidney failure), often on a background of a non-reconstructible gastrointestinal tract.

Unfortunately, there is no consensus on what defines a multivisceral transplant (MVTx). Sometimes the inclusion of the pancreas is considered to be a MVTx. UNOS defines a multivisceral transplant as one that includes intestine, liver and either pancreas or kidney. The international transplant registry (ITR) defines a MVTx as one that includes the stomach. The term modified multivisceral is used if the liver is excluded. Transplantation of the colon together with the intestinal allograft was previously avoided because of the risk of infection, but is now sometimes carried out[13]. After the transplant procedure, a feeding tube is inserted to provide early enteral nutrition, until the patient tolerates oral feeding. Some patients must (re)acquire feeding skills if they have not eaten for a long while or never learned to have oral intake. An ileostomy is constructed to allow surveillance biopsies. Graft rejection and most infections can be diagnosed from these biopsies. When graft function is stable without rejection, the ileostomy may be reversed.

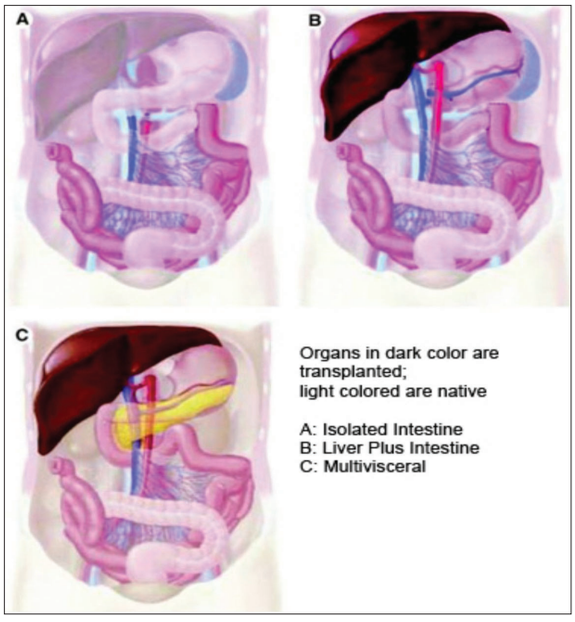

FIGURE 2. Types of transplants
From: TM. Fishbein et al. Gastroenterology. 2003;124:1615-28.

Postoperative care

Intensive care support of early post-transplantation period

Clinical monitoring and support of patients in the early period of post-intestinal transplantation must be very systematic and carried out in an intensive care unit. It requires frequent monitoring of hemodynamic and cardio-pulmonary parameters as well as the control of metabolic, nutritional and hydroelectrolytic and acid-base disorders. In this initial phase a high levels of immunosuppressive drugs is used to modulate the host immune system reaction against the huge immunocompetent cell population of transplanted intestinal graft, to avoiding rejection. This may cause many side effects such as renal dysfunction, hypertension, neuropsychiatric problems and infections, especially opportunistic. Furthermore, intestinal grafts always have injuries resulting from ischemia and reperfusion injury, with a potential occurrence of bacterial translocation[66-84].

The hormonal function of the transplanted graft is usually little affected in intestinal transplantation and hormone release mediators of vasomotor phenomena, such as neurotensin, serotonin, VIP and cholecystokinin, is conveniently maintained[66-84].

Monitoring and Control of Nutritional Support

Within the first two week of intestinal transplantation there is a almost complete regeneration of the lymph drainage by reconstruction and dilatation of lymphatic vessels. However, the absorption of fat takes longer to be standardized, probably by interfering factors arising from the recovery of intestinal mucosa. There is also increasing in the total amount of lipids in the stool, which is reduced to the normal as soon as the absorption of fat is restored[66-84].

The intrinsic innervation is preserved in the transplanted graft, but the disconnection of the extrinsic innervation is strongly related to disorders of intestinal motility observed in intestinal transplantation. The graft's extrinsic reinnervation process is longer, taking about 6 months to settle. Disconnection of the extrinsic innervation manifests as difficult to control diarrhea which persists for several months and improve after the reconstruction of the extrinsic innervations[66-84].

The absorptive function of intestinal graft is little affected. In rats with intestinal transplantation was observed that the weight growth curve was similar to that of normal animals. In clinical intestinal transplantation was noted that, despite

the slow recovery of the graft, there is progressive improvement of absorptive capacity, encouraging the discontinuation of TPN in most patients. In children, although small bowel transplantation promotes the removal of the NPT, they have growth rates below the normal children[66-84].

TPN is reintroduced as soon as the patient becomes hemodynamically stable, preferably on the first post-operative day. The conversion of parenteral nutrition to enteral or oral diet is time variable and occurs earlier in isolated intestinal transplantation fashion. Enteral feeding via jejunostomy is initiated after assessing the integrity of the mucosa by endoscopy and when bowel movement is observed, habitually around 7-10 days after surgery. The infusion is continuous and initially with low volume. This initial stage elemental diets or semi-elemental containing glutamine is preferred[66-84].

