Small bowel transplantation (SBT) has witnessed a dramatic upswing over the last five years thanks to the remarkable improvement of its outcome. This has been due mainly to the improvement of immunosuppressive protocols. The pioneers in SBT using animal models include Alex Carrel (1902, first transplantation of an intestinal segment in the dog) (1), Lillehei (1955, first orthotopic SBT in the dog) (2), and Monchik and Russel (1971, first model of SBT in the rat) (3). Initial clinical experiments (4) were doomed to failure because of inadequate immunosuppressive therapy was used. Renewed interest in SBT in the 1980s came with the introduction of cyclosporin into immunosuppressive protocols. However, appreciable improvement of outcomes did not come until ten years later with the advent of tacrolimus. The initially disappointing results were associated with the specific properties of the small bowel in contrast of other solid transplants. The small bowel is the largest immunological organ with a vast number of immunocompetent cells. It is the only organ used for transplantation which is not sterile, which has a complex dense intramural nervous network and, last but not least, which does not have a simple clinical test to determine bowel graft function and to monitor rejection the way it is with the other solid transplants (creatinine with the kidney, transaminases and bilirubin with the liver) (5).

**SUMMARY**

Small bowel transplantation is a logical alternative to definitive total parenteral nutrition in patients with chronic intestinal failure. It has become a life-saving procedure for patients with intestinal failure who cannot be treated using conventional therapeutic procedures. Indications in children (over 50% of recipients) include the short gut syndrome, primary disorders of intestinal motility and mucosal diseases. In adults, the main indication for small bowel transplantation is inadaptable short bowel syndrome after total or subtotal resection. Patients with irreversible intestinal failure and total parenteral nutrition without concomitant liver disease should be considered candidates for isolated small bowel transplantation. Patients with irreversible intestinal failure and end-stage liver disease are candidates for a life-saving procedure such as combined liver-small bowel transplantation. Appropriate timing for transplantation is controversy. Advanced disease is associated with a poorer outcome because of progressive liver failure or infection. For this reason, small bowel transplantation candidates should be included on a waiting list as soon as possible. The recent improvement in small bowel transplantation outcome gives hope that the procedure will become a standard therapeutic option in patients with irreversible intestinal failure.

**Key words:** small bowel transplantation, indications, outcome, authors’ own experience.

**INDICATIONS FOR SBT**

More than 50% of patients are children. SBT is intended for patients with irreversible intestinal failure, i. e., those whose bowel is unable to maintain nutritional, fluid, and electrolyte balance. They are patients dependent on total parenteral nutrition (TPN), with no possibility of vascular access, and patients with recurrent catheter-induced sepsis. Chronic TPN often results in irreversible liver impairment requiring combined liver-bowel transplantation. Intestinal failure develops in children with (a) loss of absorption capacity following extensive resection (short bowel syndrome), (b) inability to maintain normal bowel function (enterocyte dysfunction), and (c) loss of intestinal motility, i. e., chronic idiopathic intestinal pseudoobstruction (6).

**Short bowel syndrome**

Logically, the first indication for SBT was intestinal failure following extensive small bowel resection. In children, the most frequent causes for resections include volvulus (28%), gastroscisis (19%), necrotizing enterocolitis (12%), and intestinal atresia (8%) (Fig. 1). A major factor after extensive resection is the presence or absence of the ileocaecal valve. It is widely accepted that children without the ileocaecal valve and a bowel stump longer than 40 cm, and those with the ileocaecal valve and a bowel longer than 20 cm are capable of adaptation and long-term survival while not requiring TPN (7).

**Enterocyte dysfunction**

This includes two congenital enterocyte disorders, i. e., microvillus inclusive disease of brush rim development and epithelial dysplasia, with the latter being associated with enterocyte and basement membrane abnormality.
**Loss of intestinal motility**

The term intestinal dysmotility primarily covers the extensive form of Hirschsprung disease involving the small bowel and chronic idiopathic pseudoobstruction syndrome. While only a short bowel segment is involved in most patients with Hirschsprung disease, 6% of patients show almost complete aganglionosis. Patients with chronic pseudoobstruction exhibit impaired control of neuromuscular intestinal motility. While, clinically, it manifests as mechanical obstruction with intestinal dilatation, there is no apparent obstruction or mucosal disease; 20-25% of patients with the pseudoobstruction syndrome have to rely on chronic TPN.

