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Review Article

SMALL BOWEL TRANSPLANTATION

Transplante de intestino delgado

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HEADINGS - Small bowel. Transplantation.

ABSTRACT- ***Background*:** Small bowel transplantation evolution, because of its complexity, was slower than other solid organs. Several advances have enabled its clinical application. ***Aim***: To review intestinal transplantation evolution and its current status. ***Method:*** Search in MEDLINE and ScIELO literature. The terms used as descriptors were: intestinal failure, intestinal transplantation, small bowel transplantation, multivisceral transplantation. Were analyzed data on historical evolution, centers experience, indications, types of grafts, selection and organ procurement, postoperative management, complications and results. ***Conclusion***: Despite a slower evolution, intestinal transplantation is currently the standard therapy for patients with intestinal failure and life-threatening parenteral nutrition complications. It involves some modalities: small bowel transplantation, liver-intestinal transplantation, multivisceral transplantation and modified multivisceral transplantation. Currently, survival rate is similar to other solid organs. Most of the patients become free of parenteral nutrition.

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DESCRITORES - Intestino delgado. Transplante.

RESUMO - ***Introdução***: O transplante de intestino delgado, em razão de sua complexidade, apresentou evolução mais lenta que os demais órgãos sólidos. Diversos avanços permitiram sua aplicação clínica. ***Objetivo:*** Revisão da evolução do transplante de intestino delgado e seu estado atual. ***Método*:** levantamento bibliográfico nas bases de dados MEDLINE e ScIELO. Os termos usados como descritores foram: intestinal failure, intestinal transplant, small bowel transplant, multivisceral transplant. Foram analisados dados sobre evolução histórica, centros, indicações, tipos de enxertos, seleção e captação de órgãos, manejo pós-operatório, complicações e resultados. ***Conclusão*:** Apesar de desenvolvimento mais lento, o transplante intestinal é hoje a terapia para pacientes portadores de falência intestinal irreversível que apresentam complicações da nutrição parenteral. Envolve algumas modalidades: intestino delgado isolado, fígado-intestino, multivisceral e multivisceral modificado. Atualmente a sobrevida é semelhante aos demais órgãos sólidos. A maioria dos pacientes fica livre da nutrição parenteral.

INTRODUCTION

The small bowel transplantation (SBT) had lowering development, when compared to other solid organs. Currently, it is the only chance of cure for patients with intestinal failure who developed complications related to the use of parenteral nutrition. SBT are complex procedures in patients with compromised clinical condition. It comprises a number of surgical procedures where the principal to be transplanted is the small intestine. Although there are variations of terminology, the terms often described are: isolated intestine, multivisceral, and modified multivisceral liver - intestine. There is a need for intense immunosuppression because of the large immune response to the graft. Thus, opportunistic infections and proliferative diseases are more prevalent compared to other solid organ transplants. Due to the large amount of tissue transplanted, Graft Versus Host Disease is also more

prevalent. Finally, it is the most expensive transplant procedure.

This article aims to assess the evolution of SBT and its current state.

METHOD

Literature from MEDLINE and SciELO were searched. The terms used as descriptors were: intestinal failure, intestinal transplant, small bowel transplant, multivisceral transplant. Were analyzed data on historical developments, transplant centers, indications, graft types, selection and organ procurement, postoperative management, complications and outcomes.

History

In the early 20th century, Alexis Carrel performed experiments involving transplantation of organs, including the small intestine. Pioneering studies were performed in dogs by Lillehei et al[31] in 1959. The first clinical transplants were performed in pediatric patients in 1964 in Boston[5].

The better documented history of the SBT procedure was held by Lillehei et al [32] in 1967. The initial results were poor due to technical complications, sepsis and lack of effective immunosuppressive regimens in controlling rejection. In 1968, Okumura[38] did the first clinical trial in Latin America at the Hospital das Clínicas, Faculty of Medicine, University of São Paulo. None of four initial patients survived more than one week. This disappointing results and the introduction of parenteral nutrition by Dudrick et al[13] in 1968, diminished SBT enthusiasm.

