Transplant International ISSN 0934-0874

REVIEW

Present status and future perspectives of intestinal transplantation

Andreas Pascher, Sven Kohler, Peter Neuhaus and Johann Pratschke

Department of Visceral and Transplantation Surgery, Universitaetsmedizin Berlin – Charité, Berlin, Germany

Keywords
combined liver-intestinal transplantation, intestinal transplantation, multivisceral transplantation.

Correspondence
Andreas Pascher MD, PhD, Department of Visceral and Transplantation Surgery, Charité – Universitaetsmedizin Berlin, Campus Virchow Klinikum, Augustenburgerplatz 1, 13353 Berlin, Germany. Tel.: +49 30 450 652253; fax: +49 30 450 552900; e-mail: andreas.pascher@charite.de

Received: 12 June 2007
Revision requested: 29 June 2007
Accepted: 28 December 2007

doi:10.1111/j.1432-2277.2008.00637.x

Summary

Intestinal transplantation (ITx) is the only definitive therapy for irreversible intestinal failure. Owing to the limited short- and long-term graft survival over the years, ITx has been a complementary treatment to home parenteral nutrition. However, the development of intestinal and multivisceral transplantation has been significant over the past 15–20 years owing to the progress in immunosuppressive therapy, refinement of surgical techniques, post-transplant care, intestinal immunology, and immunological as well as anti-infectious monitoring. The improvement of patient- and graft survival over the last few years together with data on the cost effectiveness of ITx, following 2 years after transplantation, may require a redefinition of the indication for ITx.

Introduction

Intestinal transplantation (ITx) is the only curative therapy for irreversible intestinal failure. Since its beginnings in the late 1980s, ITx has developed significantly slower than other forms of solid organ transplantation. This was mainly because of the high immunogenicity of the intestine, owing to the high burden of lymphocytes in the gut-associated immune system. Moreover, the high risk of graft-versus-host disease (GvHD), which amounted to 15% and 47% for intestinal and multivisceral transplant recipients respectively, in the early years (1991–1995), [1] and the risk of bacterial translocation in any relevant disturbance of mucosal integrity, potentially leading to sepsis with life-threatening complications, were the feared complications.

The first successful multivisceral transplantation (MVTx) was performed in 1987 in Pittsburgh, USA, in a child receiving an immunosuppression treatment based on cyclosporin A [2]. However, the small child died of B-cell lymphoma 6 months after transplantation. In August 1988, Deltz *et al.* [3] at the University of Schleswig-Holstein, Kiel, Germany performed the first successful isolated ITx with a graft from a living donor. After the surgery, this patient survived 56 months with a functioning graft. Grant *et al.* [4] in London, Canada, Margreiter *et al.* [5] in Innsbruck, Austria, and Goulet *et al.* [6] in Paris, France, performed further ITx, predominantly in the form of MVTx.

With the introduction of tacrolimus, the number of ITx and MVTx steadily grew until the end of the 1990s. After insurance systems in the USA approved of ITx in 2000, the number of ITx increased significantly to approximately 130–150 transplantations per year worldwide.

While 1- and 3-year graft survival was 30% and 20% respectively, before 1991, the corresponding survival rates increased to 60% and approximately 50% between 1995 and 1997. The current 1-year graft and patient survival rates for isolated and combined intestinal transplants have reached 80–90% for those patients who underwent transplantation between the years 2005 and 2007 according to

the Intestinal Transplant Registry data presented at the 10th International Small Bowel Transplant Symposium in Santa Monica, California, USA in 2007 [1,7–9]. Selected patient cohorts could even do better [10]. These impressive improvements in graft and patient outcome are certainly influenced by the refinement of surgical techniques, progress in post-transplant and intensive care treatment, as well as a better understanding of intestinal immunology. However, progress in immunosuppressive therapy, methods for monitoring and treating graft rejection, viral monitoring, as well as prevention and treatment of post-transplant lymphoproliferative disease (PTLD) may have contributed even more decisively. Nevertheless, ITx continues to be one of the greatest challenges in solid organ transplantation and to date remains a relatively uncommon procedure with approximately 1300 transplants performed worldwide, 60% of them in children, according to the Intestinal Transplant registry [1,7].

Intestinal failure

Intestinal failure may be caused by either surgical shortening of the intestine on account of a variety of reasons, such as trauma, volvulus, mesenteric infarction, or serial surgical interventions. On the other hand, it may be a functional failure despite sufficient small bowel length, e.g. caused by human immunodeficiency virus infection, microvillus inclusion disease, intractable diarrhoea, or after resection of specialized portions of the small bowel. In general, the critical length of the intestine below which an adult individual will most likely develop permanent short bowel syndrome (SBS) is approximately 80–100 cm. Apart from the total residual length of the small intestine and the presence or absence of specific portions such as the terminal ileum, the presence or absence of the ileocoecal valve contributes to the development of intestinal failure. In infants, the respective threshold is about 40 cm. In these patients, the intestinal adaptation will most probably fail or be incomplete. Parenteral nutrition (PN) has been the mainstay of treatment in recent decades. Although progress has been made during this time, PN may lead to potentially devastating complications, such as catheter-related morbidity, hepatotoxicity (steatohepatitis, fibrosis, cirrhosis) and diminished quality of life (QoL). These factors contribute to a 5-year survival rate of approximately 60% for all patients on PN [11]. Particularly, SBS on account of mesenteric infarction, a remnant intestinal length below 50 cm, missing enteral continuity with terminal jejunostomy, and age above 60 years, were identified as negative prognostic markers for long-term survival under PN [12]. In these patient groups, the 5-year survival rates were as low as 40%.

Additionally, being on PN has a severe effect on the QoL of patients suffering from intestinal failure. In contrast to a curative treatment option such as ITx, PN is not able to restore the QoL [13]. In contrast, the successful emergence of small bowel transplantation as a curative alternative has enabled many patients with bowel failure to function independently from infusions on a daily basis, and resume their personal, social and occupational lives autonomously. In summary, they will have an improved QoL, have better nutrition, and a reduction in PN-associated complications. That means QoL issues will play an increasing role in the indication for ITx.

