REVIEW

# Intestinal and multivisceral transplantation

Transplante intestinal e multivisceral

Sérgio Paiva Meira Filho[1], Bianca Della Guardia[1], Andréia Silva Evangelista[1], Celso Eduardo Lourenço Matielo[1],
Douglas Bastos Neves[1], Fernando Luis Pandullo[1], Guilherme Eduardo Gonçalves Felga[1],
Jefferson André da Silva Alves[1], Lilian Amorim Curvelo[1], Luiz Gustavo Guedes Diaz[1], Marcela Balbo Rusi[1],
Marcelo de Melo Viveiros[2], Marcio Dias de Almeida[1], Marina Gabrielle Epstein[1], Pamella Tung Pedroso[1], Paolo Salvalaggio[1],
Roberto Ferreira Meirelles Júnior[1], Rodrigo Andrey Rocco[1], Samira Scalso de Almeida[1], Marcelo Bruno de Rezende[2]

## ABSTRACT

Intestinal transplantation has shown exceptional growth over the past 10 years. At the end of the 1990's, intestinal transplantation moved out of the experimental realm to become a routine practice in treating patients with severe complications related to total parenteral nutrition and intestinal failure. In the last years, several centers reported an increasing improvement in survival outcomes (about 80%), during the first 12 months after surgery, but long-term survival is still a challenge. Several advances led to clinical application of transplants. Immunosuppression involved in intestinal and multivisceral transplantation was the biggest gain for this procedure in the past decade due to tacrolimus, and new inducing drugs, mono- and polyclonal anti-lymphocyte antibodies. Despite the advancement of rigid immunosuppression protocols, rejection is still very frequent in the first 12 months, and can result in long-term graft loss. The future of intestinal transplantation and multivisceral transplantation appears promising. The major challenge is early recognition of acute rejection in order to prevent graft loss, opportunistic infections associated to complications, post-transplant lymphoproliferative disease and graft *versus* host disease; and consequently, improve results in the long run.

**Keywords:** Transplantation; Intestine, small/transplantation; Transplantation chimera; Tissue donors; Transplantation immunology

## RESUMO

O transplante de intestino, ao redor do mundo, tem crescido de maneira sólida e consistente nos últimos 10 anos. No final da década de 1990, passou de um modelo experimental para uma prática clínica rotineira no tratamento dos pacientes com complicação severa da nutrição parenteral total com falência intestinal. Nos últimos anos, vários centros têm relatado uma crescente melhora nos resultados de sobrevida do transplante no primeiro ano (ao redor de 80%), porém, a longo prazo, ainda é desafiador. Diversos avanços permitiram sua aplicação clínica. O surgimento de novas drogas imunossupressoras, como o tacrolimus, além das drogas indutoras, os anticorpos antilinfocíticos mono e policlonal, nos últimos 10 anos, foi de suma importância para a melhora da sobrevida do transplante de intestino/multivisceral, mas, apesar dos protocolos bastante rígidos de imunossupressão, a rejeição é bastante frequente, podendo levar a altas taxas de perdas de enxerto a longo prazo. O futuro do transplante de intestino e multivisceral parece promissor. O grande desafio é reconhecer precocemente os casos de rejeição, prevenindo a perda do enxerto e melhorando os resultados a longo prazo, além das complicações causadas por infecções oportunistas, doenças linfoproliferativas pós-transplante e a doença do enxerto contra hospedeiro.

**Descritores:** Transplante; Intestino delgado/transplante; Quimeras de transplante; Doadores de tecidos; Imunologia de transplantes

## INTRODUCTION

Currently, intestinal transplantation is the only possibility of cure for patients with intestinal failure (IF) who have severe complications related to prolonged use of total parenteral nutrition (TPN).[1] Transplantation, on the other hand, reestablishes the oral nutritional capacity in these patients.[2-6]

Intestinal transplantation may be isolated or in combination with other organs (multivisceral).