The development of anesthesiology, intensive care and the introduction of ciclosporine[9] in 1979, allowed the improvement results of solid organ transplantation in general. In 1987, Starzl Thomaz et al[43] performed the first multivisceral transplantation with survival, using a technique described in 1960. In 1989, Goulet et al[16] performed the first isolated small bowel transplantation with long-term survival. At the same time, Grant et al[19] reported the first combined transplantation of liver and small bowel. Despite the successful use of cyclosporine in other types of transplantation in the 80`s, the results remained and SBT had limited success.

The use of Tacrolimus in the 90`s, took SBT to another sphere. It provided better control of rejection, with significant improvement in survival of patients and grafts. In 2001, Tacrolimus was accepted in the U.S. as a therapeutic modality for patients with intestinal failure who have complications of parenteral nutrition. In recent years the survival of patients in the first year approaches other solid organs.

Centers

Due to the complexity of the procedure, few centers performed SBT in the world. Usually the programs developed in the institutions where there was a well-established liver transplant programs with a large number of cases. Between 2005 and 2007, just 28 Intestinal Transplant Centers worldwide reported to the Intestinal Transplant Registry, performing 389 intestinal transplants in 377 patients[18]. Despite the initial pioneering, Brazil remained for many years without a well- established program. There are some recent reports, but with no success[11].

Indications

The intestinal failure is clinical condition characterized by reduced functional capacity of the gastrointestinal tract to maintain digestion, absorption of nutrients and fluids needed for maintenance in adults, and or to the growth and development in children[17]. It is a result of major resections, trauma and enterocytes diseases may be an association of these manifestations. Many diseases do not cause loss of function itself, but require multiple bowel resections in its natural history. About 60% of cases occur in the pediatric population. The most frequent causes are necrotizing enterocolitis, gastroschisis, intestinal atresia, volvulus, and Hirchsprung disease (aganglionosis). Among adults, mesenteric ischemia, inflammatory diseases, actinic enteritis, trauma and tumors are the most common causes [34].

It is estimated that 2-3 people per million inhabitants per year had intestinal failure[23], of whom 15% are candidates for SBT[24] for irreversible intestinal failure and complications of parenteral nutrition. The mortality in this group is high, reaching 40% at five years in patients less than 50 cm of small bowel[10], being due to infections and/or thrombosis of catheters and liver disease.

Currently the failure of parenteral nutritional therapy, ie, patients who experience complications are candidates for SBT. Complications more accepted as indications are: thrombosis of two of the six major venous accesses; liver disease; episodes of catheter-related infections (two or more per year, fungemia, shock or respiratory failure); alterations of growth and development in children and refractory electrolyte changes[48].

In multivisceral transplantation, there are other indications: abdominal catastrophes, benign or malignant tumors of low grade, spindle mesenteric thrombosis and diffuse mesenteric portal thrombosis [48].

Abdominal catastrophes include chronic debilitating situations caused by abdominal trauma, severe acute pancreatitis, extensive intestinal resection and multiple abdominal interventions, leading to short bowel syndrome, multiples

enterocutaneous fistulas, intestinal obstruction or chronic diffuse mesenteric vascular thrombosis. Complete replacement of all organs of the abdominal cavity (multivisceral transplantation) may be the only alternative to reestablish normal physiology[37].

Complex portal venous thrombosis system may also be indication for multivisceral transplantation. The situation most commonly involved in this context is liver transplantation with portal vein thrombosis. In the past, the presence of portal vein thrombosis in candidates for liver transplantation has been contraindication to the procedure. It has important technical difficulties and higher mortality. The classification proposed by Yerdel[50], can guide the surgical decision: grade I - commitment of less than 50 % of the lumen, with a small extension to the superior mesenteric vein; grade II - involvement of more than 50% of lumen, including total obstruction, but with small extension to the superior mesenteric vein; grade III - complete occlusion of the portal vein and superior mesenteric vein proximal; grade IV - complete occlusion of the portal vein and superior mesenteric vein distally.

