ORIGINAL ARTICLE

Twenty-eight years of intestinal transplantation in Paris: experience of the oldest European center

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SUMMARY

Our aim was to describe our achievements in pediatric intestinal transplantation (ITx) and define areas for improvement. After a period (1987–1990) of nine isolated small bowel transplants (SBTx) where only one patient survived with her graft, 110 ITx were performed on 101 children from 1994 to 2014: 60 SBTx, 45 liver–small bowel, four multivisceral (three with kidneys), and one modified multivisceral. Indications were short bowel syndrome (36), motility disorders (30), congenital enteropathies (34), and others (1). Induction treatment was introduced in 2000. Patient/graft survival with a liver-containing graft or SBTx was, respectively, 60/41% and 46/11% at 18 years. Recently, graft survival at 5/10 years was 44% and 31% for liver-containing graft and 57% and 44% for SBTx. Late graft loss occurred in 13 patients, and 7 of 10 retransplanted patients died. The main causes of death and graft loss were sepsis and rejection. Among the 55 currently living patients, 21 had a liver-containing graft, 19 a SBTx (17 after induction), and 15 were on parenteral nutrition. ITx remains a difficult procedure, and retransplantation even more so. Over the long term, graft loss was due to rejection, over-immunosuppression was not a significant problem. Multicenter studies on immunosuppression and microbiota are urgently needed.

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Key words
graft loss, intestinal transplantation, multivisceral transplantation, survival

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Introduction

One of the first intestinal transplantations (ITx) was performed in 1987 in our institution, in a child with short bowel syndrome (SBS), after extensive experimental work on piglets [1]. Despite immunosuppression based only on cyclosporine, one patient has enjoyed full intestinal function since 1989 [2,3]. When tacrolimus became available in the 1990s, ITx developed worldwide [2], although it remains a rare and difficult procedure. In 2015, the Intestinal Transplant Registry (ITR) recorded 1697 children, and half of them are still alive [3,4]. The number of ITx decreased from 2007 onwards, due to improvements in intestinal failure (IF) care, limiting the indications, but also due to the high morbidity and mortality of ITx patients [5,6]. We analyzed the evolution over 28 years in the oldest and largest European pediatric transplantation center, the results on mid- and long-term survival, achievements, and failures, to define

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areas where research and multicenter studies are most urgently needed.

Patients and methods

From 1987 to 1990, nine children received isolated small bowel transplantation (SBTx) with a cyclosporine-based immunosuppression. Two patients were still alive at the time of publication and are included in this report: one, whose donor was an anencephalic neonate, is the world's longest survivor with a functional graft; the second, in whom the graft implanted in 1989 was removed 6 months later, was retransplanted with a combined liver and small bowel graft (L-SBTx) in 1997. The ITx program reopened in 1994 when tacrolimus became available.

From 1994 to 2014, 110 transplantations were performed on 101 children; this forms the core subject of our report (Table 1). The annual number of ITx is shown in Fig. 1. Nearly half of the children were followed up before ITx in our IF unit, the largest in France. Thirty-four children came from abroad (mostly up to 2010). Sixteen children (only two after 2010) were in the intensive care unit just before transplantation. Sixty patients received SBTx, 45 L-SBTx, one a multivisceral transplantation (MVTx), three MVTx and a kidney, and one a modified MVTx (mMVTx, without liver). Indications included short bowel syndrome (n = 36), motility disorders (n = 30), congenital enteropathies (n = 34), and others (n = 1). End-stage intestinal failure-associated liver disease (IFALD) was present in nine patients (only three in the last 10 years). One received a SBTx despite severe IFALD, because of extensive thrombosis. The indications for kidney Tx were renal dysplasia and drug toxicity.

All grafts were obtained from deceased ABO-compatible donors, with the exception of one. Median donor–recipient weight ratio was 1.2 for MVTx, 1.5 for L-SBTx, and 1.7 for SBTx. The grafts were retrieved and preserved indifferently in intra- or extracellular preservation solutions.