Intestinal and multivisceral transplantation is the least often performed surgical procedure when compared to other transplants of solid organs, and represents

the greatest challenge in management. There are still few accredited and capable centers in the world. In the United States, in 1997, there were 198 centers and, in 2012, this number dropped to 106, and of these, only 18 performed more than 10 procedures a year.[7]

Over the last 5 to 10 years, intestinal and multivisceral transplantation has evolved in a manner similar to that of other transplants, starting from an experimental procedure and then moving on to a real therapeutic option.[8]

IF happens due to the absorption deficiencies of the macro- and micronutrients, so that the daily requirements cannot be met by oral or enteral nutrition. During the 1950's, it was considered incompatible with life,[9] but with the development of TPN at the end of the 1960's, this allowed increased survival in patients with IF. However, intestinal and multivisceral transplantation became of victim of its own success, since due to the prolonged use of central venous catheters, many patients began to present with severe complications, such as infection, thrombosis, and cholestatic hepatic disease induced by TPN.[1] Recent series demonstrated an 87% survival in 5 years in patients who depend on TPN and do not present with complications. Multicenter studies suggest that 19 to 26% of the patients who depend on TPN will develop some type of complication and will be candidates for intestinal and multivisceral transplantation.[7] Recently, intestinal transplantation has allowed improved survival and quality of life for these patients.[10]

It is estimated that one to three persons per million of the population, per year, will present with IF, and of these, 10 to 15% will be candidates for intestinal and multivisceral transplantation.[2,3,11,12] In childhood, IF occurs in about 2 to 6.8 individuals per million in developed countries. In Brazil, approximately 200 people a year will be candidates for intestinal transplantation. Despite technological advances and clinical needs, there are no specialized reference centers in rehabilitation and intestinal and multivisceral transplantation in Brazil.[13,14]

Patients who present with large resections that result in less than 100cm of jejunum-ileum in addition to the loss of the ileocecal valve will certainly become dependent on TPN. In patients with less than 50cm, the 5-year mortality rate reaches 40%, and in patients with cholestasis due to TPN, the survival rates will drop to 20%.[1] Other conditions may also progress to IF, and concomitantly evolve to the need of TPN, such as the loss of enteric absorption capacity due to (viral) enteropathy, and other causes, including diseases associated with

intestinal motility changes (pseudo-obstruction). Most intestinal transplants occur in the pediatric population (60%) and result primarily from some conditions, such as necrotizing enterocolitis, gastrosquisis, intestinal atresia, volvulus, pseudo-obstruction, agenesis, aganglionosis, among others.[9] In the adult population, ischemia, intestinal inflammatory diseases, volvulus, pseudo-obstruction, trauma, thrombosis, and tumors are among the most common causes.[9]

The clinical progression of IF has a difficult prognosis, and is associated with a few risk factors that lead to the need for continuous use of parenteral nutrition. In children, the presence of the ultrashort bowel syndrome (<10/20cm of intestines) associated with the alteration of residual motility, partial loss of the colon, and absence of the ileocecal valve are related to the prolonged use of TPN in 100% of cases.[15,16]

Suddan[7] demonstrated excellent survival results in patients with prolonged TPN use with no severe complications (87% in 5 years), due to new catheter technology and its handling by specialized teams, with new closing techniques (antibiotics or ethanol) making them long-lasting. However, 15 to 20% of these patients developed some type of catheter-related complication.[7]

This article had the objective of assessing the progression of intestinal and multivisceral transplantation and its current status.

## HISTORY

Intestinal and multivisceral transplantation was performed for the first time in dogs in 1959 by Lillehei et al. [17] It was a study model in which the objective was to observe what would happen with lymph drainage of all abdominal organs after their total denervation.[17] During the period from 1964 to 1970, eight transplant attempts were tried in humans. All the patients died and only one survived for more than 1 month.

The negative results of these first transplants occurred due to technical and infectious complications and problems with conventional immunosuppression. During the 1980's, professor Roy Calne and collaborators introduced cyclosporine, a new immune suppressor in clinical practice that renewed optimism in the field of solid organ transplants.[1]

In 1983, a 6-year-old child receiving prolonged TPN due to short bowel syndrome with end-stage hepatic disease induced by chronic TPN use was submitted to the first multivisceral transplant, but died hours after the transplant as a result of massive hemorrhage. At the end of the 1980's, with the launching of cyclosporine, two patients achieved a post-transplant survival of

109 and 192 days. Lymphoproliferative disease was responsible for the death of these patients.[18,19]

In Canada, Grant et al.[20] performed the first combined intestinal and hepatic transplant.