The alternatives for portal revascularization of the liver graft can be simply removing the thrombus undergoing or a graft to the superior mesenteric vein or varicose veins. In grade IV thrombosis, portal arterialization, graft renal vein and cavoportal hemi-transposition[39] are alternatives to allow the organ vascularization, without decompressing the portal territory. The maintenance of portal hypertension (ascites, gastrointestinal bleeding), and the development of thrombosis of the inferior vena cava and renal failure, are responsible for high hospital mortality (33%) and poor long-term survival (approximately 35% in five years)[39, 42]. The multivisceral transplantation has been proposed as an alternative to complex portal mesenteric system thrombosis, even in the absence of liver or intestinal failure[47].

A variety of tumors can involve the celiac axis and mesenteric root. Neuroendocrine tumors and pancreatic adenocarcinoma and desmoid tumors are examples. Resection is sometimes risky or impossible without compromising the vascularity of the abdominal viscera. The isolated intestine transplantation, including autograft and multivisceral have been proposed as alternatives to these situations[36]. Because of early and severe recurrence in carcinomas, transplantation for desmoid tumors and well-differentiated neuroendocrine has been more accept[36]. However, patient populations are small and improvement of selection criteria is needed.

Patients dependent on parenteral nutrition without complications are not candidates for intestinal transplantation, nowadays. There are reports of patients on parenteral nutrition for many years. However, their quality of life is questioned, besides the high cost of nutrition maintenance. Studies evaluating the quality of life before and after the transplant, with validated questionnaires showed improvements in various aspects, including anxiety, depression and self-image[44]. There are no controlled studies comparing parenteral nutrition with SBT.

Selecting the type of graft

The SBT can involves some others abdominal organs to be transplanted with the small intestine. The selection of organs to be included will depend on the underlying disease, quality of other abdominal organs, presence and severity of liver disease and the number of previous abdominal surgeries.

The isolated small bowel graft (Figure 1) is indicated in the presence of irreversible intestinal failure in the absence of severe hepatic dysfunction. The determination of liver disease severity and reversibility is held more securely by liver biopsy. The presence of bridging fibrosis or cirrhosis indicates the necessity of replacement of the liver. Study showed an association between the levels of bilirubin, platelet count and albumin level in the presence of liver failure in children in parenteral nutrition[28]. The arterial anastomosis is established through the superior mesenteric artery graft to the aorta. The venous drainage is made through the superior mesenteric vein to the inferior vena cava or the mesenteric portal system. Another study showed no difference in survival, however, the cumulative incidence of episodes of infection by bacteria of the gastrointestinal tract was higher in patients with systemic drainage, suggesting a protective role liver[6]. In all modes is performed an ileostomy for endoscopic surveillance, facilitating the diagnosis of rejection and perfusion disorders.

In the presence of irreversible liver disease, the liver should be included in the graft. This group of patients competes for scarce liver grafts. The system MELD/PELD liver allocation is used in many countries; however, is not suitable for those patients who are at risk of death 3.6 times higher on the list than patients with the same MELD/PELD waiting just liver[22]. U.S. data show that 74% of patients candidates for intestinal transplantation require an associate liver[15]. Enhancement of allocation models and early referral to SBT can be a solution to this problem. The grafts can be deployed separately, or in a more convenient block. To maintain the liver and intestine block, it is necessary to include the pancreatoduodenal arc graft (Figure 2). This avoids the dissection of biliary duct and portal vein, which can be difficult in small children. The arterial supply is established through an arterial graft to the aorta. Venous drainage is made through the hepatic veins to the inferior vena cava, as the mode of liver

transplantation. Venous drainage of the remaining viscera went to a shunt to the inferior vena cava or portal system.