Although ITx has been reserved for patients suffering from life-threatening complications of PN (i.e. PN-induced development of hepatic fibrosis and cirrhosis or loss of vascular access) until very recently, there is now an emerging strategy of intervening earlier. The approach for earlier intervention is not only justified by the very encouraging data on graft and patient outcome in this group of patients [14], but also by particularly high mortality rates in patients awaiting combined liver-intestine transplantation (LITx) compared to other transplant candidates [15], and also a worse post-transplant outcome in patients who were hospitalized at the time of transplantation compared to the patients who were staying at home [7].

Indications

There are a great variety of potential indications for ITx as shown in Table 1, based on data by the Intestinal Transplant Registry [1]. Whereas gastroschisis (21%), volvulus (18%), necrotizing enterocolitis (12%), pseudo-obstruction (9%), intestinal atresia (7%) and aganglionosis/Hirschsprung's disease (7%) account for almost two thirds of all ITx in infants, there is a predominance of vascular indications, like ischaemic or haemorrhagic mesenteric infarctions (22%), followed by Crohn's disease (13%), and trauma (12%) in the adult patient population, which account for approximately 50% of all indications. The proportion of patients with Crohn's disease will certainly decline with the progress in medical therapy for this condition. Tumours in general do not play a major role in ITx; however, low-grade malignancy tumours, such as desmoids, often associated with familial adenomatous polyposis (Gardner's syndrome), are an exception.

Particularly patients with very short bowels (adults <50 cm; children <25 cm) should perhaps be listed early because their prognosis on long-term PN is especially poor [16].

Referral criteria and transplant criteria were defined according to the consensus statement at the 8th Interna-

Table 1. Indications for intestinal transplantation in infants and adults.

Infants	
Gastroschisis	21%
Volvulus	18%
Necrotizing enterocolitis	12%
Pseudo-obstruction	9%
Intestinal atresia	7%
Re-transplantation	7%
Aganglionosis/Hirschsprung's disease	7%
Microvillus inclusion	6%
Malabsorption other	4%
Short gut other	4%
Motility other	2%
Tumour	1%
Other	2%
Adults	
Ischaemia	22%
Crohn's disease	13%
Trauma	12%
Desmoid	10%
Motility	9%
Volvulus	7%
Short gut other	7%
Tumour other	7%
Re-transplantation	5%
Gardner's/FAP	3%
Miscellaneous	5%

Table 2. Referall and transplant criteria for isolated and combined intestinal transplantation.

a) Referall criteria
Disease criteria
Disorders with poor prognosis (e.g. trauma, massive resection, multiple fistulae, frozen abdomen, desmoid)
Disorders of uncertain natural history
Clinical criteria
Failure of nutritional support (e.g. weight loss; hypoalbuminaemia below 3 mg/dl)
Severe or recurrent line sepsis
Severe and/or recurrent disturbance of fluid/electrolyte balance
Liver disease
Bilirubin >3 mg/dl (50 μmol/l)
Portal hypertension
Loss of conventional venous access
PN dependency beyond 6 months
b) Transplant criteria
Irreversible intestinal failure with major complications
Recurrent or life threatening sepsis
Loss of two or more central venous access sites
Recurrent and intractable fluid balance issues
Liver disease
c) Indication for
Isolated small bowel
Absent or reversible liver dysfunction
Mild portal hypertension (or none)
Combined liver/small bowel
Progressive moderate to severe liver disease
Intestinal failure with hypercoagulability syndrome
Low malignancy tumour affecting liver as well as gut
Multivisceral transplantation
Combined organ failure
Frozen abdomen
Vascular disease (e.g. thrombosis of celiac axis)
Motility disorders (e.g. chronic intestinal pseudo-obstruction)
Gardner's disease
Living related
Lack of deceased organ Tx
Identical twins
Group concerned about application (no lack of donor bowels, shorter graft, donor risk, ethics)
Isolated liver
ESLD in short gut with normal morphology
Realistic expectation of eventual gut adaptation
Previous enteral tolerance ~50%
Age under 4 years
Should be done only in centres experienced in paediatric liver and intestinal transplantation

tional Small Bowel Transplant Symposium, Miami 2003, with slight modifications as shown in Table 2a–c.

Surgical technique

Intestinal transplantation can be performed alone or in combination with other organs. As of mid-2005, 44% of all documented ITx were performed in an isolated fashion, 38% in combination with the liver, or as a multivisceral transplant (18%) [1]. The type of graft is typically determined by the patient's particular needs, i.e. the type of underlying disorder and surgical history of the patient, the type and size of the donor, and how much abdominal domain is available. With the growing short-term and long-term success of MVTx and with its immunological advantages, more therapeutic options have been given to the transplantation team to find a transplantation procedure individually tailored for each patient. The respective conditions justifying each approach are shown in Table 2.

Intestinal transplantation may be performed either with or without portions of the large intestine and is more frequently performed in adults. In deceased donor ITx, the intestinal graft usually consists of the entire jejunum and ileum. Vascular supply is mostly achieved by arterial anastomosis onto the infrarenal aorta, eventually using an interpositional graft. Venous drainage is established either into the portal system or even more frequently, into the caval vein. Although a reduced incidence of bacteraemia has been reported, hypothetic advantages of a portal drainage have not yet been proved in large cohorts [17]. At the terminal portion of the intestinal graft, a terminal Bishop–Koop enterostomy (chimney) serves as a diagnostic ostomy, whereas the large intestine is usually anasto-

mosed with the graft approximately 20 cm proximally as side-to-end ileocolostomy (Fig. 1). In living donation and in cases with severe donor-to-recipient size- or body weight mismatch, a 200-cm segment [18] is usually transplanted. Remnant portions of the native bowel should be preserved to the maximum extent for several reasons: (i) recent data suggest that increased residual or allograft bowel provides some protection from PN-associated injury. This is particularly relevant because there may be a need for some supplementation with PN for a period of time after ITx; (ii) in case of graft failure, residual native bowel increases the chance of building a new end-jejunostomy or direct anastomosis to the remnant large intestine. Graft failure with almost negligible or completely absent native bowel represents an extremely difficult challenge for the transplant surgeon until a suitable allograft is available for immediate re-transplantation.

Combined LITx is more commonly performed in children. There are two different technical approaches to LITx, either to perform en bloc or separately [19,20].

