Intestinal and multivisceral transplantation

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Intestinal transplantation is a generic term that includes different types of transplants with varying combinations depending on the organs accompanying the intestine in the graft.

HISTORY OF INTESTINAL TRANSPLANTATION

Intestinal transplantation (IT) represents the last of the solid organ transplants to be incorporated into clinical practice owing to the immunological challenges it presents. In addition to its delayed incorporation, the evolution of IT has been characterized by a somewhat staggered learning curve, with great advances alternating with periods of stagnation. Fortunately, in recent years, it has become the standard of care for selected patients with intestinal failure (IF)[1].

The first attempt to transplant the intestine was carried out by Alexis Carrel at the beginning of the 20th century. Richard Lillehei took up the experimental research in 1950, providing the first descriptions of the surgical technique[2,3]. The well-known need for IT was emphasized by the development of parenteral nutrition (PN) and the concept of intestinal failure. PN was introduced by Dudrick and Wilmore, from the Children's Hospital of Philadelphia in the 1960s, precisely to prevent the death of children with short bowel syndrome[4]. The success of parenteral nutrition highlighted the complications related to its administration, such as infections, venous access thrombosis, and liver disease.

Lillehei also carried out the first clinical IT attempt in 1967, spurred on by the appearance of the first immunosuppressants (steroids, azathioprine, etc.)[5]. The outcome was catastrophic, as were the sporadic attempts that followed in the ensuing years. IT was virtually abandoned between the 1970s and 1980s.

The arrival of cyclosporine in the early 1980s renewed interest in IT. Olivier Goulet (Paris), David Grant (London, Canada), and Eberhard Deltz (Kiel) were among the great pioneers of this new era in which long-term survival was achieved for the first time after isolated intestinal transplantation, and combined liver and intestinal transplantation. The Pittsburgh group led the way during the 1990s, consolidating the procedure and serving as a school for the subsequent opening of IT programs around the world.

The next major milestone in the history of IT was the appearance of the tacrolimus immunosuppressant, which dramatically changed the prognosis of this transplant modality, prompting the introduction of the procedure in major transplantation centers.

From 1985 to 2019, according to the official registry – *International Intestinal Transplant Registry* (ITR) (http://www.terasaki.org/itr) –, 4,103 intestinal transplants were performed worldwide, which is not insignificant, but much lower than other registries such as those for kidney transplants, with tens of thousands of patients. On the other hand, the number of annual transplants has decreased in recent years, thanks to advances in intestinal rehabilitation, from 270 cases in 2008 to 149 in 2017.

INDICATIONS FOR INTESTINAL TRANSPLANTATION

The criteria for intestinal transplantation were agreed upon in 2001[6] and were recently reevaluated (2019)[7], taking into account advances in rehabilitation and the increased perspective of differences in terms of quality of life between transplantation and PN.

It is recommended that patients with intestinal failure be referred early to **intestinal rehabilitation units** (IRU) for evaluation as potential candidates, even in the absence

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of complications related to PN administration. After evaluation, the patient is managed in a coordinated approach by the IRU and the originating center for the benefit of the patient. The updated indications are shown in Table 1, and are discussed below.

Irreversible liver damage related to intestinal failure.

Liver damage is the most frequent and serious complication developed by patients with intestinal failure. Some 40 to 60% of children requiring long-term PN and 15 to 40% of adults on home parenteral nutrition develop liver damage of variable intensity. The clinical spectrum of lesions includes hepatic steatosis, cholestasis, cholelithiasis, and hepatic fibrosis. Newborns with early jaundice (before 3rd-4th month of life), and cases of short bowel that have undergone multiple laparotomies, ultra-short bowel, or cases with absence of intestinal continuity are at increased risk of developing this complication.

The appearance of signs of portal hypertension in patients with jaundice is the classic manifestation of liver damage progression. However, the indication for liver damage in early stages can be complex, since the damage necessary for it to become an independent risk factor for patient mortality has not been defined.

Endoscopic ultrasound and different elastography modalities have begun to be used in these patients, but the results have not yet been validated. Those that have demonstrated better results in children compared to those of biopsy are transient elastography[8] (vibrational wave) and shear wave velocity elastography[9] (acoustic radiation force). As for liver biopsy, which is the gold standard, it entails a risk of bleeding for the patient, can lead to errors in heterogeneous lesions, and the exclusive assessment of the degree of fibrosis can underestimate the risk of complications in patients with intestinal failure.

Liver damage in turn is aggravated by the administration of inadequate PN. Therefore, the indication of IT is established under the following conditions:

- Hyperbilirubinemia (> 4.5 mg/dL) for more than two months, despite optimization of lipid administration included in the PN.
- Any elevation of bilirubin combined with a reduction in synthesis function (low albumin or elevated INR), indicators of portal hypertension, especially plateletopenia for more than one month in the absence of confounding infectious episodes.

Loss of deep venous access due to thrombosis:

Classically, the loss of half of the conventional access sites (jugular and subclavian veins in young children; jugular, subclavian and femoral veins in older children and adults) is accepted as an indication. This indication is much debated since alternative venous access sites, such as transhepatic veins, the azygos system, etc., have been increasingly used.

Table 1. Indications for intestinal transplantation[7].