**Adult** patients are mostly scheduled for SBT for the short bowel syndrome (8). The most frequent cause is vessel occlusion (arterial, portomesenteric, or of combined etiology) (21%), which, however, has the worst prognosis, as it is associated with primary heart disease. The second most frequent cause is Crohn disease (17%). The potential for recurrence of the underlying disease has not been defined to date. Other, less frequent causes, include loss of most of, or the whole intestine, due to injury (15%), desmoid tumors (13%), or small bowel volvulus (7%) (Fig. 2). TPN-dependent are 90% of adult patients with 50 cm of the small bowel left while they ileo-caecal valve and the whole colon has been retained (9).

**CLINICAL RESULTS**

The latest comprehensive results were presented at the 20th International Congress of the Transplant Society (held in Vienna, Austria, in September 2004) (10). In the period from April 1985 through June 2003, a total of 989 bowel transplant procedures were performed in 923 patients in 61 transplant centers; 3.2% were living-related donor procedures. Fifty percent of procedures were combined ones (liver-bowel); 47% were isolated procedures and multivisceral transplantations accounted for 12% of cases. In adults, 55% were isolated procedures, 21% combined transplantations, and 24% multivisceral procedures. The best clinical outcomes were obtained from the largest center in Pittsburgh, PA, USA, currently reporting an 86% one-year survival rate. Five years ago, the figure was a mere 62%. This marked improvement is attributable to the development of new immunosuppressive protocols.

**TYPES OF TRANSPLANTATION**

Essentially, there are three types of SBT.

**Isolated SBT**

The graft includes the whole small bowel on a vascular pedicle made up by the a. mesenterica superior and v. portae or, alternatively, a. mesenterica superior. The graft is transplanted heterotopically end-to-side (v. mesenterica superior – v. cava inferior and a. mesenterica superior – aorta subrenally). The distal part is usually brought out as an ileostomy providing access for numerous biopsies in the postoperative period. Depending on the patient’s status and postoperative course, the stomy is closed after 3-6 months (Fig. 3).

**Combined liver-bowel transplantation**

This is indicated in patients developing, in addition to intestinal failure, irreversible liver failure as a result of TPN. The graft includes the bowel and the liver. The arterial part of the vascular pedicle consists of the aortic segment with the origin of the a. mesenterica superior with the origin of the truncus coeliacus. The venous part of the pedicle includes, with an intact v. portae, the venae cavae superior and inferior.

**IMMUNOSUPPRESSION**

Initial experiments were faced with uncontrollable rejection. Improved results were not obtained until the inclusion of cyclosporin A into the immunosuppressive protocols in the 1980s. Nonetheless, the truly remarkable development of SBT came with the advent of tacrolimus in the 1990s. At present, all immunosuppressive protocols are tacrolimus-based, mostly in combination with other immunosuppressives (steroids, mycophenolate mofetil) (11). Very good results were associated with induction therapy, developed by Campath, and followed by tacrolimus monotherapy (12). These protocols are yet to be further tested in practice.

**COMPLICATIONS**

Frequent early and late complications after SBT are to be blamed for the fact that SBT has not become standard method for managing intestinal failure. On the one hand, there is the bowel as the largest immunological organ with a dense network of immunocompetent cells; on the other, the bowel is the only transplanted organ which is not sterile, and thus constantly at risk of infection with subsequent development of sepsis with all inherent lethal sequels.
for the graft and recipient alike. Graft rejection in the postoperative period develops in 57% of patients undergoing isolated SBT, 39% after combined procedures, and 48% of those undergoing multivisceral transplantation. Infections include bacterial, viral (CMV, EBV, etc.) and Candida ones. The main clinical feature of both rejection and infection is identical, i.e., diarrhea. However, clinical features are already late signs of complications, which is why frequent stage intestinal graft biopsies are mandatory, particularly in the early postoperative period. Other complications include bleeding and vascular thrombosis.

