1557

MEDICAL
INTELLIGENCE
UNIT

INTRA-ABDOMINAL ORGAN TRANSPLANTATION 2000

Linda S. Sher, M.D.
Leonard Makowka, M.D., Ph.D.

Cedars-Sinai Medical Center
Los Angeles, California

R.G. LANDES COMPANY
AUSTIN

CHAPTER 11

TRANSPLANTATION OF THE SMALL BOWEL AND OTHER ABDOMINAL ORGANS IN HUMANS

Jorge Reyes
Satoru Todo
Andreas Tzakis
Kareem Abu-Elmagd
Bakr Nour
Hiroyuki Furukawa
Thomas E. Starzl

INTRODUCTION

Intestinal failure is defined by the inability to maintain a normal nutritional status (caloric intake, fluids and electrolytes, weight, etc) by use of the gastrointestinal tract alone. Prior to the introduction of total parenteral nutrition (TPN)[1] the survival of these patients relied on the ability of the remaining bowel to undergo adaptation. The use of TPN has provided significant improvement in outcome (65–80% for 3 year survival);[2] this will vary, however, according to the etiology of the intestinal failure. Limiting factors have been the induction of liver dysfunction and cirrhosis secondary to TPN, and venous access complications of which infection and the progressive inability to cannulate are the most severe. Also, the expense of life time therapy with TPN has been estimated at between $75,000 to $150,000 per year.[3] Though some patients enjoy a normal lifestyle on TPN, many individuals are hampered by the constant hospitalizations for complications, and suffer from significant social stigmata derived from incomplete rehabilitation into society.

Intra-Abdominal Organ Transplantation 2000, edited by Linda S. Sher, M.D. and Leonard Makowka, M.D., Ph.D.;

Experimental transplantation of the small bowel was first reported as an isolated organ graft by Lillehei in 1959,[4] and one year later as part of a multivisceral graft.[5] Though liver transplantation was also in the experimental phase at this time, the clinical applicability of this procedure was rapidly expanded after the introduction of cyclosporine A. This did not occur however with intestinal transplantation where numerous clinical trials performed between 1964 and 1987 were met with almost unanimous failure.[6] Failure of this modality was attributed to rejection of the intestinal graft, sepsis, or technical imperfections. It was not until 1987 when a 3-year-old girl received a multivisceral abdominal graft that contained the stomach, duodenum, pancreas, small bowel, colon, and liver that an extended survival with intestinal graft function of 6 months was attained.[7] An even longer survival was subsequently obtained (greater than 1 year) in a recipient of a liver and small bowel graft treated by Grant et al.[8] Until 1990, there were only two survivors of isolated cadaveric intestinal grafts, one in France and the other in Germany.[9,10]

INDICATIONS

Small bowel transplantation, either alone or accompanied by the liver, may be beneficial in any patient with intestinal failure who is dependent on TPN for their survival. The clinical outcome under standard therapy (TPN) is mainly a reflection of the underlying diagnosis, and reflects septic, metabolic, and hepatic complications. The causes for intestinal failure are varied, age dependent, and can be temporary or permanent. The loss of intestinal function may be acute as in intestinal infarctions (necrotizing enterocolitis, volvulus, mesenteric thrombosis), or chronic (Crohn's disease, radiation enteritis etc).

In some patients adaptation of the remaining intestine permits recovery after a period of temporary TPN support. The minimum length of intestine required for maintenance of nutritional status has not been established. Reports advocating 10–20 cm of small intestine with an ileocecal valve, and 40 cm without[11,12] reflect clinical management experience. Adequate function of remaining intestine depends not only on the length of bowel, but also the morphology of the intestinal mucosa (both gross and histologic). Motility disorders, gut hormone interrelationships, biliary and fat metabolism, as well as intestinal microflora are important cofactors. The presence of residual ileum (for its adaptive qualities), ileocecal valve (the slowing of intestinal transit time) and the colon (increased water absorption) also enter into the equation.