Evidence of liver failure associated with established or progressive intestinal failure: – Hyperbilirubinemia > 4.5mg/dl for more than 2 months, despite optimization of lipid infusion in PN – Any combination of elevated bilirubin together with: impaired synthesis function (albumin deficiency or elevated INR), laboratory indicators of portal hypertension and hypersplenism, especially plateletopenia, for more than 1 month, in the absence of infections.
Thrombosis of 3 of the 4 superior central venous access sites (jugular and subclavian on both sides) or occlusion of the brachiocephalic trunk in children (in adults it is assessed on a case-by-case basis).
Life-threatening episodes in the context of chronic PN dependence of anatomical or functional origin: – In children, 2 admissions to PICU (excluding the one that originated the intestinal failure) for cardiorespiratory failure (need for inotropes or mechanical ventilation) due to sepsis or other complications of intestinal failure. – In adults, decision on a case-by-case basis.
Intra-abdominal invasive desmoid tumor in adolescents and adults
Diffuse acute intestinal infarction with hepatic failure
Failure of the first transplant

Severe sepsis related to the use of deep venous catheters

Patients who develop metastatic infectious complications such as brain abscess, endocarditis, and multiorgan failure should be evaluated as candidates. Likewise, patients colonized with multi-resistant germs (e.g., vancomycin-resistant *Enterococcus faecium*) and who develop frequent catheter infections with these germs should be considered candidates.

Intestinal failure usually leading to early death, despite optimal nutritional support

- Cases of ultra-short bowel syndrome, such as duodeno-colic anastomosis, cases of non-reconstructible bowel, residual small bowel less than 10 cm in young children, or less than 30 cm in older children, severe trauma that injures the main branch of the superior mesenteric artery, and intra-abdominal tumors (usually desmoid) that require near-total bowel resections. Since there is no possibility of intestinal adaptation, it is advisable to advance the indication for IT before the development of complications related to PN administration.

– Congenital disorders of the intestinal mucosa with intractable diarrhea. As in the previous case, it is preferable to anticipate the development of irreversible liver damage, which would require combined liver and intestinal transplantation.
– Intestinal failure associated with high morbidity and poor quality of life: observed in certain cases of chronic idiopathic intestinal pseudo-obstruction.

Indication of the type of transplantation: inclusion of the liver in the graft

Isolated intestinal transplantation is indicated in cases where liver disease is absent or reversible. Jaundice per se is not an indication for combined transplantation, since cases of isolated intestinal transplantation have been published with previous serum bilirubin levels above 10 mg/dl in which jaundice resolved after transplantation. Combined transplantation is indicated in cases of irreversible liver damage, hypercoagulabe states, such as protein C, S, etc. deficiency (inclusion of the liver with the graft cures the hypercoagulable disorder), and cases of intra-abdominal tumors of low malignant potential (e.g., desmoid tumors) affecting the liver and intestine.

In addition to the classic criteria, the inclusion of the liver in the graft in cases of retransplantation is discussed because of its protective role against humoral rejection.

CONTRAINDICATIONS FOR INTESTINAL TRANSPLANTATION

Exclusion criteria do not differ from those usually found in other solid organ transplants, and can be grouped into absolute and relative:

Absolute criteria
– Profound or progressive neurological deficits
– Non-gastrointestinal incurable disease
– Active sepsis
– Malignant tumors
– Unresolvable and severe psychosocial problems

Relative criteria
– Immunodeficiency
– Drug dependence
– Impossibility of ensuring deep venous access during the 6 months post-transplantation.
– Benign neoplasms with unclear prognosis.

TYPES OF INTESTINAL TRANSPLANTATION

Four main forms of IT are described in human clinical practice: isolated intestinal transplantation, combined liver and intestinal transplantation, multivisceral transplantation, and modified multivisceral transplantation. Recently, the original techniques have been modified to suit specific patient needs.

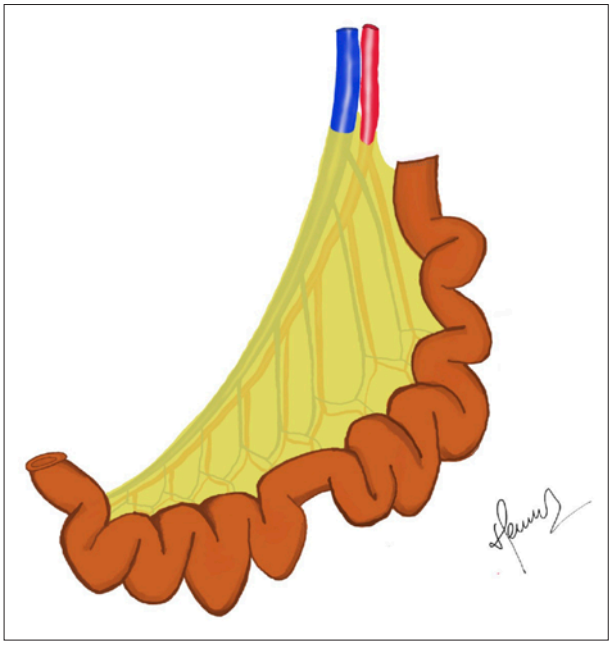

Figure 1. Isolated intestinal graft.

Isolated intestinal transplantation

This is the simplest procedure and is used in patients with intestinal failure not associated with liver damage or gastric motility disorder. It is the most frequent type of transplant in adults, 55% versus 37% in children. The graft includes the entire small intestine, with or without the colon or part thereof, as will be seen later.

The great advantage is that, in case of rejection or localized lymphoma in the graft, complete removal of the graft can be performed. Paradoxically, the impact on graft survival can be negative, as it has been seen that the inclusion of the liver in the graft is a protective factor against rejection.

The graft includes practically the entire small intestine (Fig. 1), from the ligament of Treitz to the ileocecal valve, vascularized by the superior mesenteric artery and the superior mesenteric vein. It is compatible with liver and pancreas donation. It is advisable to conduct as much dissection as possible before cold perfusion.