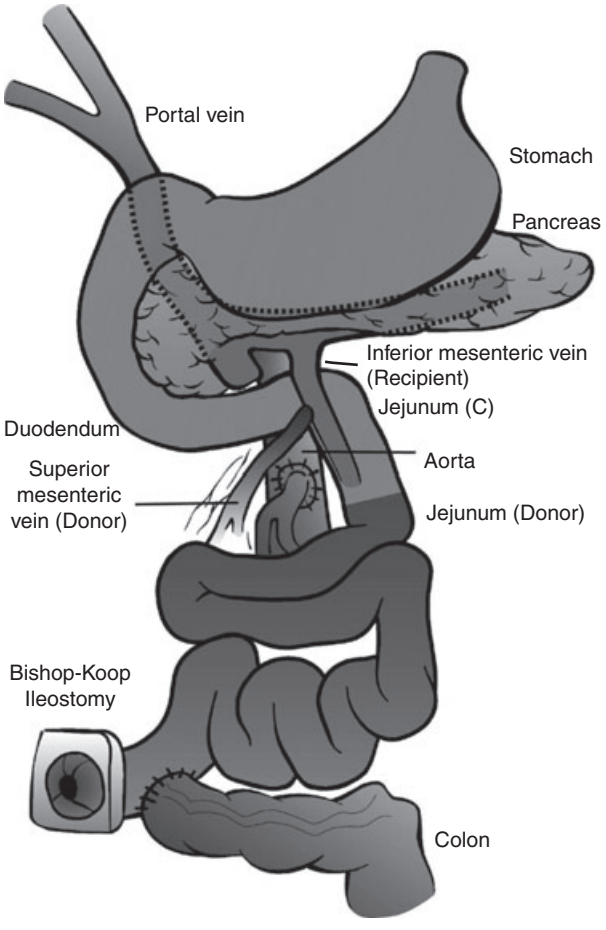

Figure 1 Schematic illustration of transplant and technique in intestinal transplantation.

Using the separate technique, the two organs can be transplanted simultaneously or sequentially from the same or a different donor. In the en bloc technique the duodenum with a segment of the pancreas (or the entire pancreas) [19] is included to avoid torsion of the portal axis and the need for biliary reconstruction. An end-to-side portocaval shunt has been typically described as the standard procedure that needs to be performed to obtain adequate venous drainage of the foregut. However, there are alternative techniques in this scenario: the recipient's portal vein can be anastomosed to the transplanted portal vein end-to-side, or the portocaval drainage can be performed as an end-to-end shunt from the recipient portal vein to the infrahepatic donor caval vein [21]. The upper gastrointestinal continuity is maintained through the native stomach and pancreo-duodenal complex; the graft duodenum serves as a conduit for bile and pancreatic secretions.

Living donor LITx has been performed without significant donor morbidity [22] and may represent an alternative source in future in case of scarcity of deceased donors particularly for paediatric recipients.

Multivisceral transplantation is defined as the removal and replacement of both the native foregut and midgut [23] including the stomach. Grafts not containing the stomach are not registered as multivisceral in the Intestinal Transplant Registry; however, the liver may either be included or not. For MVTx the native abdominal viscera are resected and the graft, which comprises the stomach, pancreo-duodenal complex, and small intestine, is transplanted en bloc. Thereby a segment of the donor aorta that contains the orifices of the celiac axis and the superior mesenteric artery (SMA) is either anastomosed as a Carrel's patch or end-to-side in terms of a 'neo-celiac axis' to the recipient aorta (Fig. 2). Venous drainage depends on whether the liver is part of the graft or not. If the liver is included, the venous drainage of the whole graft is achieved either by piggy back or by inter-positioning the retrohepatic caval portion. Otherwise, portal drainage may be established into the portal system or into the inferior caval vein. Apart from the liver, kidneys, adrenal glands and large intestine of the donor may or may not be included depending on the clinical scenario [24] (Fig. 2).

Until recently, a common requirement of MVTx has been the removal of the native duodenum, pancreas and spleen in the process of abdominal exenteration. Modified MVTx with spleno-pancreatic preservation procedures were proposed by two groups [25,26], although, the indication for their removal was frequently for anatomical reasons, more than for the underlying states of disease in those organs. In the modified multivisceral technique, the native spleen and pancreas are preserved with venous outflow through a native portocaval shunt, and native