With the improvement of graft function, the quantity and quality of food is increased until the patient achieves complete oral and general diet without supplementation by parenteral route. The clinical assessment of graft function is accompanied by body weight, height (in pediatric patients), urine volume, amount of drainage from the stoma, frequency and nature of feces and the dependence on TPN. Hematology and biochemistry exams must be performed frequently to access the degree of hydration, nutrition and renal function. Nitrogen balance and absorptive, motility and secretion functions of the graft must be periodically determined[66-84].

Monitoring and Control of Rejection

The clinical, endoscopic and histological sign of rejection are well defined by the literature. The clinical symptoms of rejection include abdominal pain, severe diarrhea alternating with ileus, fever, vomiting, malabsorption, metabolic acidosis, toxemia and sepsis. If there is clinical suspicion of rejection, the graft and the remaining recipient intestine should be immediately examined by endoscopy with multiple biopsies and histopathological examination. The zoom videoendoscopy which allows of up to 100 times magnificence allows the immediate identification of rejection and is a important new advance in this field. The overall incidence of acute rejection in intestinal transplantation in the initial series of the University of Pittsburgh was 85%. Now with the change of immunosuppressive regimen combined with immunomodulation and preconditioning of the recipient, the rejection rates were significantly reduced[66-84].

Recent research shows that it is possible to induce specific grafts hyporeactitivty through a combination of intestinal transplantation with bone marrow infusion from the same donor. Some ongoing clinical protocols using strong imunossupression with antithymocyte globulin and tacrolimus monotherapy. Induction immunosuppressive therapy is carried out with 5-10 mg/kg of antithymocyte globulin or CAMPATH (anti CD 52) and 2 grams of methyl-predinizolona[5,6,23]. Tacrolimus is used as the primary drug to prevent rejection. The dose of tacrolimus should be adjusted to maintain plasma levels of the drug between 15 and 20 ng/mL in the first 3 months, with subsequent reduction. After four months the patients without rejection episode will be considered to reduce the dose or administration. The treatment of acute rejection is achieved by steroid pulse and subsequent recycling (1gr EV metilpredinizolona followed by 200 mg the next day and subsequent reduction of daily 40 mg) to 20 mg / day, which can be reduced depending on the immunological outcome. In more severe cases of rejection or that refractory to corticosteroids, a monoclonal anti-CD3 (OKT3), anti-thymocyte globulin (ATG) or anti-CD52 (Campath-1H) may be used[66-84].

Chronic rejection is still poorly known immune response, with no specific treatment and may cause graft removal and retransplantation, limiting patient survival. The grafts of isolated intestinal transplantation have a higher risk of acute and chronic rejection than grafts containing the liver (31% vs. 7% respectively). Other risk factors for chronic rejection refers to the frequency and aggressiveness of rejection, age (higher in adults) and race (higher in blacks). Tacrolimus is related to combat chronic rejection, but their effectiveness is limited[66-84].

Monitoring and control of infections

Prevention of infection is made by large spectrum antibiotics (ampicillin and cefotaxime) in the first five postoperative days. Culture of blood, stool, urine, wound exudate, stoma and peritoneal secretion, are frequently repeated and, if positive, appropriate antibiotic therapy should be initiated according to the sensitivity of the microorganism found. Gancyclovir (antiviral), Bactrim (antibiotic) and Mycostatin (antifungal) are administered for prophylaxis of CMV, P. carinii and candidiasis, respectively. The intestine of the donor and recipient should be treated by decontaminating solution containing amphotericin B, polymyxin B and gentamicin. This decontamination solution should also be used in the rejections episodes to prevent serious bacterial translocation[66-84].

CMV negative patients should not receive

grafts from CMV positive donors. This combination increases the incidence and severity of rejection, promote CMV infection difficult to control and lymphoproliferative diseases, affecting the graft and patient survival. Another important infection in this transplant is that caused by Epstein Barr. This virus interacts with the recipient's immune system causing lymphoproliferative disease known as post transplant lymphoproliferative disease (PTLD). This serious condition is difficult to treat and also impair graft and patient survival[66-84].

Outcome of ITx

Survival, Complications and Rejection

ITx can play a potential life-saving role in patients with IF, if referral is timely. Multicenter European survival rates are 73% and 59% for 1 and 3 year patient survival. These rates match American results of 79.9% and 66.1% coming from expertise centers where high numbers of ITx are performed.