Isolated intestinal grafts were transplanted with an anastomosis of the graft's superior mesenteric artery on

Table 1. Recipient characteristics.

Age (years)		5.3 [0.4–19]
Weight (kg)		14 [5–66]
Care centers before transplantation	Necker-Enfants malades	44
	Other centers in France	24
	Europe*	32
	Outside Europe	1
Cause of intestinal failure	Short bowel syndrome	36
	Motility disorder	30
	Congenital enteropathy	34
	Other	1
Median waiting time before transplantation (months)		14 [0.3–49]

*Germany, Italy, Switzerland, Belgium, Portugal, Spain, Cyprus.

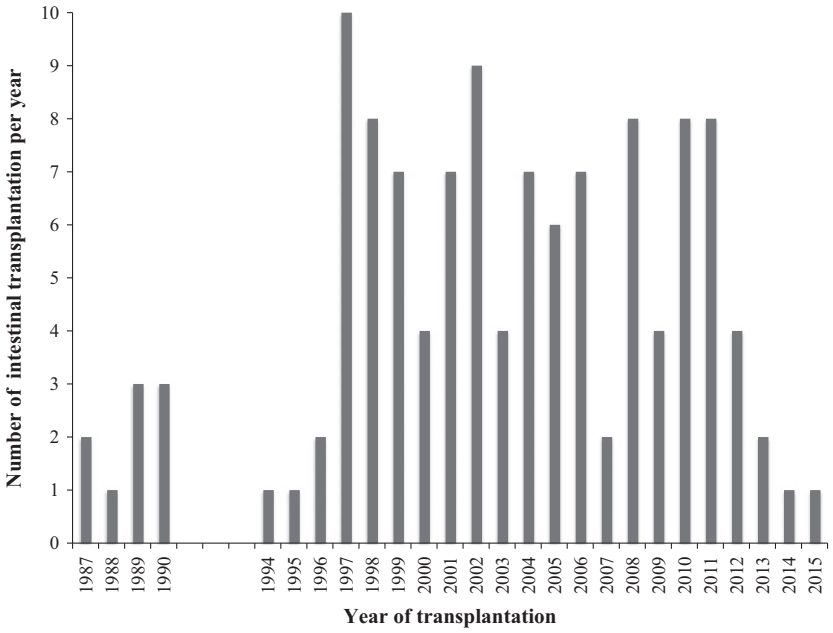

Figure 1 Number of intestinal transplantations per year.

the recipient's infrarenal aorta, and of the graft's superior mesenteric vein on the recipient's inferior vena cava. An iliac artery or vein was used between the mesenteric vessels and the aorta or vena cava to lengthen the mesenteric vessels and ease the anastomosis when needed. For liver-containing grafts, the "en bloc" procedure was used, except for the first two patients in whom the liver and small bowels were separately implanted with a duct-to-duct biliary anastomosis [7]. The pancreas of the graft was reduced, except in the nine more recent L-SBTx in whom the whole pancreas was transplanted. The right colon was included in the graft of 77 children. For all children, an ileostomy of the terminal ileum was created. The colon was anastomosed to the recipient's rectum when the primary disease was not a motility disorder. Otherwise, a colostomy was performed; later on, a colonic pull-through (Swenson or Duhamel technique) was carried out.