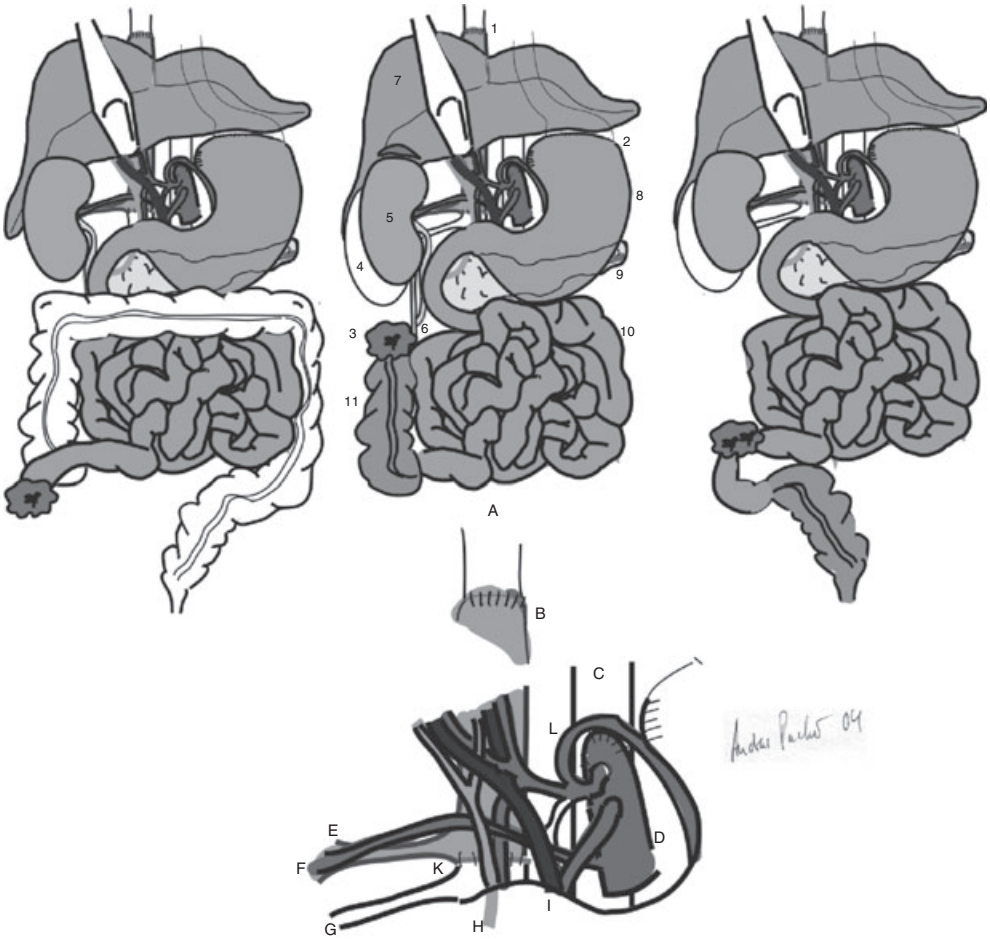

Figure 2 Schematic illustration of transplant technique in multivisceral transplantation. Variations of one procedure according to the individual patient's needs based on one common principle. 1, Suprahepatic cavo-caval anastomosis; 2, end-to-side gastro-gastrostomy (cardio-fundostomy); 3, terminal ascenostomy of the colonic graft; 4, right recipient kidney; 5, kidney graft; 6, end-to-side uretero-ureterostomy; 7, liver graft; 8, stomach graft; 9, pancreas graft; 10, small intestine graft; 11, large intestine graft. A, donor-vena cava inferior/right atrium; B, recipient-vena cava inferior (suprahepatic); C, recipient-aorta abdominalis; D, donor aorta; E, right renal vein (graft); F, right renal artery (graft); G, right renal vein (original kidney); H, ductus choledochus; I, portal vein; K, end-to-end cavo-cavostomie; L, neotruncus (end-zu-side aorto-aortostomy).

pancreatic exocrine drainage is established to the donor jejunum. Risk of transplant pancreatic insufficiency, post-transplant lymphoproliferative disorder, and postsplenectomy sepsis may be avoided by using this technique. However, there is some ongoing dispute on in terms of nomenclature. As the nomenclature of grafts containing the intestine is based on the type and number of the allografted rather than that of the explanted organs, it has been argued that the spleno-pancreatic preservation should not be classified as modified mutivisceral transplantation. In multivisceral adult recipients, Abu-Elmagd [26] described a propensity for better graft survival among those 14 patients undergoing modified MVTx with splenopancreatic preservation when compared to a total of 11 contemporaneous modified MVTx with spleno-pancreaticoduodenectomy. Preservation of the native spleen and pancreas abolished the deleterious infectious complications, cases of PTLD and GvHD, as well as post-transplant endocrine and exocrine pancreatic insufficiency. In contrast, their removal was followed by two cases each of GvHD and PTLD, and an overwhelming incidence of postsplenectomy infectious complications, which were the leading cause of death [26].

Since 2000, MVTx is performed in increasing numbers and the 1-year graft and patient survival as well as the conditional survival rates after 1 year is at least as good as the other forms of ITx [6,7,27].

One of the most challenging problems in SBS patients is the lack of sufficient abdominal domain and pre-existing damage to the abdominal wall owing to multiple surgical procedures. Thus, successful primary closure of the abdominal wall is not always feasible. Primary closure

under tension can lead to fascial ischaemia or necrosis, with subsequent dehiscence. Thus, alternative techniques to achieve abdominal wall closure are an important technical aspect in ITx. However, there is no ideal solution for avoiding or treating abdominal wall defects. Abdominal wall management can be performed using prosthetic grafts that are serially reduced in size until a clean granulating bed is established with subsequent use of a skin graft. Apart from that, silastic sheets, grafted fascia from the same donor, and acellular dermal matrix provide good options for abdominal wall closure after small bowel transplantation [28].

A recent single-centre analysis identified a high donor weight-to-recipient weight ratio as the most important determinant for abdominal wall closure problems [29]. Wound closure problems can have severe recurrence, because the rate of re-transplantations is increased [30].

Most recently, transplantation of the abdominal wall was proposed as an alternative treatment [26]. Of eight patients with nine deceased-donor abdominal wall composite allograft transplants, who received their blood supply via the inferior epigastric vessels continuously from the donor's femoral and iliac vessels, there were six survivors, five of whom had intact, viable abdominal wall grafts. Two patients had had a clinically mild episode of acute rejection of the skin of the abdominal wall which was resolved with corticosteroid therapy. There was no clinically apparent GvHD. It was concluded that an abdominal wall composite allograft could facilitate reconstruction and closure of the abdominal compartment in ITx recipients with complex abdominal wall defects.

Immunosuppression

While the clinical feasibility of ITx and MVTx was shown in the first clinical applications between 1988 and 1990, the mid-term and long-term outcome remained poor. A revolution of immunosuppressants in ITx came about in 1990 when Murase *et al.* [31] reported the successful use of tacrolimus in isolated ITx and MVTx in a rat model. Others confirmed the higher efficacy of tacrolimus when compared to cyclosporin A in the ITx-rat model [32,33]. Afterwards, tacrolimus stimulated the development of ITx towards a causative therapeutic option in intestinal failure, and to date, it is the maintenance immunosuppressive drug of choice [1,7]. Initially, the immunosuppressive cocktail comprised predominantly tacrolimus, steroids, and azathioprine, the latter commonly being substituted by mycophenolate mofetil from 1997 onwards. Because of the high risk of acute rejections, exceeding 80%, the intestinal recipients were systematically maintained on intense immunosuppression with the risk of long-term related morbidity and mortality. A variety of immunosuppressive combinations have been used without having defined the optimal regimen to achieve long-term graft survival while avoiding side-effects.

Because of the relatively high risk of early and late intestinal rejection, induction immunosuppressive agents were used at different periods of time. Modern induction agents are nowadays used in an estimated 90% of cases as part of the overall regimen. Cyclophosphamide gained only little importance in improving success rates [9,10]. Contrarily, monoclonal anti-interleukin 2-receptor antibodies (daclizumab/simulect) have made a significant contribution with regard to graft and patient survival since 1998 [34–37]. They have been accompanied by a significant reduction in the incidence and severity of rejection episodes and improvement of survival results, which have allowed decreasing tacrolimus maintenance therapy. This is of relevance, as there is increasing evidence for calcineurin-inhibitor toxicities in patients receiving nonrenal transplants [38].