Failure of multiple abdominal organs, the graft to be employed is the multivisceral (Figure 3). It is necessary a complete evisceration of the abdominal cavity. Multiorgan recipient receives in block: stomach, duodenum, pancreas, small intestine and liver. The arterial supply is established through the superior mesenteric artery and celiac trunk graft through a conduit to the aorta and venous drainage through the hepatic veins to the inferior vena cava. The gut is restored by anastomosing the esophagus or gastric reminiscent with the stomach graft.

In the modified multivisceral transplantation (Figure 4), the recipient`s liver is maintained. He receives in block: stomach, duodenum, pancreas and small intestine. Funcional disorders of the digestive tract such as intestinal pseudo-obstruction or inflammatory diseases such as Crohn's may be indications. The arterial, and continuity of the digestive tract, are established as in multivisceral transplantation. The venous drainage is through the portal vein.

Controversies exist regarding the inclusion of the colon and spleen grafts, the inclusion of colonic segments not added any morbidity, but only brought benefits continence in pediatric patients[26]. In relation to the spleen, in the same study group, tended to immunologic benefit, without altering the incidence of graft versus host disease[27].

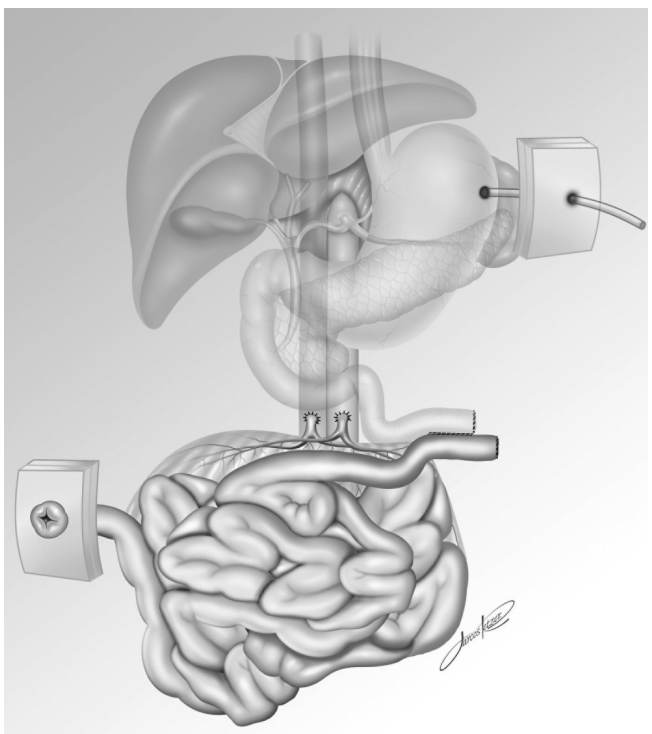

FIGURE1 - Isolated small intestine

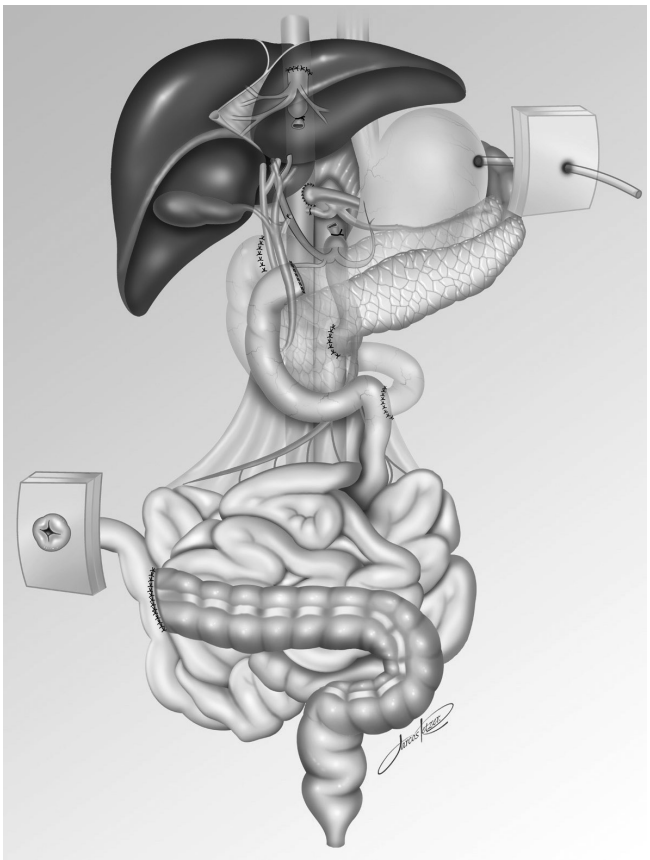

FIGURE 2 - Liver-intestine

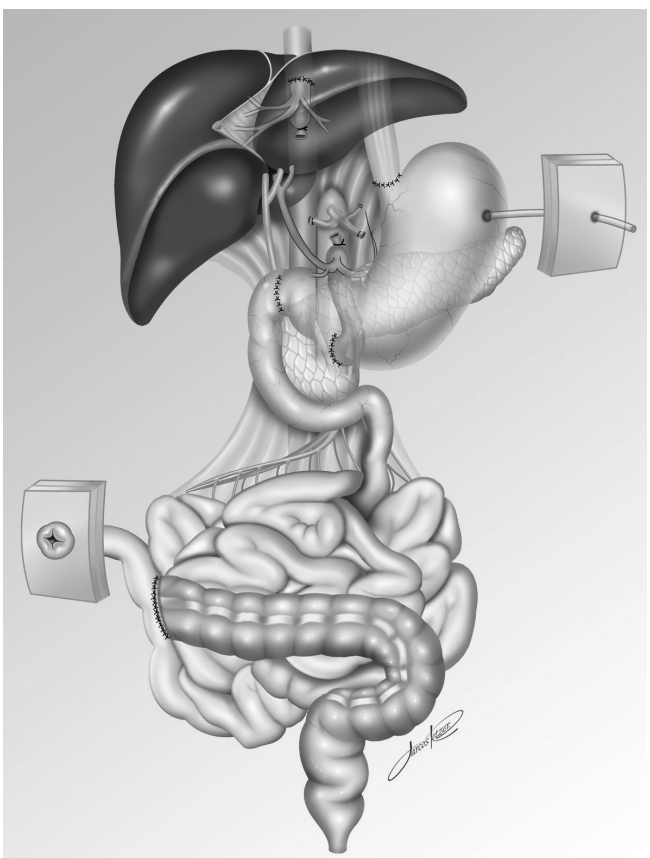

FIGURE 3 - Multivisceral

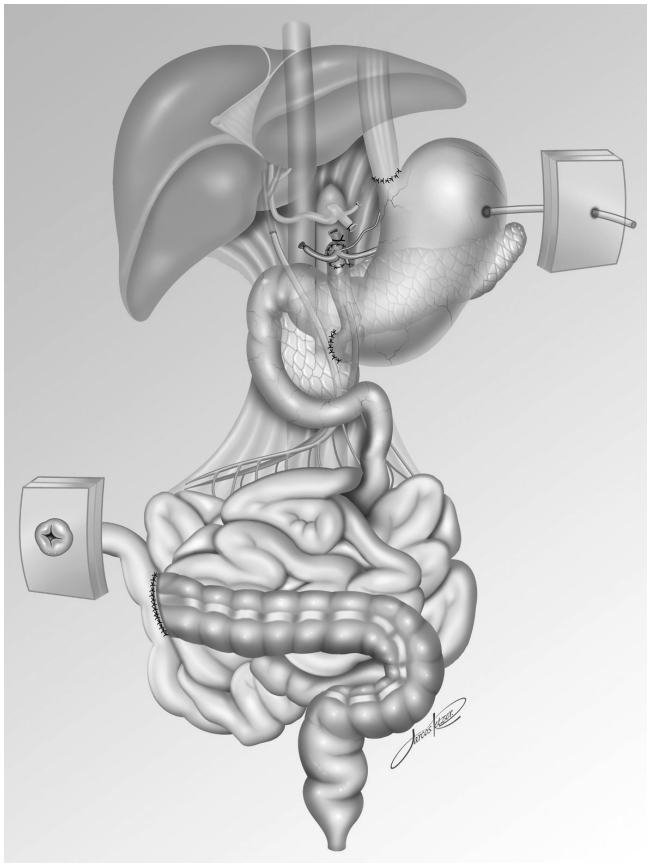

FIGURE 4 - Modified multivisceral

Donor, procurement and preservation of grafts