**OUR EXPERIENCE**

In our center, experiments with animal models (rats, dogs) are being carried out for several years investigating ischemia-reperfusion injury to the graft, rejection and, last but not least, the importance of primary lymphatic vessel reconstruction (13, 14). Recently, a clinical experiment was approved by the Institutional Review Board and launched in an effort to master the operating technique in the donor and to study ischemia injury to intestinal grafts (Fig. 4).

**CONCLUSIONS**

Small bowel transplantation is an alternative to total parenteral nutrition in patients with intestinal failure. Rejection and infection continue to be the main complications. It is to be hoped that improving outcomes as a result of refined immunosuppressive protocols and refined/better diagnosis of early phases of rejection will soon make small bowel transplantation standard method for the treatment of patients with intestinal failure.

**Abbreviations**

- CMV - cytomegalovirus
- EBV - Epstein-Barr virus
- SBT - small bowel transplantation
- TPN - total parenteral nutrition

**REFERENCES**

Comments upon the article by M. Kudla et al.
“Small Bowel Transplantation”

Workers at the Institute for Clinical and Experimental Medicine (IKEM) present comprehensive information on the transplantation of an organ which is the last to enter the field of clinical medicine to date. In doing so they are reacting to the stimulus of Professor Prokop Málek, IKEM’s first Director, who pioneered transplantation in our country.

Professor Málek saw progress in combining experimental medicine with specific clinical activity, and he also thought of bowel transplantation long before it was clinically feasible. As a philosopher of science, he defined development of a therapeutic procedure in three stages: (1) stage of biological experiment; (2) stage of clinical experiment; (3) stage of clinical application.

He provided an impetus to pathophysiological studies, which were also to pave the way for the technique of bowel transplantation. As a tutor, he encouraged Vladimir Kočandrle to study regeneration of lymphatic vessels after bowel transplantation - the result of which was an international study which is still cited (1). Using lymphangiography, the study documented lymphatic vessel regeneration after small bowel autotransplantation in dogs, but not after allotransplantation, when - given the possibilities at that time - the transplant succumbed to rejection earlier. Our group investigated the issue of endotoxin transport from the bowel via lymphatic and venous routes after intestinal ischemia (2), an unthinkble process in intestinal transplantation. After ischemic intestine revascularization, the endotoxin, as determined by the limulus test, was transported by the lymphatic and venous routes, whereby only the former was employed before ischemia. However, these were experiments performed 30 to 40 years ago. It is rewarding to read in the article by Kudla et al. that pathophysiological studies related to intestinal transplantation have not ceased.

The first clinical experiments with intestinal transplantation date back to the early 1960s. At that time, patients would die of starvation if a major part of their small bowel was either resected or destroyed by injury. Intravenous administration of nutrients was unavailable at that time, and it was generally believed the intestinal graft would function normally. However, the first small bowel recipients died because of technical complications, rejection or infection. Intestinal transplantation was unsuccessful until the mid-1980s, when cyclosporin was introduced. The real breakthrough came in the 1990s with the introduction of tacrolimus into immunosuppression. The reasons why successful intestinal transplantation is more difficult, compared with the transplantation of other organs, is that the large numbers of white cells in the intestine pose a major stimulus for rejection to develop, and the large number of bacteria in the intestine raise the risk of infection. A small bowel transplant recipient requires doses of immunosuppressives large enough to prevent rejection but not so large as to permit infection to be contracted. The story of progress in intestinal transplantation is thus a story of progress in immunosuppressive therapy.