At present, the most common induction immunosuppressive agents are anti-IL-2-receptor antibodies as documented in an overview characterizing immunosuppressive strategies in the five busiest ITx centres worldwide [37]. They are followed by anti-lymphocyte globulin and alemtuzumab [9,10,39]. Their application has lead to 1-year graft survival rates as high as 80 to 90%, and in certain subgroups even higher. According to the mid-2005 data analysed by the Intestinal Transplant Registry, the use of thymoglobulin might be the most promising approach in the future [1,7]. Notably, alemtuzumab has been withdrawn from paediatric immunosuppressive protocols because of its high rate of side-effects [40].

Significant progress in improving long-term graft survival, reducing rejection rates, and reducing tacrolimus-associated toxicity can be achieved with sirolimus, which was introduced into clinics in 1998. Combined application of anti-IL-2R mAbs and sirolimus reduced the 30-day incidence of acute rejections, still one of the main risks for graft failure, from almost 90% down to 17%. This resulted in 1-year graft survival rates of approximately 92% [40]. As there have been concerns regarding the higher risks of impaired wound healing and incisional hernias, many centres prefer the delayed use of sirolimus a few weeks after ITx.

Recent data suggest a potential future role of anti-inflammatory mAbs against tumour necrosis factor-α to reduce the rates of steroid and/or OKT3-refractory rejections as well as late ileal ulcerations, which may be the manifestation of some sort of allograft enteropathy. Not only could this expand the arsenal of drugs to prevent severe acute rejection but also to help improve long-term survival by avoiding or treating chronic allograft damage [41,42].

Outcome and complications

Patient and graft outcome

Over the past 20 years, there has been a remarkable improvement in short-term patient- and graft survival. After the year 2000, the Intestinal Transplant Registry reported both, patient and graft survival rates of about 80% [1,7]. No difference between isolated ITx, MVTx or combined LITx has been observed, suggesting that improvements in transplant technique and postoperative care have compensated for the higher perioperative risks in the patient group needing composite grafts. Even in the period between 2000 and 2005, there was a further improvement of survival rates [7]. The registry analysis in 2005 showed increased use of induction therapy, transplantation of a higher ratio of patients waiting at home, and transplantations carried out in centres with experience of performing more than 10 intestinal transplants in total as the main contributing factors. With regard to the proportion of patients waiting at home, a change of paradigm may have taken place, leading to earlier referral of patients to intestinal failure and transplant centres. In addition, the strategy of transplanting earlier, before the occurrence of major complications of PN, certainly has had beneficial effects on the pretransplant condition of patients.

The improvement of short-term survival notwithstanding, the registry analysis displayed disappointing data on long-term survival. The conditional graft survival has not improved when comparing the early days of ITx and the present. The average 5-year-survival rate at the first year after transplantation has remained stable at approximately 60–65%. These data may be interpreted in different ways; however, one of the most evident arguments is, that the amount of immunosuppression in the long run is still a major problem and that chronic graft rejection or, more generally, enteropathy as well as late onset acute rejection do occur nevertheless. One further perception of the registry data analysis was that the presence of the liver in a composite graft improved the long-term survival.

Of note, the causes of death in the early and late phase after ITx are quite similar, with sepsis and rejection being the most prominent at 40–50% and 10% of the recipients respectively [1,7]. In contrast, PTLD predominates in the later phase after ITx. Its frequent manifestation in the intestinal graft itself constitutes some diagnostic dilemma, because the differential diagnosis against rejection is sometimes difficult. Despite significant changes in immunosuppressive therapy and in the use of more powerful agents in particular, the total rate of PTLD has remained relatively stable with a frequency of 6–8% since the mid 1990s [1,7]. Although with a peak incidence at 25 months after transplantation, precursor forms of PTLD can occur much earlier [43]. The outcome of PTLD has fortunately been improved dramatically by the use of rituximab [44].

Intestinal graft rejection

Acute cellular rejection (ACR) of the small intestinal graft occurs more frequently and with greater severity than in any other abdominal organ. This has been exemplified when comparing rejection rates and severity of the different allograft organs within a given patient who has received a multivisceral transplant [45]. The potential reasons include a higher immunogenicity and the fact that the intestine contains approximately 75% of the donor lymphoid volume. Although ACR is now reasonably identifiable by bowel biopsy histology, and there has been a consensus on international pathology grading systems [45,46], acute rejection is less well characterized and understood than in other solid organs. An in-depth analysis of ACR episodes at one of the most experienced centres worldwide showed that about one-third of the recipients did not experience acute rejection [47]. Also as described before, [47,48] there was increased freedom-from-rejection; however, there was a more significant decrease in the incidence of severe rejection when a multivisceral graft was used, particularly in children. The authors also pointed out that the routine use of induction therapy contributed to an increased rate of freedom-from-rejection [47].

Among patients who experienced rejection, the first episode occurred at a median time of two-and-half weeks after transplantation, emphasizing the need for performing frequent endoscopies and histopathological evaluations of the graft within the first few months after transplantation. As most first-rejections and as the overall number of rejection episodes decreased over time and were mostly clustered within the first year after transplantation, the frequency of monitoring could then be lowered. The average length of rejection episodes, correlated with the histopathological severity, appeared to double with each increasing grade level, starting at 1 week and lasting up to 4 weeks in grade 3 rejection. Interestingly, the occurrence of a mild or moderate rejection had no significant effect on graft survival; however, two critical variables were identified that affected graft survival: progression to a severe rejection and a lengthy (≥21 days) rejection. The authors concluded that both should be avoided by initially implementing steroid bolus therapy early and aggressively, as well as escalating therapy towards anti-lymphocyte agents in case of unresponsiveness to steroids at a maximum of 2–3 days. A further observation in this study was that most of the patients who developed chronic rejection had experienced only moderate rejections. This points to the fact that severe

rejection leads more often to rapid loss of the graft, while repeated episodes of rejection of a lesser degree may trigger chronic allograft impairment with 'creeping' loss of function, which may be subclinical over a long period [47].

With regard to the progress in histopathological classification of ACR, several unique histopathological features of allograft acute rejection were observed in patients pretreated with depleting antibodies, i.e. alemtuzumab and antilymphocyte globulin. These characteristic features comprised a scattered lamina propria neutrophilic inflammation often preceding the onset of acute rejection, a more prominent eosinophilic infiltrate in lamina propria or eosinophilic cryptitis, the absence of crypts with intact surface villous epithelium in certain acute rejection episodes, and the finding that the mucosal damage associated with moderate or severe acute rejection can completely recover after additional immunosuppressive treatment [49].