Neither the donors nor the grafts were pretreated. The postoperative treatment and monitoring were described previously [8]. To summarize, the immunosuppression was based on tacrolimus, steroids, and azathioprine up to 2004. Induction with basiliximab was added from 2000, or antithymocyte globulins from 2011, if the patient had preformed donor-specific antibodies (DSA). The target level of tacrolimus and the initial dose of steroids were lower from 2005 onwards (15–20 ng/ml then 10–15 ng/ml; 2 then 1 mg/kg, respectively). Anti-infectious prophylaxis included gut decontamination (tobramycin, colimycin, together with vancomycin until 2008) for 1 month, oral amphotericin B, and trimethoprim–sulfamethoxazole for 1 year. Cytomegalovirus (CMV) was prevented with 6-month acyclovir, and switched to ganciclovir or valganciclovir from 2000 on. Since 2003, preemptive therapy with rituximab has been used to treat Epstein–Barr virus (EBV) infection in the first year of ITx. EBV infection was diagnosed when EBV polymerase chain reaction increased. To monitor early rejection after ITx, biopsies were performed through the stoma three times a week during the first month, once or twice a week up to discharge, and when indicated (mostly increased stoma output or low albumin). After stoma closure, the biopsies were performed during endoscopy, according to protocol every 5 years and when indicated. Dedicated pathologists in our institution systematically reviewed all biopsies. Donor-specific HLA antibodies (DSA) were monitored from 2008 onwards, once a week during the first hospitalization, then at least once a year and when indicated.

Enteral tube feeding was initiated in the second week post-SBTx with a protein hydrolysate, and then a lactose- and fiber-free diet until parenteral nutrition (PN) weaning [9]. Oral feeding was allowed after the first month. Lactose, fibers, and proteins were progressively introduced.

Statistical analysis

Patient and graft survival were analyzed using the Kaplan–Meier method. Confidence interval at 95% (CI: 95%) was assessed using the Rothman method. The log-rank test was used for comparison. Event-free survival was calculated up to graft loss or death. Early events were considered to be those occurring within the first year post-ITx, late events after this time frame. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model with a significant *P*-value of 0.05. Retransplanted patients were included in the survival analysis but excluded from the risk factors analysis due to their small number, and are described separately.

Results

Overall survival

From 1994 to December 2014, the actuarial patient and graft survival at 10 years were, respectively, 52% and 33% with a median period between ITx and death of 4 months [0–130]. Early and late deaths occurred, respectively, after 1.4 and 83 months.

Survival for liver-containing grafts

Patient and graft survival was 48% at 10 years and 45% at 18 years. Death occurred at a median of 2 months post-ITx [0–128]. When looking at ITx performed in the last 5 and 10 years, respectively, 44% and 31% of patients with L-SBTx were alive and off PN in 2015 (Table 2). Eighty percent of deaths ($n = 17$) after L-SBTx and 100% of deaths ($n = 3$, including the child transplanted with an ABO-incompatible graft) after MVTx occurred early. The leading cause of early mortality was multiorgan failure (MOF) (35%). Late death was mainly due to liver failure ($n = 2$, 50%), in children for whom retransplantation had been denied, due to comorbidities and family decision.

Survival for SBTx

Patient survival was 59% at 10 years and 56% at 18 years. Graft survival was 30% at 10 and 18 years

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Table 2. Causes of graft loss.

	Cause of small bowel loss	SBTx n = 61	L-SBTx n = 49	Post-transplantation time (months)
Early graft loss	Acute humoral rejection	3	1	1–3
	Acute cellular rejection	3	1	1, 2, 2.5, 6
	Chronic rejection	2	0	4, 10
	CMV infection	1	0	8
	Adenovirus	1	0	9
	Thrombosis	2	0	First day
	Other	1	0	First day
Late graft loss	Chronic rejection	7	0	22–115
	Acute rejection	1	0	41
	CMV infection + rejection	3	0	14, 61, 65
	Acute rejection + adenovirus	0	1	15
	Lymphoma	1	0	24

(Fig. 2). When considering ITx performed in the last 5 and 10 years, respectively, 57% and 44% of patients with SBTx were off PN in 2015. The median period between ITx and death was 12 months [0–130]. The leading cause of early mortality was sepsis (42%), due to bacteria in eight patients (three Enterobacter, three Klebsiella, one Proteus, one Haemophilus) and aspergillus in two. No early death after SBTx has been due to bacterial or fungal sepsis since 2007. The child with IFALD receiving SBTx died. One-third of deaths after SBTx occurred late and were due to infection in two patients, MOF in one, liver failure in one, probable acute electrolyte disturbance in one, and traffic accident in one patient.