The appearance of tacrolimus, in 1990, was a milestone in intestinal transplant. The medication resulted in improved integration of the graft and better survival rates. Since then, there have been various advances in intestinal and multivisceral transplantation.[20] The positive results are also related to the development of multidisciplinary teams in the treatment of IF, early indication for the transplant list, use of induction therapy by means of monoclonal and polyclonal anti-lymphocytic antibodies, and in more aggressive methods to prevent and treatment of viral infections, as well as in the early detection and treatment of rejection.[21]

These factors contributed to an improvement in results of intestinal transplantation, with an estimated 1-year survival rate of 80%.[1,22] Today it is known that the Achilles heel of multivisceral transplantation is the intestine, and that when the liver is combined with the graft, there is great immune protection of all the grafted organs, with a significant impact on graft survival.[18]

## INDICATIONS

The indication of transplantation as to the choice of organs to be used in grafting varies according to the underlying disease, that is, the presence or not of chronic liver disease, number of prior abdominal operations, as well as function and quality of other organs.[1] The common element in all the variants is the small intestine, which can be transplanted in association with other organs (liver, stomach, colon, pancreas, and spleen).

As to use of better nomenclature to define the techniques used in intestinal transplantation, literature has not been very consistent. Several specialists from the largest transplant centers concluded that the term "multivisceral transplant" had various interpretations in different transplant programs. The general consensus was that the terminology to be used would be a descriptive system in which two components would be used: first, if the transplant included the liver or not, and second, relative to the intestinal organs to be removed from the receptor.[7]

Historically, the most commonly used combination of grafts was implantation of the bowel associated with the liver and/or pancreas, separately. However this was abandoned and replaced by monobloc transplantation of the intestines, liver, and pancreas (referred to by various centers as the multivisceral or Omaha technique), since it avoids dissection of the hepatic

hilus and of all the duodenum pancreatic complex. Some centers still associate other organs to the gastrointestinal tract, such as the stomach, duodenum, colon, and spleen. Nomenclature and the variations on the techniques are described as multivisceral transplantation; if the liver is not included in the graft, the term "modified multivisceral" is used. Currently, "multivisceral" is considered the transplant of the stomach, intestine, liver, and pancreaticoduodenal complex, and modified multivisceral when it is without the liver.[7]

Presently, the indications of intestinal and multivisceral transplants are established by the international medical community,[1] and in the United States they can be divided into two groups: approved and not approved by Medicare (Charts 1 and 2).

**Chart 1**. Indications approved by Medicare

| |
|---|
| Loss of two or more of the six primary central venous accesses (jugular, subclavian, and femoral) |
| Episodes of catheter-associated infections, two or more per year, fungemia, shock, or adult respiratory distress syndrome |
| Refractory hydroelectrolytic disorders |
| Hepatic disease associated with TPN, reversible |
| Growth and development deficit in children |

Source: https://www.medicare.gov/
TPN: total parenteral nutrition.

**Chart 2**. Non-approved indications by Medicare

| |
|---|
| Extensive mesenteric-portal thrombosis |
| Abdominal catastrophes |
| Low-grade malignant or benign tumors |

Source: https://www.medicare.gov/

## TYPES OF TRANSPLANTS

One of the types of transplants is the isolated small bowel, indicated for patients with irreversible IF, in which only the small bowel is transplanted; usually patients with severe complications of parenteral nutrition, in the absence of severe liver disease.