Another entity, subclinical rejection (SCR) in various solid organ transplants has been described well, but not in intestinal transplants. A recent study analysed the clinicopathological characteristics associated with a SCR episode within 3 months after ITx. In a total of 2744 small intestinal transplant biopsies taken within 3 months after ITx in 151 patients, 171 cases (6.2%) were determined as SCR and 78 patients (51.7%) experienced an SCR episode within 3 months after ITx. SCR predominated in adult patients and had a significant impact on overall graft survival at 5 years after transplantation. SCR within 3 months after transplantation reduced 5-year graft survival significantly from 60% (w/o SCR) to 37%. SCR episodes were associated with a significantly higher hazard rate of death on account of infection [50].

Similar to SCR, acute vascular rejection (AVR) is also an inadequately characterized entity in human small-bowel transplantation whose frequency and severity is not well understood. The reason for the lack of data is associated with the limited access to full-thickness or transmural biopsies of the grafted intestine. In comparison with severe AVR, changes identifying early, mild or developing AVR have not been known. In a newly proposed scoring system to evaluate subtle mucosal vascular changes, small-vessel congestion and erythrocyte extravasation are the most prominent criteria. In a series of 188 biopsies from 21 patients obtained in the first 3 months after transplantation, most of the patients had a transient rise in vascular injury, often within 30 days after undergoing transplantation. Of note, graft survival was significantly lower in the patients showing early vascular lesions. AVR-lesions were not related to ACR, HLA type or HLA antigen disparities, but correlated with significantly higher peak panel reactive antibodies (PRA) and a higher incidence of positive T-cell and B-cell cross-match [51].

There has been some progress in establishing improved monitoring strategies which may, at some time or at least in some cases, obviate the need for graft biopsies such as zoom video endoscopy (ZVE), [52] or help to identify potential sites of rejection.

Additionally, noninvasive supportive markers, such as citrulline and calprotectin [53,54] show promise as peripheral and adjunctive measurements of altered graft function.

In a multivariable analysis, presence of mild, moderate, or severe ACR, presence of bacteraemia or respiratory infection, paediatric age, and time from transplant to blood sampling were identified as factors associated with significantly lowered citrulline levels. Using a <13 vs. ≥ 13 μmol/l cut off point, the sensitivity for detecting moderate or severe ACR and the negative predictive value were high (96.4% and >99% respectively). Specificity was 54–74% in children and 83–88% in adults. It was concluded that levels ≥ 13 μmol/l practically ruled out moderate or severe rejection. Citrulline levels <13 μmol/l were advised to alert the clinical team that a serious problem could develop in a previously stable intestinal recipient [55]. However, plasma citrulline only reflects the extent of mucosal injury regardless of the aetiology. It does not seem to be a predictive marker for rejection or viral enteritis, as its values may decline only when diffuse mucosal damage has occurred [56].

Apart from improved monitoring strategies, there has also been some promising data in the therapy of rejection refractory to agents like OKT3 or thymoglobulin. Recent data suggest a potential future role of anti-inflammatory mAbs against tumour necrosis factor (TNF)-α to reduce the rates of steroid and/or OKT3-refractory rejections as well as late ileal ulcerations, which may be the manifestation of some sort of allograft enteropathy [41,42,57]. An alternative agent could be alemtuzumab, [39] which was reported to be comparable to OKT3 for steroid-refractory rejection. However, these agents need further evaluation in larger patient cohorts in a prospective fashion.

Viral infections and post-transplant lymphoproliferative disease

Viral infections constitute a further main area of post-transplant care. Advances in prophylaxis and surveillance for viral infections and the prevention and management of Epstein–Barr virus (EBV)-driven PTLD have contributed immensely to improve graft outcome. Whereas PTLD had occurred at high rates in the early years (1991–1995: ITx: approx. 15%, MVTx: approx. 48%, LITx: approx. 15%), the incidence was reduced to 8–12% after 1995 and has stabilized to a rate of approximately 6–8% since then [1].

There is little consistency in viral prophylaxis as reviewed recently by Horslen [37] who compared the procedures in the five high-volume ITx centres in the USA. Viral prophylaxis may be performed with ganciclovir, valganciclovir, and additive cytomegalovirus hyperimmunoglobulin. The protocols in different units, as reported by Horslen [37], and the protocol used at the Charité, Berlin, are shown in Table 3. In contrast to the other centres, we do not routinely apply antiviral prophylaxis after transplantation, but only apply in the case of anti-rejection therapy (valganciclovir). Pre-emptive antiviral treatment with intravenous ganciclovir commences after two sequentially and significantly positive CMV-early antigen pp65 or CMV-DNA positive tests.

The mainstay of antiviral surveillance is routinely monitoring for the evidence of a virus, particularly by assessing CMV- and EBV-DNA as well as CMV pp65 antigen, in blood or tissues [37]. Increasing EBV-DNA levels may for example be a prelude to PTLD [58,59]. Routine monitoring for adenovirus or other enteroviruses is done less frequently, in our centre only when there is significant suspicion. Apart from antiviral therapy, pre-emptive reduction of immunosuppression, i.e. of tacrolimus and other immunosuppressants by 25–50%, is a common practice [60].

With PTLD diagnosed, a stepwise increase of therapy will be implemented – starting with reduction of immunosuppression for low-grade PTLD, continuing with anti CD20-directed rituximab therapy against higher grades of PTLD, and ending with formal non-Hodgkin's lymphoma treatment protocols in the case of highly aggressive PTLD, nonresponsive recurrence, or progression of disease [61]. Some centres even add cyclophosphamide at an early stage [37,62].

Graft-versus-host disease

Graft-versus-host disease has been a relevant clinical problem in isolated or combined transplantation of the intestine ever since the procedure has been performed. According to the data by the Intestinal Transplant Registry, the GvHD incidence was as high as 47% after MVTx and approximately 15% after ITx and LITx until 1995. Thereafter, the incidence decreased to 8% in ITx and approximately 12% in MVTx and LITx respectively. After the year 2000, an average incidence of 7–8% was reported [1,7].