Two patients (one SBTx, one L-SBTx) died of lymphoma: one was early and EBV induced, before the implementation of rituximab prophylaxis, and the second was late and non-EBV induced.

Graft loss

The small bowel graft was removed in 28 SBTx patients after a median of 10 months [0–115], 22 of 28 despite induction therapy. Ten of them subsequently died, after a median of 45 months [4.4–130], from complications of retransplantation in seven, and of PN in three. The graft was lost early in 15 (median 2.5 months) and late in 13 patients (median 41 months) (Table 3). The main cause was rejection. Noncompliance was obvious in the case of two patients. No grafts have been lost due to CMV infection as the implementation of ganciclovir prophylaxis. Late acute rejection followed an episode of acute diarrhea in five patients.

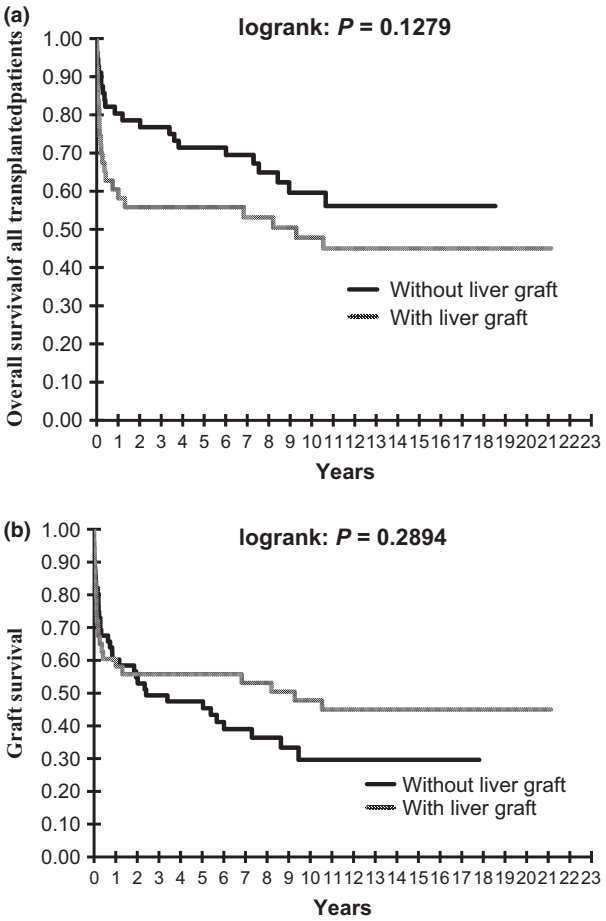

Figure 2 Patient (a) and graft (b) Kaplan–Meier survival curves according to type of transplant.

Vascular complications and bleeding

These occurred in 19 patients (19%) (11 L-SBTx including one retransplantation, eight SBTx), during surgery or

Table 3. Follow-up of the 55 living patients according to the type of graft and delay from transplantation.

	Alive with graft $n = 41$		Alive without small bowel graft $n = 14$		Total $n = 55$	
Follow-up	*SBTx*	*L-SBTx*	*SBTx*	*L-SBTx*	*SBTx*	*L-SBTx*
<5 years	8	5	3	1	11	6
5–10 years	8	1	8	0	16	1
>10 years	3	16	2	0	5	16
Total	19	22	13	1	32	23

in the early postoperative phase: acute bleeding ($n = 9$, 5 L-SBTx, 4 SBTx), aneurysm ($n = 2$, L-SBTx), abdominal compartment syndrome ($n = 3$, 2 L-SBTx, 1 SBTx), thrombosis [$n = 3$, 2 arterial (L-SBTx), one venous (SBTx)], parietal hematoma ($n = 1$, SBTx), porto-caval stenosis ($n = 1$, SBTx). Ten patients (seven L-SBTx, three SBTx) died and five lost their small bowel graft.