As tacrolimus, currently the dominant component of all immunosuppressive protocols, plays a major role in the history of intestinal transplantation, it is appropriate to mention its effect. Like cyclosporin, it is a calcineurin inhibitor. Both agents have a similar mode of action consisting in blocking the transcription of lymphokine genes as a result of T-cell receptor inhibition. In the mode of action, the phosphatase calcineurin is inhibited with subsequent inhibition of interleukin-2 production. Just as with cyclosporin, regular monitoring of blood levels is critical, since side effects are dose-dependent.

These side effects include nephrotoxicity, neurotoxicity, hyperlipoproteinemia, and a decrease in insulin secretion. Biologically, tacrolimus is up to a 100 times more effective than cyclosporin, so it is administered at lower doses and inhibits some cytokines in a different manner.

Development worldwide is seen as rapid by the authors. Efforts at evaluating clinical transplantation procedures, whose numbers began to grow, made it imperative to establish an international registry, the Intestinal Transplant Registry. Overall, 75 transplant centers from all parts of the world receive forms with specifically formulated questions for each case and present at symposia, at two-year intervals, data on cumulative patient and graft survival rates and a host of important data. The next symposium is to be held in Brussels in 2005. The most recent published data refer to the year 2003 based on reports from 61 centers (3). A reference to this is also made in the main article. A multivariate analysis of 989 transplant procedures made in 923 patients over the past 5 years showed better survival rates in patients awaiting transplantation at home, receiving antibodies in induction immunosuppression and undergoing transplantation in more experienced centers.

Small bowel transplantation has become a life-saving procedure in children and adults with loss of intestinal function who are unable to further receive total parenteral nutrition. Still, the incidence of rejection, sepsis, and lymphoproliferative disease continues to be higher than with other transplant procedures. While isolated transplantation is associated with the best outcomes according to some reports, this is not so according to others. As chronic total parenteral nutrition may lead to liver failure, combined liver-intestine transplantation may be considered in such cases. An alternative in patients with extensive malignant tumors is multivisceral transplantation of all abdominal organs. The three-year graft/patient survival rates (in percent), as reported by the registry in 1996, for patients receiving tacrolimus were 29/47 with isolated bowel transplantation, 38/40 for the liver-intestine combination, and 37/43 for multivisceral transplantation. I cannot help thinking that the combination with the liver seems to protect the recipient against loss of the intestinal graft.

Intestinal transplantation is mainly the domain of pediatric surgeons. According to the most recent report, 61% of recipients were below 18 years of age. A recent report from the Pediatric Hospital in Pittsburgh, PA, USA, refers to outcomes of transplantation between June 1990 and December 2003 (4).

Over the above period, a total of 122 children underwent 70 liver/intestine transplant procedures, 42 isolated bowel, and 17 multivisceral transplant procedures. Their mean age was 5.3 ± 5.2 years, with boys making up 55% of patients. Twenty-nine percent of patients had augmentation by bone marrow autotransplantation (we are considering this approach to be also employed for isolated islet of Langerhans transplantation). Cumu-
lative survival rates (Kaplan-Meier) for recipient/graft for all types of transplantation were 81%/76% at one year, 62%/60% at three years, and 61%/51% at five years. Survival with multivisceral transplantation was 100%/100% over the past year. The same procedure also showed the lowest incidence of cytomegalovirus (CMV) and EB infection. The authors ascribe these results to improved immunosuppression using modern antibodies and withdrawal of corticosteroids. Here, one can indeed speak about the stage of routine clinical application.

I am truly impressed by the program of related-donor intestinal transplantation, a technically feasible procedure, perhaps the most feasible of all transplant procedures. This may be exemplified by the case of a father donating his intestine to his 16-year-old paraplegic son with life-threatening complications on total parenteral nutrition (5). The transplant was a 200-cm ileal resecate with the ileocolical artery and vein. The donor was left 300 cm of the jejunum and 20 cm of the distal ileum with the ileocolical valve. Within one year post-transplant, the boy gained 20 kg and intestinal function tests were normal.