The multivisceral transplant covers the bloc transplant of the stomach, pancreaticoduodenal region, small bowel, liver with or without the colon and spleen. It is indicated in irreversible IF, complicated by advanced liver failure demonstrated by clinical signs of cirrhosis or by histology consistent with chronic liver disease; and unresectable benign or low-grade malignant tumors, involving the mesentery, associated with hepatic metastases, in the absence of extra-abdominal disease; including desmoid and neuroendocrine tumors. In the absence of hepatic metastases and celiac vascular involvement, the multivisceral transplant may be

performed sparing the recipient liver (modified multivisceral). For the neuroendocrine tumors, the evaluation of distant metastases should follow the previously established protocol for hepatic transplant, bearing in mind the need to exclude distant metastatic diseases. Diffuse thrombosis of the mesenteric-portal system and other non-classic indications should also be considered, such as abdominal catastrophes.

Vianna e Mangus demonstrated surprising results of survival in multivisceral transplants in patients with extensive mesenteric-portal thrombosis, who – to date – are contraindicated to have an isolated liver transplant.[6]

Modified multivisceral transplant is a variation of the multivisceral transplant, in which the liver of the recipient is spared.

Intestinal and multivisceral transplantation can be associated with the kidney transplantation in the presence of renal failure.

## CONTRAINDICATIONS

Contraindications of the intestinal and multivisceral transplants follow the same applied to solid abdominal organs, such as severe cardiopulmonary disease, sepsis, aggressive malignant disease, and severe neurological damage. HIV is considered a relative contraindication.[1]

## RESULTS OF INTESTINAL AND MULTIVISCERAL TRANSPLANTATION

Early overall survival of the patient and of the graft after intestinal transplant has shown a significant improvement over the last 10 years.[1,2] The most recent results reveal more than 2,000 transplants performed in more than 60 centers worldwide, in which 50% of the recipients are alive and most are independent from TPN.[1,12] In 1998, survival of the graft and the patient in the first year was between 52 and 69%, respectively, whereas, in 2012, it increased to 75 and 85%, respectively.[12] Most patients presented with good graft function and are free from TPN.

Patients who are hospitalized, submitted to a previous transplant and induction with alemtuzumab, presented with a lower graft and patient survival rate during the first year, 65% and 63%, respectively, and in the third and fifth year, it was 49% and 47%, respectively. The 37 patients (22 children and 15 adults) who presented with none of the factors mentioned above achieved first and third year survival rates of 89 and 71%, respectively.[23]

In a multicenter study in the State of São Paulo, Bakonyi et al.[16] evaluated 248 patients submitted to some form of intestinal resection at 7 intensive care units of teaching hospitals. They observed that 24 patients presented with short bowel syndrome and required TPN, and that 5 of them had indications for intestinal transplantation as per international criteria. Of the patients with indication for transplantation, only two remained alive when the research was concluded.[16]

It is believed that the perfecting of the surgical technique, immune suppression with perioperative induction using anti-lymphocyte antibodies, control of viral infections, perfecting of the multidisciplinary team, rigorous selection of donors, effective clinical postoperative management, and advances in detection and treatment are factors related to satisfactory results.[3,24]

Despite all these advances, sepsis is still the primary cause of mortality and is associated with the use of high doses of immune suppressors to counterbalance the high level of rejection. These drugs also contribute to the appearance of renal insufficiency and lymphoproliferative disease. The graft *versus* host disease and the need for new surgical approaches are complications that contribute to the lack of success in intestinal and multivisceral transplantation.[25]

As is true with all transplants, this balance between infection and rejection should be more firmly managed in the case of intestinal and multivisceral transplants.

Hospital readmission of these patients is more frequent in comparison with other transplants and is generally associated with infection, rejection, dehydration, and gastrointestinal complications.[26] Acute cellular rejection still shows a high frequency when compared to that of transplants of other solid organs, occurring in 50 to 75% of patients, most commonly during the first trimester, having a direct impact on the long-range result of the graft.[1] Diagnosis is based on the combination of clinical signs, endoscopic findings and histology. The multivisceral transplant, on the other hand, has a lower rejection rate relative to isolated intestinal transplantation, due to the immune protection afforded by the liver.[27]

Brazil has carried out six intestinal and multivisceral transplants, with the *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* as the worldwide pioneer. The first was performed by Professor Okumura in the 1960's.[28] Recently, three other institutions performed four intestinal transplants, but the results were disappointing considering early death of the recipients.[3,4,28]