Biliary complications

Eight patients presented a biliary complication after L-SBTx: common bile duct stenosis ($n = 4$) or necrosis ($n = 2$), and biliary leakage from the duodenal stump ($n = 2$). Two patients died after 16 and 83 months, and the others are alive with a functional graft.

Univariate and multivariate analysis

Risk factors associated with death identified in univariate analysis were L-SBTx and vascular complications or bleeding ($P = 0.03$). Risk factors associated with graft loss were older age at the time of the ITx ($P = 0.007$), vascular ($P = 0.04$), and biliary complications ($P = 0.01$). All these factors remained significant in multivariate analysis.

Retransplantation

Ten patients received a second graft in our unit (including one-first transplanted in 1989). The indications for the first ITx were motility disorders ($n = 2$), congenital enteropathies ($n = 5$), and short bowel syndrome ($n = 3$). The first graft was a SBTx ($n = 9$) or a L-SBTx ($n = 1$), implanted at a median age of 5 years [3–11], and removed a median of 26 months later [1–105], for CMV ($n = 2$), chronic ($n = 4$), or acute rejection ($n = 4$). The second procedure was SBTx in three patients and L-SBTx in seven patients, at a median age of 12.7 years [5–16]. Immunosuppression included induction in all of them, basiliximab in six, and antithymocyte globulins in the four more recent ones. Seven patients died, three after SBTx, and four after L-SBTx, after a median of 3.8 months [0.7–46], of MOF ($n = 3$), acute bleeding ($n = 1$), liver failure ($n = 2$), and lymphoma ($n = 1$). Three more patients were retransplanted in adult units (L-SBTx). Only one was alive and well at the time of publication, and the others died from rejection and sepsis.

Long-term outcome

Among the 55 living patients, 40 were totally free from PN and one received 20% of her needs through PN. Seventeen (31%) were less than 5 years after ITx, 13 of 17 off PN, 17 (31%) between 5 and 10 years, 9 of 17 off PN, and 21 (38%) more than 10 years, 19 of 21 off PN, including the oldest survivor, and the three retransplanted patients (Table 2).

The immunosuppression in the 41 patients off PN was tacrolimus and low-dose steroids (except two), plus mycophenolate ($n = 7$), sirolimus or everolimus ($n = 16$), and azathioprine ($n = 2$). All were at home, and 14 needed enteral nutrition because of anorexia. Three (one recently transplanted) had an ileostomy.

Donor-specific antibodies

They were screened from 2008 only, and a specific treatment with plasmapheresis and intravenous immunoglobulin was started if humoral rejection was diagnosed. The short-term results have already been reported on 22 patients [10]: 7 of 22 patients had preformed DSA and 19 of 22 *de novo* DSA. The prognosis depended on the presence of symptoms and pathological findings, asymptomatic patients having a good outcome. The correlation with mid- and long-term survival was hampered by the lack of initial data.

Graft function

Anthropometric parameters in all patients were between −2 and +2 SD for height and weight with a normal weight for height ratio, except in one child with growth failure due to severe intrahepatic cholestasis associated with microvillous atrophy [11].

Results on graft absorption in the first 31 patients were previously published [12], showing total energy absorption of between 80% and 90%, with mostly fat malabsorption. The follow-up study confirmed these results (data not shown). A study on long-term graft biopsies is under way and will be subsequently reported.

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Comorbidities

One patient with a family history of autoimmune diseases had insulin-dependent diabetes. Five patients were treated for high blood pressure. Measured glomerular filtration rate (mGFR) was between 30 and 70 ml/mn/1.73 m^2 in three patients, more than 70 in the others. The lowest mGFR was found in patients transplanted more than 10 years ago. mGFR stabilized or improved after adaptation of immunosuppression (decreased of tacrolimus dosage, addition of mycophenolate or azathioprine) in all patients with mGFR lower than 80 ml/mn/1.73 m^2. Results of mGFR in 27 patients and kidney biopsies in 14 have been previously published: significant lesions were seen as early as 2 years post-ITx [13].