Upon implantation, the superior mesenteric artery is anastomosed to the infrarenal aorta and the graft mesenteric vein to the infrarenal vena cava or superior mesenteric vein of the recipient, if possible. As alternatives, the left renal vein and the splenic vein have been used. Although a priori venous drainage to the recipient's mesenteric vein seems the most physiological option, no significant alterations have been detected in patients with systemic drainage of the graft. In these cases, portal flow is partially maintained by the inflow of blood from the stomach, duodeno-pan-

creatic axis, spleen, and remaining intestine. On the other hand, physiological drainage to the mesenteric vein could be compromised in case of hepatic fibrosis.

Intestinal continuity is restored by anastomosis of the proximal side of the graft to the remaining native bowel – with the type of anastomosis depending on the center's preference, end-to-end, end-to-side, side-to-side, etc. Usually, a terminal stoma is left at the distal end.

In cases where the colon is included, a double-barrel ostomy is left in the ileum and the colocolic anastomosis is performed, so that continuity is fully restored months later by a simple ileostomy closure, without the need for laparotomy. This part is common to all types of transplantation.

Liver and intestinal transplantation

It is indicated when intestinal failure has produced irreversible liver damage. Other indications include the presence of portal hypertension and portomesenteric thrombosis, intestinal ischemia due to hypercoagulable states (since liver transplantation would correct the coagulation disorder). According to the international registry, it is historically the most frequent type of transplantation in children, 50% vs. only 21% in adults. The higher frequency in children is related to the different etiology of intestinal failure in the two age groups; but, above all, to the greater susceptibility of children to develop liver damage related to the administration of PN. Currently, the most commonly used technique for liver and intestinal transplantation is the "en bloc" graft, which includes the donor's pancreatic duodenal complex with the intestine. An exception to en bloc transplantation is that of living donor liver and intestinal transplantation, used rarely, in which the liver and intestine are implanted separately, but in the same surgical procedure.

The graft includes the liver and the entire small intestine from the pylorus to the terminal ileum, with the duodeno-pancreatic axis included in the graft (Fig.2). It is usually harvested en bloc with the spleen, but the spleen is removed at the operating table, prior to implantation. The pedicle is formed by the thoracic and abdominal aorta, which is sectioned proximal to the origin of the renal arteries, including, therefore, the superior mesenteric artery and the celiac trunk.

In the recipient, an aortic arterial segment is placed to the infrarenal aorta before the anhepatic phase. This makes the aortic anastomosis of the implant more comfortable. The implantation itself begins with the anastomosis of the suprahepatic cava, and then the definitive arterial anastomosis is performed, connecting the graft aorta to the graft to the segment previously anastomosed to the aorta. The infrarenal aortic cava intersection can be ligated if the *piggy-back* technique has been performed during hepatectomy, or it can be used as a drainage pathway from the native portal vein corresponding to the native splanchnic remnant (stomach, duodenum, pancreas, and spleen).

Intestinal continuity is reestablished by anastomosing the jejunum of the graft to the remnant of the native duodenum or jejunum. End-to-end, side-to-end, and side-to-side anastomoses have been used, the latter with manual or mechanical suture. The type of anastomosis used depends on each case and the preference of the group.

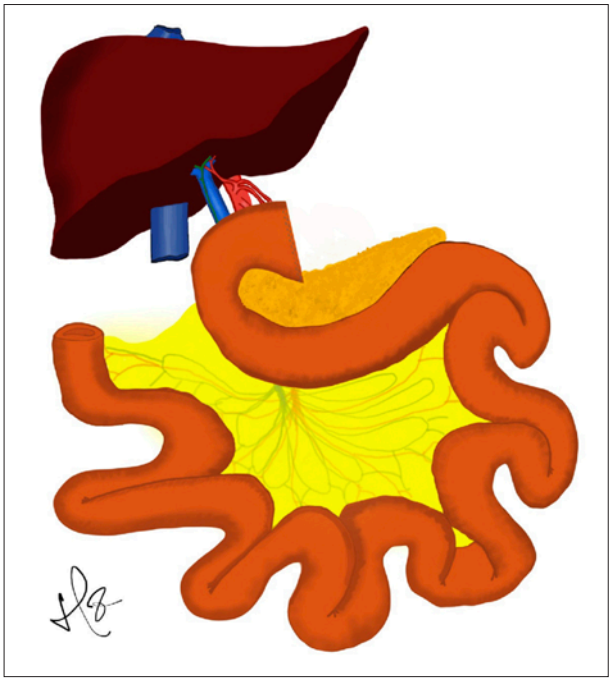

Figure 2. Liver and intestinal graft.

The distal end of the ileum is managed in a manner similar to that described for isolated intestinal transplantation.

Multivisceral transplantation

Classically, this was considered as such when three or more abdominal viscera were included with the graft, usually the stomach, duodenum, pancreas, liver, and intestine; but ever since the "en bloc" liver and intestinal transplant technique has been implemented, the term is used for cases in which the stomach or part of the stomach is included with the graft.

During the recipient's surgery, the most proximal part of the body of the stomach is preserved, and therefore, also the left gastric artery. If the spleen is preserved, the splenic artery and the splenic vein in continuity with the portal vein will also be preserved.