The selection of grafts from deceased donors is following similar liver criteria with some changes[48]. Ideal donors are preferably younger and with little or no vasoactive drugs. Patients with short bowel syndrome present the abdominal cavity retracted, needing for use smaller donors (30 to 40%). Preference is given to ABO identity. With the development of effective drugs for prophylaxis and treatment of cytomegalovirus seropositive donors are accepted, avoiding only for receivers with negative serology. Decontamination of the gastrointestinal tract and use of antibodies in donor lymphocytes showed no benefits related to infection, rejection episodes or incidences of graft versus host disease. Typically donors are also liver and pancreas grafts. Facing the bloodstream shared the simultaneous harvesting of these grafts can be a challenge, but is possible to perform the procedure without compromising the graft[1].

The University of Wisconsin solution has been considered the gold standard for preservation of organs of the digestive system, no different to the intestine. However, there are reports of the use of other solutions, Celsior[30] and HTK[33]. SBT results are similar to University of Wisconsin solution for ischemic periods up to 8 h.

Postoperative management and complications

Postoperatively, in addition to surgical complications (bleeding, fistula, dehiscence and wound infection) may occur episodes of rejection, opportunistic infections and nutritional rehabilitation.

The biggest obstacle to intestinal transplantation is graft rejection. It is the main factor in morbidity and mortality. Rejection has a negative impact on survival of graft[18]. The acute cellular rejection occurs in 50-75% of patients, most commonly in the first 90 days[3]. Chronic rejection occurs in 15% of patients[3].