In 2011, *Hospital Israelita Albert Einstein* conducted the first multivisceral transplant in Brazil in a patient

with extensive portal-mesenteric thrombosis, due to chronic cryptogenic liver disease, portal hypertension, recurrent episodes of upper digestive hemorrhage, weekly paracentesis, and significant cachexia. The patient presented with an important biliary non-anastomotic complication, probably related to ischemia/reperfusion injury and required internal and external transparietohepatic drainage. Length of hospital stay was 30 days, and death occurred in 8 months due to infection. Recently, the group did the second case in a patient with history of bariatric surgery and cirrhosis due to non-alcoholic steatohepatitis, with complex thrombosis of the portal mesenteric system.

This patient presented with a good perioperative evolution, but progressed with graft *versus* host disease on the 16th postoperative day, with no response to treatment, and died on the 34th postoperative day. It is known that extensive thrombosis of the entire portal mesenteric territory remains a great challenge to liver surgeons, in which the alternative techniques of solution for this problem show insignificant success rates, with high mortality and morbidity rates. Tzakis et al.[23] reported in a study with 23 patients submitted to hemitransposition of the vena cava, who presented with complex portal mesenteric thrombosis, survival rates of 68 and 38%, respectively, in the first and fifith year, besides an elevated incidence of reoperations and new interventions. Vianna et al. reported survival rates in the first and fifith year of 80% and 72%, respectively, with the patients submitted to multivisceral transplantation for the same etiology.[29]

Brazil still needs a better approach for intestinal and multivisceral transplantation, with public health policies focused on the issue of this disease, with specialized teams within the Unified Healthcare System in intestinal rehabilitation. Another point to be considered is the potential pediatric donors, since the pathologies that lead to intestinal and multivisceral transplants prevail in this population.

## REFERENCES

1. Vianna RM, Mangus RS, Tector AJ. Current status of small bowel and multivisceral transplantation. Adv Surg. 2008;42:129-50. Review.

2. Abu-Elmagd KM, Costa G, Bond GJ, Soltys K, Sindhi R, Wu T, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg. 2009;250(4):567-81.

3. Galvão FH, Waitzberg DL, Bacchella T, Gama-Rodrigues J, Machado MC. [Small intestine transplantation]. Arq Gastroenterol. 2003;40(2):118-25. Review. Portuguese.

4. Galvão FH. Transplante de intestino e multivisceral. In: Waitzberg DL, editor. Nutrição oral, enteral e parenteral na prática clínica. São Paulo: Atheneu; 2008: p.1539-50.

5. Lee AD, Gama-Rodrigues J, Galvao FH, Waitzberg DL. Study of morbidity in orthotopic small intestine transplantation with Wistar rats. Experimental study. Arq Gastroenterol. 2002; 39:(1):39-47.

6. Vianna RM, Mangus RS. Present prospects and future perspectives of intestinal and multivisceral transplantation. Curr Opin Clin Nutr Metab Care. 2009;12(3):281-6. Review.

7. Sudan D. The current state of intestine transplantation: indications, techniques, outcomes and challenges. Am J Transplant. 2014;14(9):1976-84.

8. Grant D, Abu-Elmagd K, Reyes J, Tzakis A, Langnas A, Fishbein T, Goulet O, Farmer D; Intestine Transplant Registry. 2003 report of the intestine transplant registry: a new era has dawned. Ann Surg. 2005;241(4):607-13.

9. Goulet O, Ruemmele F, Lacaille F, Colomb V. Irreversible intestinal failure. J Pediatr Gastroenterol Nutr. 2004;38(3):250-69. Review.

10. O'Keefe SJ, Emerling M, Koritsky D, Martin D, Stamos J, Kandil H, et al. Nutrition and quality of life following small intestinal transplantation. Am J Gastroenterol. 2007;102(5):1093-100.

11. Gupte GL, Beath SV. Update on intestinal rehabilitation after intestinal transplantation. Curr Opin Organ Transplant. 2009;14(3):267-73. Review.