The graft is therefore similar to the liver and intestine graft but includes the stomach (Fig. 3). The vascular portion of the graft is similar to liver and intestinal transplantation, including the native portal vein anastomosis in case the spleen has been preserved. After the vascular portion, gastro-gastric anastomosis is carried out, usually with a double layer of suture, due to the risk of bleeding in the postoperative period. In addition, pyloroplasty is performed to try to reduce the emptying problems derived from the denervation inherent to the procedure. Ileostomy care is similar to isolated intestinal transplantation.

Modified multivisceral transplantation

It is similar to multivisceral transplantation with the only exception that it does not include the liver. It is indicated in cases of intestinal failure in which the stomach and/or pancreas or both have to be removed in the recipient, such as cases of severe gastric dysmotility, pancreatitis, or pancreatic lesion. Other indications include some cases of tumors with no tendency to metastasize but which are locally aggressive (usually desmoid), trauma, and severe thrombosis of the splanchnic territory.

During the recipient's surgery, the liver is preserved with the corresponding hepatic artery, the apex of the body of the stomach with the left gastric artery, and if possible, the spleen, with the splenic artery and vein. If the spleen is preserved, during the implantation phase, the superior mesenteric vein is clamped at the level where it has been divided, and the portal flow to the liver from the splenic vein is maintained. If the spleen is not preserved, only the hepatic arterial tributary is maintained.

The graft aorta artery is anastomosed to the previously placed infrarenal aortic graft, and all venous drainage from the graft drains through the portal vein, which is anastomosed to the native portal vein or superior mesenteric remnant. Gastric anastomoses with pyloroplasty are then performed, followed by ileostomy, as in multivisceral transplantation.

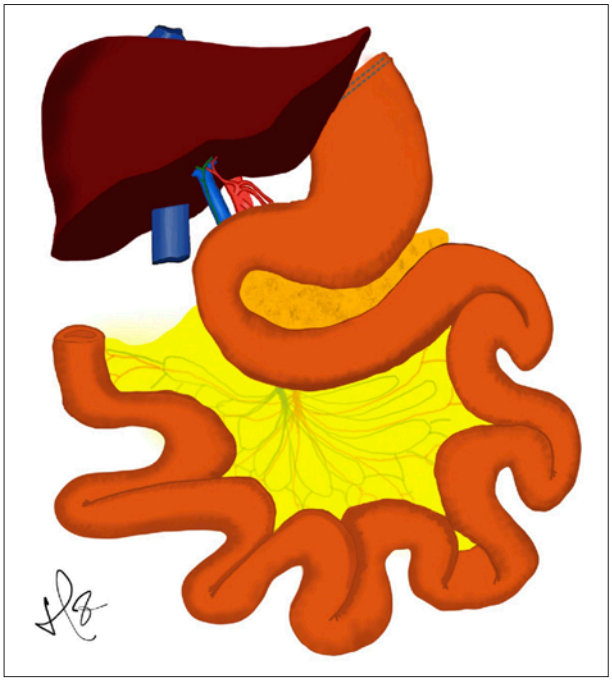

Figure 3. Multivisceral graft.

TECHNICAL VARIANTS

In recent years, the original techniques have been modified, and significant refinements have been made to meet the different needs of recipients. A major limitation is the shortage of suitable donors, especially if the candidate is a young or very low weight child. As a consequence, the waiting list is very long, close to one year, and pre-transplantation mortality is high, estimated to be close to 30-50% in the group of candidates between 0 and 5 years of age. The physical and nutritional deterioration of the child worsens while awaiting transplantation, and the progression of the liver disease often makes it necessary to change the indication to combined liver and intestinal transplantation. In order to break this vicious circle, various strategies and surgical techniques have been developed with the aim of adapting to the needs of the recipient and increasing the likelihood of access to transplantation.

Inclusion of the liver in the transplant

The classic indications for intestinal transplantation were performed according to the patient's needs, so that the liver was only included in cases of associated liver failure or in those in which the inclusion of the liver could provide the added benefit of curing the primary disease, such as in cases of protein C or S deficiency. However, it has been demonstrated that graft survival is greater in cases in which the liver is included in the graft (liver and intestinal, or multivisceral). The mechanism, or one of the mechanisms, involved in the protective effect of the liver is its ability to prevent the emergence of *de novo* donor-specific antibodies[10], which in turn lead to graft loss through the development of humoral rejection.

Isolated liver transplantation in intestinal failure

In very selected cases, in which the main limiting factor to intestinal adaptation is severe liver damage, isolated liver transplantation has been proposed. The advantages of this strategy are clear: the alternative techniques of liver transplantation with reduced grafts are better established and their results documented; there is greater availability of organs; and less immunosuppression is required. However, experience with this strategy is still limited, and the results reported are contradictory. Optimal candidates would be children with end-stage liver disease with probability of intestinal adaptation:

- Age < 4 years (higher probability of adaptation).
- Good characteristics of the residual intestine with respect to length, quality, type of residual intestine, and motility.
- Demonstrated enteral tolerance of approximately 50% of the needs.

Problems of abdominal wall closure: graft reduction and closure techniques. Abdominal wall transplantation

The shortage of suitable donors means that donors who are heavier than the recipients are often used. In addition, recipients frequently present loss of dominance of the abdominal cavity due to previous surgeries and complications. The problem of closure is therefore the result of

the combination of the characteristics of the donor and the weight of the recipient.

The first solution, frequently used in the 1990s, was to anatomically reduce the size of the graft during harvesting or at the operating table. Numerous successful transplantations were performed, although some presented considerable complications, especially when the technique was taken to the extreme of using the same donor for two different recipients.