Candidates with intestinal failure can be divided into those with surgical and nonsurgical etiology. This division has implications with regards to the type of transplant to be performed. Patients with surgical causes suffer from loss of bowel from intestinal atresias, infarctions consequent to volvulus, necrotizing enterocolitis, vascular catastrophes (trauma or thrombosis), Crohn's disease, etc. Nonsurgical causes of intestinal failure have included motility disorders such as intestinal pseudoobstruction syndromes, absorptive insufficiency as seen in microvillus inclusion disease, polyposis syndromes with chronic bleeding and protein losing enteropathy, and incarcerating desmoid tumors.

Table 11.1. Small intestinal transplantation referrals 1990 to 1992

	Pediatric		Adults
Number of referrals	83		88
Diagnosis of pediatric patients		Diagnosis of adult patients	
Necrotizing Enterocolitis	21	Crohn's disease	24
Gastroschisis	15	Thrombolytic disorder	19
Volvulus	12	Trauma	12
Pseudoobstruction	9	Pseudoobstruction	7
Hirschsprung's disease	5	Radiation enteritis	5
Intestinal atresia	5	Desmoid tumor	4
Microvillus inclusion disease	2	Familial polyposis	3
Malrotation	2	Volvulus	3
Other	12	Other	11

Table 11.1 lists the indications for intestinal transplantation at the University of Pittsburgh in adults and children between May 1990 to January 1993. Patients presenting with intestinal failure and TPN induced liver disease are candidates for liver/small bowel transplantation. Guidelines used in assessing the need for a concomitant liver transplant has been the degree of liver dysfunction (hyperbilirubinemia, transaminase abnormalities, hypoalbuminemia, and coagulopathy) severity of fibrosis on liver biopsy, and the presence of portal hypertension as manifested by hepatosplenomegaly, ascites and esophageal varices. Patients who have suffered mesenteric vascular thrombosis secondary to deficiencies of proteins S and C (hepatic derived) should also receive a concomitant liver transplant to provide for these proteins.[13]

Of 34 patients transplanted at the University of Pittsburgh during this time period, 22 presented in terminal stage of intestinal failure with total bilirubin levels between 2.3 and 50, and evidence of portal hypertension (bleeding esophageal varices). Septic complications had been seen in all patients. Similar patients should be transplanted as soon as evaluation is completed. Sudden unpredictable deterioration has led to the demise of 29 out of 171 patients referred. Choosing the optimum time for transplantation of the intestine alone is difficult since the clinical course and life expectancy are variable. It has been our policy to select patients that have persistent liver function test abnormalities (no synthetic dysfunction) with changes on liver biopsy (mild fibrosis, esteatosis, cholestasis) reflecting TPN injury. Also, patients who have had multiple septic episodes from line infection and consequent thrombosis of access sites, and who are progressively depleting these sites should also be considered for intestinal transplantation.

EVALUATION OF CANDIDATES

Areas that must be covered when evaluating a potential small bowel transplant recipient include diagnosis, nutritional history and present nutritional status, and possible recipient anatomic abnormalities (both gastrointestinal and vascular). This should allow for accurate planning of graft type, however, the final decision may be made at the time of exploration.

A complete understanding of the etiology for the intestinal failure, as well as knowledge of all previous operative procedures performed is paramount to a successful operation. Assessing for anatomic and functional integrity of the remaining gastrointestinal tract can be accomplished by routine barium tests, motility studies and absorption studies when indicated. All pathologic specimens available should be reviewed. Review of infectious complications will guide prophylactic antibiotic therapy and possible need for gut decontamination.