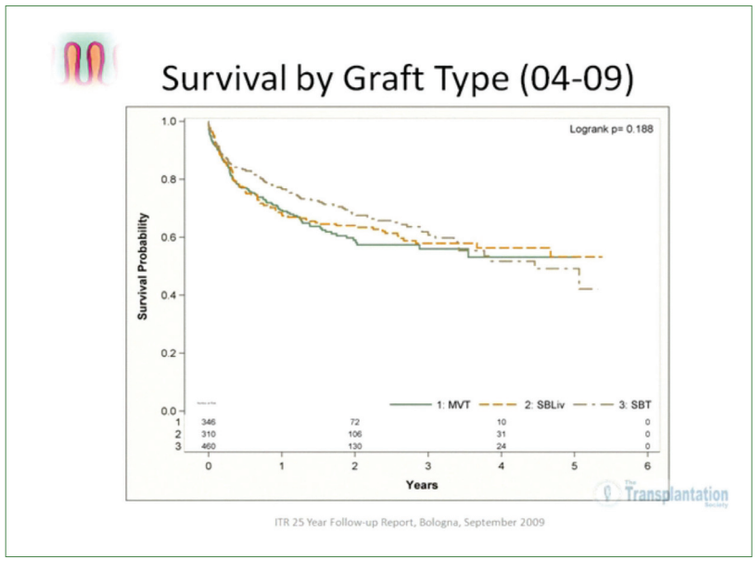

FIGURE 3. Shows the most recent worldwide results based on the international transplant registry (ITR) as presented during the 11th international small bowel symposium in Bologna, September 2009.

Based on literature, both European and US short term survival rates are higher after ITx without liver (I-ITx) compared to combined intestine-liver transplantation (L-ITx): 73-81% for I-ITx and 0-39.1% for L-ITx. This possibly reflects that the patient with an indication for L-ITx generally has a poorer pre-transplant condition or is referred late. The negative outcome of combined L-ITx emphasis the importance of prevention of PNALD. However, there is still ongoing debate whether there is a long-term protective effect of the liver as acute and chronic rejection rates for L-ITx and MVTx are lower than for I-ITx (1). Clearly, latest ITR results support this protective effect of the liver with a better long term survival for L-ITx and MVTx compared to I-ITx.

With the first real 'long-term' results becoming available, factors affecting survival prognosis are being identified. Undeniable, hospitalization seems to be a negative prognostic factor in patients indicated for ITx, also probably because of poorer clinical status compared to patients at home. Furthermore, ITx centre expertise (high numbers of procedures performed) positively affects prognosis.

Rejection and infectious complications are the main postoperative problems. Acute rejection occurs in 79% of patients undergoing I-ITx and is the leading cause of graft loss (14). Graft loss due to rejection is 56.3%. Other causes of graft loss are ischemia/bleeding/thrombosis (20.6%) and sepsis (8.8%). Sepsis and multi-organ failure (MOF) are the leading causes of death (www.intestinaltransplant.com). Approximately one-half (47%) of deaths in intestinal transplant patients have been attributed to sepsis, while another 26% have been attributed to MOF to which sepsis was likely the contributing factor. Immunosuppression exposes the post-transplant patient to an increased risk for (a)typical postoperative infections. Furthermore, the immunogenic character

of the intestine - a high volume of lymphoid tissue in both the mesentery and the Peyer patches of the intestinal graft and the exposure to the external environment - will greatly contribute to this problem. Other causes of death are graft thrombosis (10%), post transplant lymphoproliferative disease (PTLD, 10%), and rejection (4%). PTLD – a lymphoma that occurs after transplantation - is a complication of over-immunosuppression and is frequently associated with EBV infection.

Graft versus host disease (GVHD) fortunately occurs less frequent (0-16%) as to be expected based on the lymphoid nature of the intestinal graft. Strategies to prevent GVHD include simultaneous bone marrow infusion, graft irradiation and the administration of antilymphocyte serum. Unfortunately, GVHD is associated with a high mortality caused by nonspecific presentation and diagnostic delay.

Despite these substantial risks, post-transplant patient condition is quite good as the majority of patients has a well functioning graft and a (sub)normal Karnofsky score (Figure 4).