In this country, we have not moved past the stage of biological experiment, yet pediatric surgeons are no doubt capable - both technically and in terms of immunosuppression - of undertaking a clinical experiment. There seem to be centers in the world, which have reached the stage of clinical application. Still, many questions remain to be answered in experiment; for instance, what about the endotoxin, normally inactivated in the liver. Does not this play a role in the development of rejection or complications?

REFERENCES

Translation: René Prahl

**COMMENTS**

Comments upon the article by Kudla M., Baláž P., Adamec M.: “Small Bowel Transplantation”

This review article provides brief information on current experience with intestinal transplantation procedures performed in clinical practice in international centers. In their article, the authors also report about their experimental experience with intestinal transplantation in an animal model and on their preparation of a clinical experiment in their center.

Small bowel failure due to its absence, loss due to resection or injury by a pathological process is accompanied primarily by impaired water, electrolyte and nutrient resorption with clinical manifestations such as diarrhea, dehydration, mineral deficiency and malnutrition. Some patients with “short bowel syndrome” tolerate oral intake of modified and individualized diet, provided at least 60 cm of the small bowel has been left (ileum in optimal cases). Patients with less than 60 cm of the small bowel, additionally after colon resection, have to resort to parenteral nutrition, which can today be provided at home. The intestine of about one in three of these patients can adapt, to an extent, within months to years, to gradual renewal of oral intake. Intestinal transplantation is then indicated in cases where it is impossible to cover nutritional requirements by parenteral nutrition because of vanishing venous access or because of severe hepatic dysfunction and, perhaps, parenteral nutrition altogether in the future.

Compared with transplantation of other organs, development of small bowel transplantation is faced with many problems as it involves the transfer of a large volume of lymphatic tissue, which in itself raises the risk for acute rejection and requires intensive immunosuppression. This is associated with susceptibility to viral and bacterial infections, enteritis, septic states and poor transplant function. Intestinal transplantation procedures were occasionally performed in clinical practice as early as the 1960s and 1970s; however, increased success came about with the administration of cyclosporin in the late 1980s. Improved results were obtained with the advent of tacrolimus a decade later. Many experimental and, later, clinical studies were required to tackle technical issues including reconstruction of the vascular bed or of lymphatic drainage, cold and warm graft ischemia, ischemia-reperfusion graft injury, techniques of detecting rejection as well as selection of optimal preservation solutions for perfusion of a harvested intestinal graft, and development of the optimal protocol of immunosuppressive therapy.

The impressive advance made in the last decade in clinical intestinal transplantation in some international centers, which is reflected in improved survival rates and quality of life of transplant recipients, gives hope to our patients. The authors’ center has been involved in experimental intestinal transplantation for several years, has experience with organ transplantation and immunosuppression and, hence, has all the prerequisites for bringing this difficult method of transplantation into clinical practice.

Translation: René Prahl
On the article by Kudla M., Baláž P. and Adamec M. “Small Bowel Transplantation”

Small bowel transplantation (SBT) is not yet performed in the Czech Republic (CR), so it continues to pose an unresolved societal-medical problem - particularly as regards children, who comprise up to 60% of all SBT candidates. Seen from this perspective, any attempt to perform SBT in the CR is commendable - as is keeping the broader medical public up to date in the form of a review article authored by colleagues from IKEM Prague. Although the review article does include basic information on the issue, some comment and clarification is required.

To begin with, one cannot agree with the claim that the small bowel is the only transplanted organ which is not sterile; the lungs represent a similar organ with bacterial contamination. As for the percentage proportion of children in SBT programs, I feel it is necessary to note that children account for almost two thirds of all patients (1, 2). A total of 606 SBT procedures were performed in 560 pediatric patients (57% of boys and 43% of girls) below 18 years of age in 42 transplant centers from April 1985 through April 2003. The majority of pediatric patients with SBT were in the age group of 1-13 years. Long-term survival of pediatric small bowel transplant recipients is about 51%.

One problem that complicates development of SBT is procurement of suitable donors. Therefore, as with the kidney, liver, lungs and pancreas, grafts are currently being obtained from living related donors (L-R SBT). To date, 25 L-R SBT procedures have been reported to the international registry.