With the present sophistication of multivisceral harvesting techniques and graft acceptance the intestine can be transplanted with other organs such as the liver, stomach, duodenum, pancreas and colon. The graft type will depend on the individual evaluation focusing on functional integrity of the gut and the presence of pathology in the other abdominal organs. The

Table 11.2. Evaluation protocol for intestine and other abdominal organ transplants

Assessment of disease status

History and physical examination:
- Etiology of intestinal failure
- Previous surgeries
- Associated anomalies

Assessment of other organs

Radiology:
- Upper and lower GI barium studies
- Liver Ultrasound
- Chest roentgenogram

Absorption Studies:
- D-Xylose absorption test
- 72 hour fecal fat test

Routine Laboratory Data:
- Hemoglobin, leukocyte count and differential count
- Platelet count, prothrombin time, partial thromboplastin time
- Bilirubin, alkaline phosphatase, serum glutamic-pyruvic transaminase (SGPT), aspirate aminotransferase (AST)
- Protein electrophoresis
- Alpha fetoprotein
- Urinalysis
- Blood urea nitrogen (BUN), serum creatinine
- 24 hour creatinine clearance

Liver Biopsy (when indicated)

Assessment of nutritional status

Nutritional evaluation:
- Weight, height, triceps, skinfold, midarm circumference
- Transferrin, albumin, prealbumin serum amino acid, analysis
- Vitamins A, D, E, B_{12}, Thiamine
- Triglycerides

Specific transplant & infection work-up

Immunological Studies:
- Blood Type (ABO)
- Tissue typing
- Cross matching

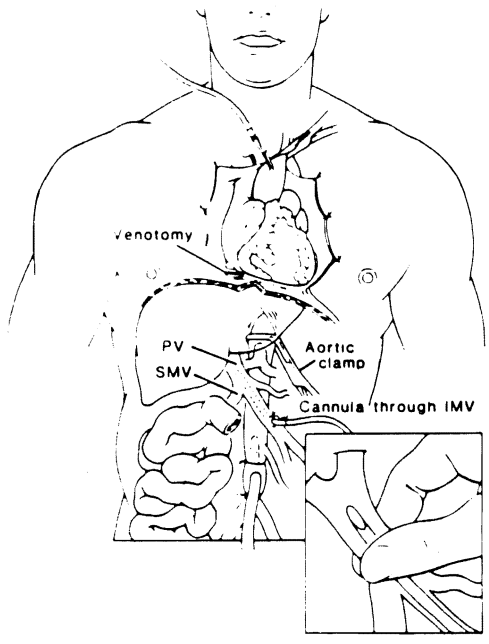
Investigations for Infection:
- Blood, urine, throat, feces, ascites culture: bacterial, fungal, viral
- Hepatitis screen
- Quantitative stool cultures

typical case is that of TPN cholestatic liver disease leading to end stage liver failure. Assessment of hepatic integrity is by standard liver transplant protocols (jaundice, synthetic function analysis, presence of portal hypertension). Patients with motility disorders involving the entire gastrointestinal tract are candidates for replacement of this entire system. Also, patients with end stage liver disease and concomitant thrombosis of the entire splanchnic venous system, a heretofore contraindication for liver transplantation alone, can now potentially be saved with a complete multivisceral transplant.

A thorough nutritional evaluation should be performed to better understand existing problems (obesity, vitamin deficiencies, eating disorders, etc) and correct them prior to transplantation. This includes baseline anthropometrics and laboratory data. A detailed summary is provided in Table 11.2.

THE DONOR OPERATION

All referrals for potential liver donation are also considered for possible small intestinal donation. The donor is usually of similar or smaller size than the recipient, and the ABO blood group should be identical; the HLA matching is random. Adequacy of the intestine is assessed by the donor team at the time of surgery. Details of the technique and donor preparation are as outlined in Figure 11.1. Mechanical preparation of the intestine is not performed prior to the donor operation.