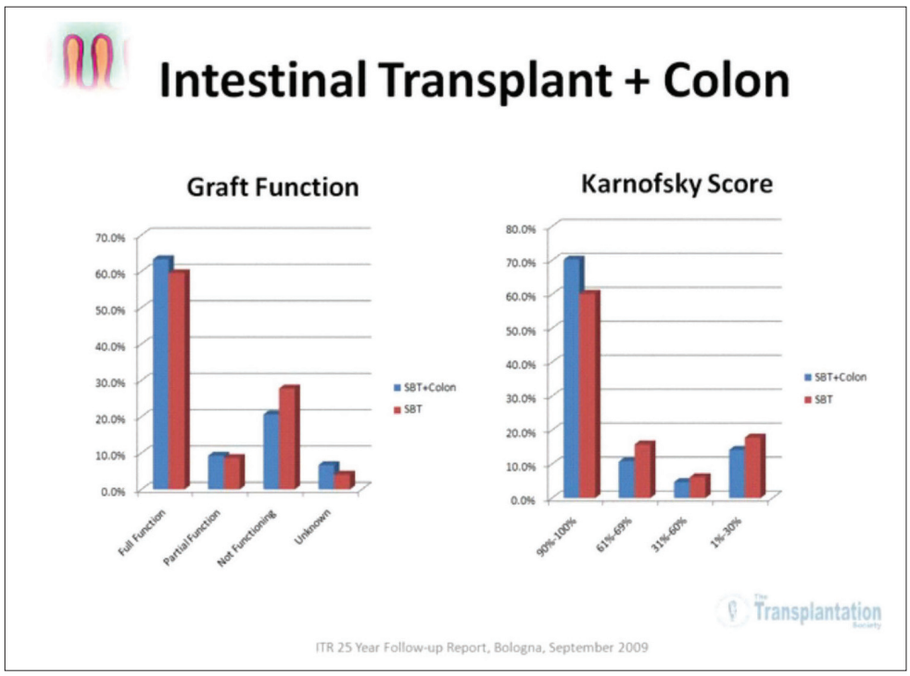

FIGURE 4. Intestinal Transplant + colon

However, the development of solutions to prevent rejection and infectious complication will be the main future target in order to improve the long term outcome of ITx.

In Brazil, beside the two pioneer cases of Clinic Hospital of University of Sao Paulo Medical school by Professor Okumura in the 60s, the Santa Casa of Sao Paulo performed a case in 2000, and the Hospital de Base in Sao Jose do Rio Preto Medical School (FAMERP) conducted three cases. The cases cited had limited survival in 3 cases and in one case the graft was removed and the patient achieved intestinal adaptation.

Difficulties

Clearly, this transplant type seems to be challenging as the success of ITx continues to lag behind that of other transplanted abdominal organs. The outcome of solid organ transplantation is highly dependent on the quality of the graft, placing the intestine at a disadvantage from the start. As a fact, the small bowel is the most perfused organ under physiological conditions, receiving up to 25% of all cardiac output, of which up to 90% is consumed in the (sub)mucosa. This physiological feature leads to the extreme vulnerability of the mucosal layer to ischemia [15]. Unfortunately, a relatively long ischemic period bridging the gap between organ retrieval and implantation is insurmountable during cold storage (CS) during which substantial damage is encountered. Furthermore, brain death, surgical manipulation and ischemia reperfusion injury (IRI) compromise the mucosal barrier [16;17;17;18;18-21]. This consequently

leads to bacterial translocation (BT) and inflammatory upregulation, predisposing the host to sepsis and rejection, the main causes of morbidity and mortality.

Intestinal preservation

A specific limitation to successful ITx is the lack of a specific tailored intestinal preservation strategy. The current standard is a vascular flush with University of Wisconsin solution (UW) followed by CS in UW with the intestinal lumen stapled-off (closed). This standard is by default as a part of the multivisceral organ procurement procedure designed for optimal preservation of the liver and kidney[22]. Although UW has been established as one of the best organ preservation solutions (PS), this solution is unable to prevent substantial intestinal epithelial damage[23-25]. No single PS has proven to optimally maintain intestinal graft quality[26-33].

How to protect the intestine during organ preservation still remains an unanswered question. The intestine might require a tailored strategy because of its distinct features and extreme vulnerability. The development of a more effective intestinal preservation strategy might be essential to achieve improved long term results in ITx.

The intended optimal preservation strategy will imaginably result from a synergic effect of different vital essentials within a “package of conditions” that is yet to be defined.

Roskott AM, Galvão FH, Nleuwenhuljs VB. Intestinal Transplantation (ITx): “Who, when and how?” a general overview. Rev Med (São Paulo). 2009 jul.-set.;88(3) ed. especial:150-62.

ABSTRACT: Organ transplantation has become a substantial part of modern medicine. Intestinal transplantation (ITx) was introduced in the late sixties as a heroic procedure to treat intestinal failure. The Clinic Hospital of University of Sao Paulo Medical School is one of the world’s pioneer in this procedure. With the biotechnological evolution in medicine, intestinal transplantation emerged in the 1990s as the only curative, permanent therapeutic option for patients with irreversible intestinal failure. At that time, the clinical results were also disappointing mainly due to the high rates of post-operative infectious complications and graft rejection. However, the development of intestinal and multivisceral transplantation has been profound owing to the progress in immunosuppressive therapy, refinement of surgical techniques and post-transplant care. This study aims to give a general overview about when the ITx must be considered an option of treatment and how it must be done.

KEY WORDS: Intestines/transplantation. Parenteral nutrition. Intestines/pathology.

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