Several strategies and immunosuppressive regimens (irradiation graft infusion of donor bone marrow cells) were utilized without impact[3]. Best results were obtained with induction therapy with anti-lymphocyte antibodies, monoclonal or polyclonal, being used in most centers[3,14,29,46]. The most commonly used drugs for induction are thymoglobulin, alemtuzumab, basiliximab and daclizumab. The maintenance immunosuppression with tacrolimus is carried out, keeping the first month levels 12 to 15 ng/ml and reduced to 12 to 8 ng/mL after this initial period[48]. As in the other abdominal organs transplants, corticosteroids are also used, and removed in accordance with the type of grafts and preferably each center. The crossmatch may help in individualizing immunosuppression. Study in 130 intestinal transplants, the crossmatch was positive in 18% and was associated with increased frequency and severity of episodes of rejection[7], being more important in isolated intestinal grafts.

The diagnosis of acute cellular rejection is performed by clinical, endoscopic and pathologic anatomy. In the presence of acute cellular rejection patients are very symptomatic, with fever, abdominal pain, vomiting, swelling of the stoma and gastrointestinal bleeding. The commitment starts at the terminal ileum. The routine ileostomy facilitates endoscopic assessment and biopsies. The endoscopic surveillance, with a magnification of 100x, is held two to three times per week in the first three months, being held once a month from then and according to the situation[48]. The closure of the ileostomy varies by center and type of transplant (liver grafts with or without), being held from three to 12 months[48]. A number of endoscopic findings may be associated with acute rejection: mucosal erythema, congestion, shortening and flattening of the villi, friability and ulcerations[25]. Endoscopy alone has a sensitivity of only 52% but a specificity of 93%[25]. The gold standard for the diagnosis of acute cellular rejection is histology. On suspicion of rejection several biopsies should be performed because the lesion can spare a few segments.