12. Mazariegos GV, Steffick DE, Horslen S, Farmer D, Fryer J, Grant D, et al. Intestine transplantation in the United States, 1999-2008. Am J Transplant. 2010;10(4 Pt 2):1020-34.

13. Van Gossum A, Vahedi K, Abdel-Malik, Staun M, Pertkiewicz M, Shaffer J, Hebuterne X, Beau P, Guedon C, Schmit A, Tjellesen L, Messing B, Forbes A; ESPEN-HAN Working Group. Clinical, social and rehabilitation status of long-term home parenteral nutrition patients: results of a European multicentre survey. Clin Nutr. 2001;20(3):205-10.

14. Howard L, Ament M, Fleming CR, Shike M, Steiger E. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. Gastroenterology. 1995;109(2):355-65.

15. Fishbein TM, Matsumoto CS. Intestinal replacement therapy: timing and indications for referral of patients to an intestinal rehabilitation and transplant program. Gastroenterology. 2006;130(2Suppl):S147-51. Review.

16. Bakonyi Neto A, Takegawa B, Ortolan E, Galvão F, Mendonça F, Sbragia L, et al. Demographic of short gut syndrome: increasing demand is not followed by referral of potential candidates for small bowel transplantation. Transplant Proc. 2004;36(2):259-60.

17. Lillehei RC, Goott B, Miller FA. The physiological response of the small bowel of the dog to ischemia including prolonged in vitro preservation of the bowel with successful replacement and survival. Ann Surg. 1959;150:543-60.

18. Selvaggi G, Weppler D, Nishida S, Moon J, Levi D, Kato T, et al. Ten-year experience in porto-caval hemitransposition for liver transplantation in the presence of portal vein thrombosis. Am J Transplant. 2007;7(2):454-60.

19. Starzl TE, Rowe MI, Todo S, Jaffe R, Tzakis A, Hoffman AL, et al. Transplantation of multiple abdominal viscera. JAMA. 1989;261(10):1449-57.

20. Grant D, Wall W, Mimeault R, Zhong R, Ghent C, Garcia B, et al. Successful small-bowel/liver transplantation. Lancet. 1990;335(8683):181-4.

21. Murase N, Demetris AJ, Matsuzaki T, Yagihashi A, Todo S, Fung J, et al. Long survival in rats after multivisceral versus isolated small-bowel allotransplantation under FK 506. Surgery. 1991;110(1):87-98.

22. Yildiz BD. Where are we at with short bowel syndrome and small bowel transplant. World J Transplant. 2012;2(6):95-103. Review.

23. Tzakis AG, Kato T, Levi DM, DeFaria W, Selvaggi G, Weppler D, et al. 100 Multivisceral Transplants at a Single Center. Ann Surg. 2005;242(4):480-90; discussion 491-3.

24. Roskott AM, Galvao FH, Nieuwenhuijs VB. Intestinal transplantation: Who, when and how? A general overview. Rev Med (São Paulo). 2009;88(3):150-62.

25. Ashokkumar C, Talukdar A, Sun Q, Higgs BW, Janosky J, Wilson P, et al. Allospecific CD154+ T cells associate with rejection risk after pediatric liver transplantation. Am J Transplant. 2009;9(1):179-91.

26. Pécora RA, David AI, Lee AD, Galvão FH, Cruz-Junior RJ, D'Albuquerque LA.

Small bowel transplantation. Arq Bras Cir Dig. 2013 ;26(3):223-9. Review. English.

27. Okumura M, Fujimura I, Ferrari AA, Nakiri K, Lemos PC, de Andrea EA, et al. [Transplantation of the small intestine. Case report]. Rev Hosp Clin Fac Med Sao Paulo. 1969;24(1):39-54.Portuguse.

28. Galvão FH. Transplante intestinal. In: Moraes IN, editor. Tratado de clínica cirúrgica. São Paulo: Roca; 2005. p. 2080-5.

29. Vianna RM, Mangus RM, Kubal C, Fridell JA, Beduschi T, Tector J. Multivisceral transplantation for diffuse portomesenteric thrombosis. Ann Surg. 2012;255(6):1144-50.