In one of the largest single centre analysis regarding GvHD, 250 patients who underwent transplantation between 1990 and till the end of 2003 were analysed. GvHD was suspected clinically in 23 patients who presented symptoms such as skin rashes, ulceration of oral mucosa, diarrhoea, lymphadenopathy, or native liver dysfunction. Fourteen patients (5.6%) had GvHD confirmed by histopathological criteria including keratinocyte necrosis, epithelial apoptosis of the native gastrointestinal tract, and epithelial cell necrosis of oral mucosa. The majority of cases of GVHD were resolved with steroid administration and optimization of tacrolimus immunosuppression. The incidence of histologically proven GVHD after clinical ITx was 6.5% (eight of 122) in children and 4.7% (six of 128) in adults [63].

In another series, primary multivisceral recipients who received a donor's spleen ($n = 60$) were compared with those who did not receive a spleen ($n = 81$). Observed incidence of GvHD was 8.25% (five of 60) in the spleen group and 6.2% (five of 81) in the control group ($P = 0.70$). Thus, transplantation of the spleen obviously does not increase the risk of GvHD. However, an increased incidence of autoimmune haemolysis was observed in the spleen group. In univariate analysis, splenic recipients showed superiority in freedom-from-any rejection and freedom-from-moderate or severe rejection. No significant differences were observed regarding infectious complications [64].

Disease recurrence

Very little is known about the potential risk of disease-recurrence after ITx for autoimmune disorders of the small intestine, such as Crohn's disease. There are occasional case descriptions, e.g. on a late-onset manifestation of Crohn's disease recurrence 8 years after ITx which responded to steroids [65]. However, systematic studies to determine the frequency, predictors, and clinical implications of recurrent Crohn's disease have not been

Table 3. Prophylactic antiviral therapy and duration of use at five intestinal transplant programmes in USA and The Charité, Berlin.

Antiviral agent	Omaha	Pittsburgh	Miami	UCLA	Mt Sinai	Berlin
Cytogam	1 year	2 weeks	4 months	3 months		–
Ganciclovir intravenously	2 weeks	2 weeks (high risk 3 months)		2–3 weeks	100 days 2 weeks	–
Antivirals by mouth	1 year	None	6 months (children) 3–6 months (adults)	5 years	3 months	Only pre-emptive therapy

Modified after Horslen *et al.* (37).

reported. The most detailed data to date were provided by a case series of four adult recipients of an ITx caused by Crohn's disease complicated by short gut syndrome and total PN failure (three males, three females; mean age 48.1 years). Despite the absence of any endoscopic or clinical manifestations of Crohn's disease throughout their follow-up period, two patients had granulomatous enteritis characteristic of Crohn's disease in multiple biopsies, one patient in eight of 44 examinations (18%) ranging from 34 days to 20 months postoperatively and the other in six of 32 examinations (19%) ranging from 20 days to 22 months postoperatively. No comparable changes occurred in other patients without Crohn's disease followed endoscopically under the same protocol. According to the reported data, histological recurrence of Crohn's disease can occur after ITx without any clinical and endoscopic manifestations. They may occur more frequently than expected and as early as 3 weeks after transplantation. Based on rare data, they may not necessarily portend early clinical recurrence or mandate aggressive therapy to prevent allograft loss [65,66].

Quality of life and cost-effectiveness

Being on PN severely affects the QoL of patients suffering from intestinal failure. In contrast to a curative treatment option, such as ITx, PN does not restore QoL, e.g. after an acute incident like mesenteric infarction [13]. In contrast, the successful emergence of ITx as a curative alternative has provided many patients with bowel failure to be independent from infusions on a daily basis and to resume their personal, social and occupational lives autonomously. In summary, they will have an improved QoL – have better nutrition, and reduction in PN-associated complications. A recent review by Sudan *et al.* [13] concluded that because of the limited number of studies and the preliminary nature of findings, strong conclusions cannot yet be drawn regarding the QoL after ITx; however, the available limited data were judged as encouraging, suggesting that QoL was reasonably good after ITx and perhaps similar to that of normal individuals.

Some overview may be obtained by the QoL-data from the International Intestinal Transplant Registry in which proxy assessments from either a physician or nurse caring for the intestinal transplant recipients are reported [1]. Eighty-five per cent of ITx-recipients had a Karnofsky score of 90–100% more than 6 months after transplantation. These data suggest that the majority of ITx recipients have an excellent QoL. However, the assessments were not made by the recipients themselves but by proxy caregivers and no assessment was made in which QoL was impaired in those patients with low indices [13].

Others found that most patients were completely off PN after ITx and had few re-hospitalizations or complications beyond the first year after ITx. A high proportion of patients underwent successful social and occupational rehabilitation [67,68]. This coincides with our experience in which approximately 50% of patients were able to return to work after ITx.

Moreover, necessary considerations have to be given to the economic aspects. In contrast to the USA, where ITx has been an accepted treatment by the health insurance systems for more than 5 years, financial coverage has to be managed individually in many European countries. The average costs for isolated ITx were independently assessed by the Pittsburgh group (1994–1998) and the Omaha group (2002–2003), which has been estimated to be approximately US$132 000—135 000 [13,57]. This is comparable to the estimates at our centre (Charité, Berlin), where the average costs for ITx amounted to €138 000 between the years 2000 and 2004. The costs for combined LITx were estimated to be approximately US$207 000–214 000, and US$219 000 for MVTx [13,69]. Considering re-hospitalization costs of about US$9000–23 500 per year after ITx and, in comparison, annual costs of about US$100 000–150 000 for PN in patients with intestinal failure, ITx was calculated to be cost-effective as early as 2 years after transplantation [13,70].

Future perspectives

The further development of ITx may depend on several factors, including progress in immunosuppressive strategies with reduction of long-term risks to the patient and the graft posed by total immunosuppressive exposure.

New strategies of induction therapy could guide the way towards reduced long-term immunosuppression. Different ways have been described in a limited number of patients and need further confirmation. However, there seems to be a common misunderstanding that immunosuppression minimization protocols are tolerogenic. According to strict definitions, the term tolerance (or better: acceptance) should only be used in the absence of chronic immunosuppression.