On the other hand, numerous techniques have been described to allow for wall closure, sequential closure with the aid of synthetic mesh, one-time closure with synthetic or biological mesh, enlargement of the cavity by means of expanders, and closure with vascularized or non-vascularized fascia from the donor. They have all yielded acceptable results, so their use depends on the group's experience with one or the other.

Finally, abdominal wall transplantation was described in 2000. In the original description, the abdominal wall block was vascularized through the epigastric vessels, in continuity with the femoral vessels, so that the implantation was performed in a manner similar to renal transplantation. Subsequently, the Bologna and Oxford groups made modifications introducing microsurgical vascularization to the femoral and radial vessels, respectively. Abdominal wall transplantation has the advantage of acting as an immunological witness, since it warns in case of rejection before presenting abdominal symptoms, as well as in case of graft versus host disease, since the skin corresponding to the transplanted wall is not affected, thus standing out from the rest of the skin that does present the characteristic rash.

Living donor intestinal transplantation

Considering the high pre-transplantation mortality rates, it is logical to resort to living donation in order to expand the number of available donors, thus trying to avoid the progression of liver disease in children on the intestinal transplant list. In the event of liver failure, liver and intestinal transplantation by living donor can be used, in which both organs are implanted independently and sequentially, in the same surgical act or in the following days. The liver is transplanted first, and when the liver has recovered from ischemia and both donor and host are perfectly stable, the intestine is implanted.

The advantages of the living donor procedure include possibility of scheduling the procedure, better histocompatibility, shorter cold ischemia time, possibility of administering desensitization treatment, and better intestinal preparation.

The graft consists of a segment of approximately 160 cm of ileum (200 cm in an adult recipient), provided that the resection is less than 40% of the total length of the donor intestine, and preserving a minimum of 20-30 cm of terminal ileum.

The results published to date[11-13] are similar, and even superior to those of cadaveric donors, given the hypothetical immunological advantage due to haploidentity in the case of using related donors. The procedure is technically complex, but the main limitation is not technical but ethical. Living donation is considered when the expected long-term survival of the recipient is high, as in liver or kidney transplantation, or when there is no other source of donors available, as in some Asian countries.

Preservation of the recipient's spleen

The spleen, as it is well known, plays a very important role in cellular and humoral immunity and in the complement pathway. In patients with portal hypertension, who are usually candidates for liver and intestinal or multivisceral transplantation, the spleen is often removed together with the liver and the duodenopancreatic block simply to increase the space in the cavity to accommodate the graft.

In an attempt to avoid the situation of asplenia in these patients, the inclusion of allogeneic spleen in multivisceral transplantation became popular for some years. This technical modification decreased the number of rejections but increased hematologic complications and graft-versus-host disease in recipients.

The next technical modification –preservation of the native spleen– was initially described in modified multivisceral transplant recipients, in which the spleen is preserved along with the liver and duodeno-pancreatic axis; and then in multivisceral transplants[14,15] in which the spleen is preserved in isolation with its pedicle, forcing drainage of the splenic vein after implantation, usually into the infrahepatic vena cava of the graft. This technique has been shown to reduce the risk of graft-versus-host disease and other hematologic complications, such as autoimmune anemias.

Graft from DCD (Donor after Cardiac Death) donors

Until a few months ago, the use of intestinal grafts from DCD donors was banned due to the false paradigm that susceptibility to ischemia made the clinical use of these organs unfeasible. Preclinical[16] and clinical[17] evidence recently demonstrated that multivisceral grafting from DCD donors with normothermic perfusion can be used safely in patients. However, the indications and limitations of the use of these organs remain to be defined.

COMPLICATIONS

Many of the complications of IT are a consequence of the peculiarities of the gastrointestinal tract: the great mass of intestinal lymphoid tissue, continuous renewal of the intestinal epithelium, and colonization by germs.

Technical complications

Technical complications are more frequent in very young children (under 2 years of age) and are accountable for half of graft loss cases. In transplants that include the liver,

biliary complications have virtually disappeared with the "en bloc" technique, which does not require biliary reconstruction. Some cases present long-term biliary stenosis, most likely of ischemic or autoimmune origin, but these are secondary to technical complications.

Necrotizing enterocolitis is a rare but serious complication, as it is accompanied by intestinal gangrene. Pathogenesis is unknown, although it is assumed that ischemia-reperfusion phenomena after cold ischemia of the graft, as well as episodes of hypovolemia, are involved. Wall closure, as seen above, frequently produces complications in children with short bowel syndrome.

Rejection

Rejection is the most frequent complication of IT, the first cause of graft loss, and the second cause of mortality, only behind sepsis. Diagnosis is often problematic and is still based on histological criteria. For this purpose, sampling by endoscopy, at regular intervals, and on demand when the clinical situation requires it is the usual diagnostic procedure.

Histologically, acute rejection is characterized by infiltrate of activated lymphocytes in the lamina propria, lesion of the crypt epithelium and apoptosis. It is graded into indeterminate, mild, moderate, and severe. The main characteristics of the different rejection grades are shown in Table 2.

Table 2. Histological criteria and rejection grading in intestinal transplantation.

Grade	*Main findings*
Indeterminate	Minimal localized inflammatory infiltrate, minimal crypt injury, increased apoptosis in crypts (usually < 6 apoptosis/10 crypts), minimal or no distortion of architecture, no mucosal ulcers, insufficient changes for diagnosis of mild acute rejection.
Mild	Localized mild inflammatory infiltrate with activated lymphocytes, mild crypt injury, increased apoptosis in crypts (> 6 apoptotic bodies/10 crypts), mild distortion of architecture, no mucosal ulcers.
Moderate	Scattered moderate inflammatory infiltrate in lamina propria, diffuse epithelial damage in crypts, increased apoptosis in crypts with confluent apoptosis, marked distortion of architecture, mild to moderate intimal arteritis may be seen, no mucosal ulcers.
Severe	Moderate rejection lesions and mucosal ulcers. Severe intimal arteritis or transmural arteritis may be seen.