At least 11 patients had social or professional difficulties and three suffered from addictions.

Discussion

This is one of the largest and longest series of patients after ITx performed in childhood. Our pioneering and distressing experience in the 80s paved the way for the reopening of the program in 1994. Although the results were inconstant over time due to the heterogeneity of patients (various indications of Tx, numerous preoperative management issues due to referral from other French or foreign centers) and the difficulties of the procedure, we did introduce changes in the selection of patients, immunosuppression protocols, surgery, control of rejection, and infections that seemed to improve the overall results of ITx in our cohort over time.

The improvement in IF care observed in our unit with a low mortality of children on long-term PN [14,15] spread in Europe from the 2000s with the development of IF networks, explaining the absence of non-French-resident children in our recent candidates [16]. In retrospect, the sickest patients with lowest odds of survival should not have been transplanted. Recently, all children were called from home, with the exception of two whose early death confirmed the contraindication [17].

The first immunosuppression protocol without induction was inefficient for SBTx, as nearly all patients lost their graft, or died of infection during rejection treatment. This protocol with high-dose steroids and tacrolimus, the same for SBTx and L-SBTx, explained severe infections, graft losses from viruses, and death from bacteria and fungal infection in these fragile patients. We can hypothesize that some of these early graft losses might also be due to nondiagnosed humoral rejection. Immunosuppression adapted to the type of graft and recipient's sensitization, as well as the recognition and treatment of humoral rejection [10], might explain the improvement in our last 5- and 10-year survival rates. More efficient antibiotics, echinocandins and ganciclovir were also dramatic improvements from the 2000s [18–20], with no more deaths from sepsis or graft removal from CMV. Preemptive treatment of EBV with rituximab, such as after bone marrow transplant, became standard in our unit [19], and no child has died from post-transplant lymphoproliferative disease since then.

We previously demonstrated the long-term stability of the graft function [12], and confirmed that most patients were weaned from PN. However, some lost their graft up to 8–9 years after ITx, after a progressive enteropathy due to chronic rejection, or an episode of acute diarrhea, mostly without an infectious trigger, and followed by acute rejection and graft failure. On the other hand, severe long-term complications of over-immunosuppression, such as lymphoma or renal failure, were rare [21]. We thus recently added sirolimus to the long-term therapeutic protocol, as an immunosuppressant, antitumoral, and renal-sparing drug, in order to prevent both immune-mediated late graft loss and hopefully lymphoma, without further injuring the kidneys [22,23].

Until the mid-2000s, our patients' survival rate after both L-SBTx and SBTx was the same. Early deaths after L-SBTx were frequent and mostly due to surgical problems or infection. Early deaths after SBTx were more rare, but patients in whom SBTx had failed died later of IFALD or complications of retransplantation. The more recent SBTx patients, who lost their small bowel graft, fared well on PN. Due to the good results of long-term PN, retransplantation was discussed only when home PN was impossible.

The long-term quality of life analysis recognized serious problems that could be a target for prevention. A study of long-term psychological outcomes is under way.

The ITR and leading teams reported the same difficulties and poor long-term survival, with only half of the patients alive after 10 and 20 years [24–27]. The improvements made in the early post-Tx phase [26] did not prevent attrition in graft survival, which has remained the same for the last 10 years [3]. Inpatient status at the point of surgery was a risk factor for death [3,4]. Patient selection for ITx had a positive impact, as patients now tend to be healthier, and life-saving procedures have dramatically decreased over the past 25 years [14].

The "liver factor" was demonstrated experimentally and in real life, implying that the immunosuppression needed for a transplantation including the liver was lower [25,26,28,29]. Induction therapy, introduced in the 2000s, proved to be mandatory for (isolated) SBTx. Long-term survivors off PN in all series were thus only patients with a liver-containing graft. The rare patients, who enjoy good intestinal function after SBTx without induction, including our world's longest survivor, should be explored in more depth, to understand their tolerance mechanisms [30]. One clue might be found in the immune functions that are defective in an anencephalic (donor) neonate. Performing a liver-containing ITx for only immunological reasons is nowadays debatable (except for retransplantation), due to organ scarcity, risk of surgical complications, and hope that the short-term improvements of the last 10 years will reflect in long-term results. However, despite induction therapy and the recognition of humoral rejection [10,31–33], an optimum early protocol still remains to be defined, probably after multicenter studies. We need further insights into the roles of the intestine-associated immune system, innate immunity, and microbiota [34–36].