After application of 2–3 mg/kg of rabbit anti-thymocyte globulin (rATG, thymoglobulin) just before ITx, and 2–3 mg/kg postoperatively (total 5 mg/kg), 36 patients, 5 months to 20 years of age, receiving ITx, underwent an immunosuppressive protocol aimed at minimization of tacrolimus exposure. After a mean of 15.8 ± 5.3 months follow-up, 47% of the patients were reported to be on tacrolimus or sirolimus monotherapy despite a 44% incidence of ACR in the first month. 1- and 2-year patient and graft survival was 100% and 94% respectively [71]. The same group had reported their experience with

immunosuppression minimization protocols with stepwise reduction of dose quantity or frequency of tacrolimus after 3 months in the various types of solid organ transplantation and presented results comparable to conventional immunosuppressive protocols. Whether these novel strategies should be called or will prove to be 'tolerogenic' or just help to reduce the total immunosuppressive burden is yet to be elucidated [72].

A different approach was published recently using an immunomodulatory protocol, which included donor-specific blood transfusion. This strategy dates back in times before the introduction of cyclosporine and was recently shown to promote development of regulatory cells. Additionally, low-dose steroids and low-dose tacrolimus were administered in order to avoid over-immunosuppression, which was shown to be counterproductive for tolerance induction and for the development of regulatory cells. Finally, inflammation within the intestinal graft was reduced by accepting only very good donors with low cold ischaemic times. Under this protocol, freedom-from-rejection was achieved in four consecutive intestinal transplant recipients [73]. While this approach certainly appears to be attractive and offers a new insight in the role of immunomodulation even in high risk grafts such as the intestine, it is limited by its restrictive donor criteria and lack of confirmation by large groups. However, provided that the progress in donor pretreatment, amelioration of ischaemia/reperfusion injury and early modulation of the innate immune response will be made, when more recipients become eligible for such protocols. Again, it should be commented that these protocols are immunosuppression minimization protocols rather than tolerogenic because the lack of rejection under low immunosuppression does not predict the potential to develop complete acceptance of the graft.

Apart from these promising clinical steps towards reducing long-term immunosuppression, there are experimental models evaluating protocols potentially inducing long-term acceptance. Perioperative signal-1 modification by a nondepleting anti-CD4 mAb and additional application of the anti-TNF-α monoclonal antibody etanercept in a Dark Agouty-to-Lewis rat intestinal transplant model, prolonged the survival indefinitely in approximately 50% of the treated animals without further application of immunosuppressants. Sole anti-CD4 treatment with the mAb RIB5/2 prolonged survival from about 7–21 days. Interestingly, additional TNF-α blockade reduced the expression of chemokine MIP-1α significantly, possibly indicating an additional effect of the TNF-α blockade on the immune modulation by RIB5/2 [74]. Such approaches might also be helpful in the clinical setting by circumventing the sequels of depleting induction protocols and combining it with immunomodulatory agents.

One of the most challenging problems will be the improvement of survival beyond the first year after transplantation. As reported by the Intestinal Transplant Registry, progress in recent years has manifested mainly in improving short-term graft and patient survival; conditional graft survival after the first year turned out to be disappointingly unaffected by the advances of the field in the last years. This turns the focus to previously underappreciated factors of long-term graft survival, which are far more acknowledged in e.g. kidney transplantation. Hence, modulation of early graft injury induced by brain death, ischaemia/reperfusion, and other alloantigen-independent confounding factors that contribute to chronic allograft enteropathy will have to attract more attention. With the growing number of ITx recipients, several other aspects, which also have been acknowledged and investigated in kidney transplant recipients, will be of importance: the further characterization and description of histolopathological entities, such as mucosal manifestations of humoral and AVR, chronic allograft enteropathy, and calcineurin toxicity to the intestinal graft. In addition, the influence of HLA-matching, or the role of pre-existing antibodies will only be verifiable in larger patient populations.

A very exciting current development, which certainly will stimulate further research, is the transfer of scientific knowledge from the field of chronic inflammatory bowel disease into intestinal allograft immunity. This transfer stems from the observation that intestinal allograft rejection sometimes resembles Crohn's disease clinically and pathologically.

The discovery of three polymorphisms linked with Crohn's disease defined the role of NOD2 protein as a key player in intestinal immune health. Fishbein *et al.* [75] investigated whether epithelial immune function and graft survival were influenced by NOD2 mutations in their intestinal transplant population comprising 34 consecutive ITx. They related the NOD2 genotypes to clinical outcomes and the expression of certain intestinal antimicrobial peptides (AMPs) is believed to protect the epithelium. Interestingly, 35% of the recipients had NOD2 polymorphisms, while 8.6% of the donors had comparable mutations. The likelihood of allograft failure was about 100-fold higher in recipients with mutant NOD2 alleles compared to recipients with wild type NOD2 loci. Rejection in NOD2 mutant recipients was characterized by a decreased expression of certain Paneth cell and enterocyte AMPs, prior to the onset of epithelial injury and inflammation. It was concluded that NOD2 polymorphims in the recipient represent a critical immunological risk factor for intestinal allograft rejection. NOD2 polymorphisms were associated with compromised epithelial defence mechanisms that preceded the visible epithelial injury and the inflammatory infiltration.

Summary and perspectives

Intestinal transplantation is the only definitive therapy for irreversible intestinal failure. Owing to the limited short- and long-term graft survival over the years, ITx has been seen complementary and not competitive to home PN treatment. However, the improvement of patient- and graft survival over the last years combined with the data on cost effectiveness of ITx 2 years after transplantation may require a new definition for the indication of ITx.

The reasons for improved outcome after ITx are multifactorial; however, progress in immunosuppression certainly has played the most prominent role. Particularly the implementation of induction agents has lead to 1-year graft survival rates as high as 80–90%. The advances in ITx are also reflected by the impressive reduction of rejection rates. They still embody one of the main risks for graft failure. Considering these data, ITx offers a fair chance for complete physical, social and professional rehabilitation.

Data on the influence of recipient status prior to undergoing transplantation clearly emphasize the necessity of an earlier referral of patients with intestinal failure to specialized centres prior to the onset of life-threatening complications. With a further spread of awareness and knowledge about referral criteria, transplant criteria and optimal time for transplantation, a further improvement of outcome will be achieved.

As the currently achieved survival rates of ITx already match the long-term success under PN, ITx may soon become a preferred treatment and no longer a complementary one for intestinal failure.

Authorship

AP: wrote paper, proof reading, literature search and artworks. SK: wrote paper and literature search. PN: proof reading. JP: wrote paper and proof reading.

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