Adapted from: Wu, et al. Am J Gastroenterol. 2006; 101: 1617-24.

Chronic rejection is an increasingly significant entity as experience with IT increases. It presents with diarrhea and hemorrhages, with areas of stenosis and dilatations demonstrable by radiology. Histologically, it is characterized by loss of crypts and villi, predominantly plasmacytic infiltrate and ulcerations. Epithelial lesions are a consequence of both direct damage from the immune response and indirect damage secondary to arteriopathy obliterans, as the endothelium is also a target tissue in this type of rejection.

Humoral rejection, which is well-known in renal transplantation, has recently been recognized in intestinal transplantation. Diagnosis presents more difficulties than acute cellular rejection, the most characteristic findings being capillaritis and endothelitis. The presence of C4b, a complement-derived product characteristic of this rejection, in the presence of DSA was initially considered diagnostic, but this finding is not consistent. In addition, humoral rejection almost always occurs in combination with a cellular rejection component, further complicating accurate diagnosis. Pediatric patients do not usually present with donor-specific antibodies (DSA), except in cases of retransplantation; in adults, the presence of these antibodies is somewhat more frequent. However, preformed antibodies do not seem to influence graft loss; the truly dangerous ones, those that trigger rejection and can lead to graft loss, are *de novo* antibodies[10].

Treatment of cellular rejection is based on increased immunosuppression, which usually includes steroid boluses, optimization of baseline immunosuppression (usually tacrolimus), and use of one of the agents used in induction: basiliximab, thymoglobulin, or alentuzumab, depending on the characteristics of the patient and the drugs previously used. In the case of chronic rejection, treatment is similar, although the response is much worse as the lesions are irreversible, and the final result is graft loss. In the case of humoral rejection, the most rapid treatment is the elimination of circulating antibodies through the administration of immunoglobulins and plasmapheresis. In the long term, agents such as rituximab (anti CD20) and bortezomib (a proteasome inhibitor) have shown good results[18].

Infection

It is the second most frequent complication after rejection and the main cause of death, responsible for 50% of the total. The use of deep venous access sites, sepsis of intraperitoneal origin due to technical problems (dehiscence, perforation, necrosis, etc.), and bacterial translocation predispose to the development of septic phenomena. There is also a close relationship between sepsis and rejection, with both phenomena feeding back on each other.

Infections due to opportunistic germs

Immunosuppressive medication prevents the onset of immunological complications, but depresses cellular immunity, and the baseline immunosuppression received by an IT recipient is higher than in patients with liver, heart, or

kidney transplants, for example. Consequently, infections by opportunistic germs are more frequent in IT than in other solid organ transplants. Cytomegalovirus infection has been an important source of morbidity, although it has now been well controlled with a combination of preventive and prophylactic measures. Adenovirus infections are accountable for many cases of post-transplant diarrhea and have recently been associated with pathogen infections not previously described in other solid organ transplantations, such as calicivirus infection, which produces secretory diarrhea.

Post-transplantation lymphoproliferative disease

These lesions are usually related to infection by Epstein-Barr virus, which has a special affinity for B lymphocytes. Due to immunosuppression, infected B lymphocytes proliferate, with subsequent malignization in some cases, usually in the form of non-Hodgkin's B-cell lymphoma. Children are more susceptible than adults to develop this complication, the incidence of which in some series is close to 30% of cases, although fewer cases have been observed in recent years than in historical series. Treatment involves reduction/withdrawal of immunosuppression and use of antivirals. The anti-CD20+ antibody (rituximab) is the second line of treatment. In the absence of response, low-dose monochemotherapy is recommended. The best treatment is prevention; determination of viral load in peripheral blood, by means of qualitative or quantitative DNA amplification techniques, allows immunosuppression levels in infected children to be modified. For early diagnosis, nuclear staining with in-situ hybridization of Epstein-Barr virus encoded small RNAs (EBERs) with an EBER-1 probe is used to detect the presence of the virus in tissues before the complication develops.

Dysmotility and diarrhea

Post-transplantation secretory diarrhea is sometimes a serious problem, especially in children. In some cases, it is associated with rejection, and responds to increased immunosuppression. In most cases, etiology is not very clear, involving the action of certain viruses, motility disorders, denervation with alteration of sympathetic tone, lymphatic disconnection, intestinal denervation, increased intraluminal osmotic load due to malabsorption of hydroxylated fatty acids, carbohydrates and bile salts, graft-versus-host disease, and adverse effects of immunosuppression (particularly mycophenolate mofetil).

In most cases, it is difficult to distinguish a secretory diarrhea from an infection, or even from a rejection, with the resulting doubts regarding treatment, which is very different in each case. Therefore, biopsy is usually necessary at the slightest suspicion of rejection.

Food aversion

This is a very frequent complication, especially in children with intestinal failure secondary to neonatal problems, and who have never received oral feeding, as well as in patients with chronic idiopathic intestinal pseudo-obstruction, who relate oral feeding with previous unpleasant experiences of abdominal pain, flatulence, etc. It does not seem to be corrected with time, requiring in some cases psychological support. Within 5 years of intestinal transplantation, more than half of the transplanted children suffer from this complication.