Infections are a major concern in these fragile patients. Bacterial sepsis is recorded in the ITR as responsible for mortality after L-SBTx. A median of five infections occurs after SBTx in the largest pediatric series [18,25]. Infections and rejection are risk factors for graft loss, whichever occurs first [26]. Increasing bacterial resistance to antibiotics will probably further complicate the care. Resistance of fungi to echinocandins is still rare but may increase if their use is not controlled [19]. CMV enteritis has nearly disappeared with ganciclovir [20]. Preemptive rituximab for EBV has not been widely used by others, many of whom appear to report higher incidences of lymphoproliferative disease than we have experienced [3].

Surgical difficulties on wall closure and vascular complications as cause of early death or graft failure almost disappeared with the staged abdominal closure technique from the 2000s [3,37,38]. Biliary complications were not totally prevented by the "en bloc" technique of L-SBTx. Pancreato-biliary complications, half of them strictly biliary related, were reported in 15% of composite visceral Tx, with 25% mortality, like in our series [39]. The preservation of the graft pancreas may lower this rate.

Long-term survival and late graft loss remain significant problems [40]. Balancing immunosuppression between infections and rejection is difficult. However, the ITR showed that rejection was the main cause of late graft loss, as it was in our series. Despite some successful trials of immunosuppression minimization or withdrawal [27], we think that it should not be lowered too much, especially after SBTx. Liver-containing grafts are probably better tolerated over the long-term; however, noncompliant patients showed that this is not universal. All of our patients with SBTx received low-dosage triple immunosuppression. Close monitoring of episodes of acute diarrhea and a low threshold for graft biopsies are mandatory for early diagnosis and treatment of late acute rejection. Late humoral rejection can probably occur, such as after kidney Tx [41], and should be the subject of large multicenter studies.

Retransplantation is a difficult procedure with a high mortality rate [42]. This should be kept in mind when discussing ITx in a child. We think that the graft must include the liver, especially if the first graft was lost to rejection, to take advantage of the "liver effect" [43]. Others have reported good overall results in 14 children after MVTx; however, sepsis and acute rejection, like in our series, were responsible for four deaths [44].

Long-term quality of life and psychosocial well-being are as important as graft function. In 2015, ITx cannot yet be proposed as an alternative to home PN on the basis of quality of life reasons alone, when PN is managed by an experienced center. The psychosocial problems of our patients were not the least of their long-term complications. Although eating disorders in children with IF are nowadays better prevented, they were still prevalent and responsible for the long-term need for enteral feeding. The recognition of psychosocial difficulties throughout these children's care should help to minimize the impact on their future. However, the collusion of long-term PN and ITx, together with a child's development, adolescence, education, and family, may lead to disastrous consequences, including noncompliance [45].

In conclusion, ITx remains a challenge. We experienced improvements in the selection of candidates, who were neither the healthiest nor the sickest, and in all aspects of early management. We realized that retransplantation was even more difficult. We are now facing late complications, responsible for graft loss or death, which seem to be due more to under- than over-immunosuppression. Late rejection will not be prevented until we understand the relationship between the graft, its specific immune system, its microbial content, and the recipient to foster their cohabitation. Both basic studies and collaborative clinical protocols are urgently needed.

Authorship

FL and SI: designed the study, collected and analyzed data, wrote the manuscript. LD, CT, FL, VC, NS, FM, FS, YA and YR: contributed to the writing of the manuscript. OG and CC: contributed significant reagents. All authors approved the final version of the manuscript.

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Conflict of interests

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