Ileal resection in donors should be made at a sufficient length from the ileocolicaecal valve, which should always be preserved. The length of harvested grafts ranged from 150 to 200 cm, and intestinal harvesting in donor did not result in dysmotility or malabsorption (3). To give just two examples, one was a 14-year-old boy with disseminated hypogangliosis of the whole intestine, who received a graft from his 43-year-old mother, while a 27-year-old patient after intestinal resection for midgut volvulus obtained a graft from her 54-year-old mother (4). Another success case report relates to L-B SBT for short bowel syndrome in 13-year-old siblings, monozygous twins, whose weight-height difference equalled within 18 months (5).

As regards indications groups of pediatric patients for SBT, the second most numerous group after short bowel syndrome patients are those with chronic intestinal pseudoobstruction, which, however, does not include patients with Hirschsprung disease! Patients with extensive, almost complete intestinal aganglionosis (a form of Hirschsprung disease) belong to the group with short bowel syndrome. The number of such patients is very low, about 1%, and differ essentially from those with so-called total large bowel aganglionosis with terminal ileal involvement, occurring in 6-10% of patients with Hirschsprung disease, with a long-term favorable prognosis.

Patients with extensive intestinal aganglionosis show better outcomes if not subjected to extensive intestinal resection but managed with TPN only. This requirement (6) may not always be easy to meet, as even after TPN initiation, extensive to complete large and small bowel aganglionosis results in chronic intestinal obstruction with bacterial overgrowth and recurrent enterogenic sepsis, requiring some form of intestinal derivation. We ourselves do not have sufficient experience with retaining a major part of an aganglionic intestine in the abdominal cavity for a long time. We only followed up one patient with extensive aganglionosis of the large and small bowels, except for a 26-cm portion of ganglionic jejunum from the duodenojejunal junction, in whom the aganglionic intestine was left in place, after establishing enterostomy, until definitive surgery at five years of age.

Regarding graft transplantation, judging by experiments, there is no principal difference between orthotopic venous anastomosis into the recipient portal vein and heterotopic anastomosis into the vena cava inferior (7), although it is generally accepted that portal drainage of the blood from the intestine is better (8).

SBT programs are usually associated with high mortality and morbidity rates, as exemplified by the Spanish transplant program, with 18 SBT candidates over a period of five years, from which four died still before SBT (all children below one year of age), while one patient died during attempted multivisceral transplantation. Two patients died from bleeding and lymphoproliferative disease progression with a functioning graft. One patient is again on the waiting list after uncontrollable graft rejection. Only two children of the group are on full oral intake at 18 and 40 months post-transplant (9).

Bacterial infection is an inherent component of SBT (10). Severe bacterial infection develops in 93% of patients. The most frequent sources are the venous catheter followed by the abdominal cavity, airways, and the operative wound. Eighty-six percent of patients develop recurrent bacterial infection within the first post-SBT month. With viral infections, the herpes simplex virus should be added to CMV and EBV.

Despite the above facts, some late outcomes and quality of life assessment in children after SBT indicate that even this area of organ transplantation could give hope to pediatric patients, as suggested by a questionnaire-based survey including 29 patients aged 5 to 18 years, who were a mean 5 years after SBT and did not differ substantially from their healthy contemporaries (11).

The introduction to the issue of SBT was obtained by the review article’s author during his fellowship at the Department of Pediatric Surgery of Hopital Necker in Paris, France, where the first pediatric SBT in Europe was performed. Additional information was obtained while treating a girl patient with chronic intestinal pseudoobstruction we sent for SBT to the above mentioned French center.

Constantly updated information on state-of-the-art of SBT is available at: www.intestinaltransplant.org

Prof. Richard Škába, MD.
Department of Pediatric Surgery
Charles University in Prague, 2nd Faculty of Medicine and Motol University Hospital
150 06 Prague 5, V Úvalu 84
Czech Republic
E-mail: richard.skaba@lfmotol.cuni.cz
REFERENCES


Translation: René Prahl