Graft-versus-host disease

This complication is rare in other solid organ transplants but is well known in the field of hematopoietic stem cell transplantation. In intestinal transplantation, it occurs in 10% of patients and mortality is usually high, around 50%[19]. Most likely, the high lymphoid load of the intestinal or multivisceral graft justifies this rarity. In fact, it occurs more frequently in multivisceral transplantation than in isolated intestinal transplantation. The picture is defined by cutaneous involvement, which consists of a disseminated maculopapular rash, including on the soles and palms. Other frequently affected organs include the lungs and native intestine. It causes diarrhea, cutaneous lesions, and cholestasis.

Treatment, paradoxically, involves increasing immunosuppression, as in acute cellular rejection. The response is highly variable and in patients who die, the cause is usually infection in the context of immunosuppressive treatment. Extracorporeal photopheresis, mesenchymal stem cell therapy, and more recently ruxotinilib (kinase inhibitor) have proven effective in some cases.

Disease recurrence

It has only been described in adults so far. There are documented cases of recurrence in Crohn's disease, and in desmoid tumors in patients with Gardner's syndrome.

Psychiatric disorders

They are more frequent in older children, as a result of the severity of the disease, prolonged dependence on parenteral nutrition, chronic disease, etc. The main disorder is depression, although psychotic symptoms have also been described. Regardless of the specific picture or the medication received, most patients require psychological support at some point.

RESULTS

Worldwide experience

Between 1985 and 2017, 2080 transplantations were performed in 2010 pediatric recipients. A total of 72 centers contributed to the registry, although in recent years, only 35 centers have provided new data; and there is evidence that at least 20 centers closed their pediatric intestinal transplant program. The clinical characteristics of the 2080 transplantations are summarized in Table 3. The most frequent type

Table 3. Clinical characteristics of all pediatric intestinal transplantations from the international registry (1985-2017).

	N=2080 transplantations
Mean age (years) at transplantation (Q1;Q3)	2,5 (1,1;6,3)
Male sex, n (%); Female sex, n (%)	1177 (57); 903 (43%)
Type of transplantation, n (%)	
IIT	725 (35)
LVT	966 (46)
MVMT	47 (2)
MVT	342 (16)
Indication for transplantation[a], n (%)	
Short bowel syndrome	1245 (65)
Motility disorder	381 (20)
Intestinal mucosal disease	174 (9)
Retransplantation	91 (5)
Tumor	22 (1)
Cause of short bowel[b], n (%)	
Gastroschisis	473 (38)
Volvulus	315 (25)
Necrotizing enterocolitis	290 (23)
Intestinal atresia	49 (4)
Ischemia	24 (2)
Trauma	24 (2)
Other	150 (12)
Rapamycin as maintenance, n (%)	160 (8)

Adapted from: Raghu, et al. Pediatr Transplant. 2019; 23: e13580.
[a]The values do not add up to the total number of transplantations due to loss of data.
[b]Some patients have more than one cause of inclusion, denominator of percentage=1245 with short bowel.

Table 4. Causes of death

Cause of death	*% of total losses*
Sepsis	57%
Other	41%
Unknown	20%*
Graft rejection/failure	19%
Cardiovascular/infarction	11%
PTLD/lymphoma	8%
Kidney failure	4%
Liver failure	4%
Respiratory failure	4%
Technical complications	3%

PTLD = Post-transplantation lymphoproliferative disease.
**It has been included because it was a cause of mortality in previously recorded periods.*

of transplantation is liver and intestinal (46%), followed by intestinal (36%), with an increasing trend in the last decade. There has been a growing trend towards the use of transplantation without the liver included, although multivisceral transplantation has increased slightly, as has the inclusion of the colon in the graft.

Survival

According to the latest data published by the ITR, overall graft survival at 1 year and 5 years is 66.1% and 47.8%, respectively; and patient survival at 1 year and 5 years is 72.2% and 57.2%.

In the univariate and multivariate regression analysis, overall graft survival was more strongly associated with being a first transplant (vs. retransplantation) (HR=0.48; 95% CI: 0.33-0.68), home versus hospitalized (HR=0.70; 95% CI: 0.58-0.85), graft with liver included (HR=0.66; 95% CI: 0.56-0.79), and mucosal or motility disorder as an indication. Patient survival was related to home transplantation and to being a first graft.

Cause of death and cause of graft loss

Sepsis is the main cause of death (Table 4), followed by graft failure and lymphoproliferative syndrome/lymphoma. In a significant proportion of patients, the cause is not well known or is not specifically recorded. Finally, by far, the most frequent cause of graft loss is rejection, followed by patient death (Table 5).

Digestive autonomy

Complete digestive autonomy was achieved in 60% of the cases, and 9% required only parenteral fluids. The percentage of patients achieving complete autoºnomy increases progressively with each registry update, and it has been shown that those in whom the colon was included in the graft achieved better results, reaching autonomy in 75% of the cases.

Quality of life

It has been shown, as in other diseases, that the patient's perception is better than that of their caregivers, and that they usually present scores on the usual quality of life scales similar to other chronic diseases or even similar to healthy controls[20-22]. However, most studies have used adapted but not specific questionnaires so that the results, despite the concordance shown therein, should not be considered definitive.