A study conducted with the evaluation of approximately 3,000 biopsies[49] identified four main parameters related to rejection, allowing quantitative or semi-analysis, and can be easily identified by pathologists: architectural distortion, intestinal crypt epithelial injury, the number of apoptosis and crypt infiltration by lymphocytes in the lamina propria. The differential diagnosis should be done with opportunistic infections (cytomegalovirus, adenovirus),

lymphoproliferative disorders and other enteric diseases. As histology, rejection can be classified into indeterminate, mild, moderate or severe. Non-invasive markers (citrulline, calprotectin) for the diagnosis of rejection are not yet part of routine clinical practice, due to the low specificity[8,12]. Mild rejection episodes may be treated with pulses of steroids. Moderate or severe episodes require therapy with anti-lymphocyte (Alemtuzumab, Thymoglobulin). Chronic rejection is a serious problem, without treatment, commonly leads to graft loss. With poorly understood mechanisms, characterized by submucosal fibrosis and obliterative arteriopathy. It is associated with episodes of acute rejection in the first month, severity and number of episodes of acute rejection and graft containing only small bowel[40].

The main goal of intestinal transplantation is the restoration of nutrition through the digestive tract. Up to 90 % of patients undergoing intestinal transplantation can be free of parenteral nutrition[2]. However, it is necessary to perform intestinal rehabilitation, since the grafts may have varying degrees of failure due to ischemia-reperfusion, denervation and rejection episodes. There are various schemes for the process of adaptation without any clear superiority[21]. Usually involve initial maintenance on parenteral nutrition with enteral gradual transition. Enteral elemental diets, oligomeric or polymeric are administered when the graft shows signs of function. The lipids are introduced slowly (after four weeks) at risk of chylous ascites. Medium chain triglycerides are used as the main source.

Infections are universal manifestations in SBT. Infections of catheters under poor conditions, intense immunosuppression, surgical procedures and large intestinal bacterial translocation after rejection are responsible for this situation. Infections are the leading cause of direct mortality. Were reported bacterial infections in 94% of recipients, with 67% viral and 28% of fungal infections[20]. The virus is responsible for 60% of the losses of grafts[41]. Cytomegalovirus infections occur in up to 40% of transplanted on three months average[41]. Infection with Epstein-Barr virus is associated with the development of lymphoproliferative disease in 12.5% of recipients[4], occurring on average 5.5 months and is more common in pediatric patients . Cytomegalovirus compromises the intestinal graft in 71% of cases and significantly affects survival[4]. Regular monitoring of cytomegalovirus and Epstein -Barr virus by PCR, aggressive prophylaxis and anti-viral immunoglobulins are routines.

The graft versus host disease is uncommon in kidney, pancreas and liver transplants; however, is expected in intestinal transplantation because of the large lymphocytes load transplanted. It is more common in multivisceral transplantation. A study showed 5.6% of patients had histologically confirmed, with a mortality rate of approximately 9%[35].

Results of intestinal transplantation

Between April 1985 and May 2007, 1,720 intestinal transplants were registered, being: 746 isolated intestine, 594 liver-intestine and 380 multivisceral[18]. The University of Pittsburgh has reached more than 500 transplants, with actuarial survival of 85% at one year and 61% in five years[3]. Graft survival was 80% at one year and 50% in five years. Series of other centers currently show a survival rate of 78-85% in a year and 56-61% between five and ten years[45].

CONCLUSIONS

Intestinal transplantation is now a well established therapy for patients with irreversible intestinal failure who have complications of parenteral nutrition. Survival of grafts and patients coming close to other solid organs. A multidisciplinary approach to patients with complicated intestinal failure, with early referral to transplant lists, early diagnosis and aggressive treatment of opportunistic viral infections, use of induction immunosuppression therapy with antibodies and early diagnosis and treatment of acute graft rejection were important for best results. Proper selection of recipients and rigorous care postoperatively are fundamental to the success of transplantation.

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