In a recent study in 38 patients with more than 10 years of follow-up[23], 11 (28%) were found to be in need of psychiatric care; 5 suffered from depression and 6 from behavioral disorders. It was observed that they continued to require an average of 5 medications daily. The mean number of daily bowel movements was 3, 4 others had a stoma and 1

Table 5. Causes of intestinal graft loss

Cause of graft loss	*% of total losses*
Rejection	56%
PTLD	10%
Infection (not PTLD)	0%*
Surgical (thrombosis, volvulus, etc.)	8%
Poor graft function	8%
Other	2%
Death	16%

PTLD = Post-transplantation lymphoproliferative disease.
**It has been included because it was a cause of mortality in previously recorded periods.*

was incontinent. More than half of them had been admitted to hospital in the last 5 years with an average duration of 7 days. Two of them suffered from alcohol addiction and 1 was a drug user. In the social sphere, of the 18 adults, 3 were in stable employment, 4 were unemployed, and the rest were still completing their education.

REFERENCES

1. 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.
2. 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.
3. Manax WG, Bloch JH, Eyal Z, Lillehei RC. Experimental preservation of the small bowel. Am J Surg. 1965; 109: 26-31.
4. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. JAMA. 1968; 203(10): 860-4.
5. Lillehei RC, Idezuki Y, Feemster JA, Dietzman RH, Kelly WD, Merkel FK, et al. Transplantation of stomach, intestine, and pancreas: experimental and clinical observations. Surgery. 1967; 62(4): 721-41.
6. Kaufman SS, Atkinson JB, Bianchi A, Goulet OJ, Grant D, Langnas AN, et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transplant. 2001; 5(2): 80-7.
7. Kaufman SS, Avitzur Y, Beath SV, Ceulemans LJ, Gondolesi GE, Mazariegos GV, et al. New insights into the indications for intestinal transplantation - Consensus in the year 2019. Transplantation. 2020; 104(5): 937-46.
8. Jain V, Poddar U, Negi TS, Saraswat VA, Krishnani N, Yachha SK, et al. Utility and accuracy of transient elastography in determining liver fibrosis: a case-control study. Eur J Pediatr. 2020; 179(4): 671-7.
9. Lawrence AE, Dienhart M, Cooper JN, Lodwick D, Lopez JJ, Fung B, et al. Ultrasound elastography as a non-invasive method to monitor liver disease in children with short bowel syndrome: Updated Results. J Pediatr Surg. 2019; 54(6): 1179-83.
10. Talayero P, Ramos Boluda E, Gómez Massa E, Castro Panete MJ, Prieto Bozano G, Hernández Oliveros F, et al., Donor-specific antibodies in pediatric intestinal and multivisceral transplantation: The role of liver and human leukocyte antigen mismatching. Liver Transpl. 2018; 24(12): 1726-35.
11. Hibi T, Chen Y, Kim JI, Lee MD, Matsuura T, Ueno T. Current status of intestinal transplantation in East Asia. Curr Opin Organ Transplant. 2020; 25(2): 165-8.
12. Tzvetanov IG, Tulla KA, D'Amico G, Benedetti E. Living donor intestinal transplantation. Gastroenterol Clin North Am. 2018; 47(2): 369-80.
13. Gangemi A, Tzvetanov IG, Beatty E, Oberholzer J, Testa G, Sankary HN, et al., Lessons learned in pediatric small bowel and liver transplantation from living-related donors. Transplantation. 2009; 87(7): 1027-30.
14. Stringa P, Papa-Gobbi R, Vela M, Gentilini MV, Machuca M, Klin P, et al., Native spleen preservation during visceral transplantation inhibits graft-versus-host-disease development: Clinical and experimental study. Ann Surg. 2023; 277(1): e235-e244.
15. Hernandez F, Andres AM, Encinas JL, Domínguez E, Gamez M, Murcia FJ, et al. Preservation of the native spleen in multivisceral transplantation. Pediatr Transplant. 2013; 17(6): 556-60.
16. Stringa P, Vecchio Dezillio LE, Talayero P, Serradilla J, Errea A, Machuca M, et al., Experimental assessment of intestinal damage in controlled donation after circulatory death for visceral transplantation. Transpl Int. 2023; 36: 10803.
17. Andres AM, Encinas JL, Sánchez-Galán A, Rodríguez JS, Estefania K, Sacristan RG, et al., First case report of multivisceral transplant from a deceased cardiac death donor. Am J Transplant. 2023 [En prensa]. doi: 10.1016/j.ajt.2022.12.021
18. Idica A, Kaneku H, Everly MJ, Trivedi HL, Feroz A, Vanikar AV, et al. Elimination of post-transplant donor-specific HLA antibodies with bortezomib. Clin Transpl. 2008: 229-39.
19. Andres AM, Santamaría ML, Ramos E, Sarriá J, Molina M, Hernandez F, et al. Graft-vs-host disease after small bowel transplantation in children. J Pediatr Surg. 2010; 45(2): 330-6; discussion 336.
20. Andres AM, Alameda A, Mayoral O, Hernandez F, Dominguez E, Martinez Ojinaga E, et al. Health-related quality of life in pediatric intestinal transplantation. Pediatr Transplant. 2014; 18(7): 746-56.
21. Ngo KD, Farmer DG, McDiarmid SV, Artavia K, Ament ME, Vargas J, et al. Pediatric health-related quality of life after intestinal transplantation. Pediatr Transplant. 2011; 15(8): 849-54.
22. Sudan D, Horslen S, Botha J, Grant W, Torres C, Shaw B Jr, et al. Quality of life after pediatric intestinal transplantation: the perception of pediatric recipients and their parents. Am J Transplant. 2004; 4(3): 407-13.
23. Norsa L, Gupte G, Ramos Boluda E, Joly F, Corcos O, Pirenne J, et al. Life of patients 10 years after a successful pediatric intestinal transplantation in Europe. Am J Transplant. 2018; 18(6): 1489-93.