Intestinal Decontamination
(Donor and Recipient)

	< Than 5 Years	5-12 Years	>12 Years
Amphotericin B	100 mg	250 mg	500 mg
Tobramycin	10 mg	40 mg	80 mg
Polymycin E	25 mg	50 mg	100 Mg

Systemic Antibiotics*

Cefotaxime - 25 mg kg dose q 8 hrs IV
Ampicillin - 25 mg kg dose q 6 hrs IV

*If the recipient has had recent bacterial or fungal infections these infectious agents should be covered in the prophylactic regimen

Fig. 11.1. The multivisceral harvest should allow for flexibility not only for the abdominal procedure but also for the thoracic organ procurement. Separate infusion of preservation fluid (inset) allows for complete blanching of the liver graft. Intestinal decontamination is begun on the donor at the time of acceptance, and continued in the recipient for a period of 4 weeks. Reprinted with permission from Starzl, TE. The many faces of multivisceral transplantation. Surg, Gynecol Obestet 1991; 172:335-344. ©JACS

The configuration of the organs to be harvested is usually designated after recipient evaluation, however some patients present the potential for unperceived operative findings. Therefore the procurement procedure should remain flexible, allowing for any final dissection to be done at the back table. The graft may consist of the full multivisceral cluster (liver, stomach, duodenum, pancreas, small bowel, and colon), or any combination that may be needed.[14] In most cases a clear limitation of the organs is known prior to transplant. The recovery time is approximately 4 hours.

Harvesting of the multivisceral graft requires encirclement of the proximal aorta near the diaphragm for later cross clamping, and the distal aorta below the origin of the inferior mesenteric artery for insertion of the canula needed for the infusion of the cold preservation solution (University of Wisconsin solution). When only a liver/small bowel graft is required a standard hilar dissection similar to that used for an isolated liver graft is performed.[15] The ascending and transverse colon are mobilized to isolate the small intestine which is divided with a stapler at the ligament of Treitz and just proximal to the ileocecal valve. Exposure of the portal and superior mesenteric veins is accomplished by dividing the pancreas immediately over these vessels and ligating all branches from it. After clamping of the proximal aorta in situ arterial perfusion is accomplished via the aortic cannula and the venous bed is decompressed using a suprahepatic caval venotomy. The liver can also be perfused separately through a cannula inserted into the superior mesenteric vein or the splenic vein. Back table irrigation of the intestinal lumen is not necessary in small bowel or liver/small bowel transplantation and is only required when the colon is included in the graft. Manipulation of the graft lymphoreticular tissue (ALG, OKT3, or irradiation) is not performed. In situations where only a small bowel graft is required the liver may be separated from the graft in situ after perfusion, or at the back table.[16]

THE RECIPIENT OPERATION

Once the donor team confirms adequacy of the donor organs the recipient is brought to the operating room for exploration. This usually requires hours of careful dissection through adhesions, focusing on the status of the liver and the preservation of remaining bowel. The final decision as to the needs of the patient in terms of organs can be made at this time. If the liver is to be removed the hepatic hilus is exposed, and the liver is devascularized by ligating the hepatic arterial branches. The common bile duct is ligated and the portal vein is exposed. A portacaval shunt is performed to allow for decompression of the remaining splanchnic organs (stomach, duodenum, pancreas, spleen).[17] In a recipient of a multivisceral graft this is not required since all of the native organs are removed.

Removal of the liver can be accomplished with removal of the retrohepatic vena cava (as for a standard orthotopic liver transplant) or in a "piggy back" fashion (preserving the retrohepatic vena cava).[18] Most patients with intestinal failure have had previous resections and we attempt to preserve as much normal residual small bowel and colon as possible. In patients with malabsorptive or intestinal pseudoobstructive syndromes all of the small intestine and colon are removed.

Revascularization of the donor multivisceral or liver/small bowel graft is accomplished by anastomosing the carrel patch containing the celiac and

superior mesenteric arteries to the recipient infrarenal aorta. An interposition graft of donor thoracic or abdominal aorta may be required. Venous drainage of the graft is into the hepatic veins of the recipient or by replacement of the retrohepatic vena cava. The portacaval shunt may remain permanently, or it can be taken down and a recipient portal vein to donor portal vein anastomosis performed. This provides drainage of important hepatotrophic factors from the native pancreas into the hepatic graft. Venous drainage of the isolated small bowel graft can be into the native superior mesenteric vein, junction of the splenic vein/mesenteric vein below the pancreas, portal vein at the level of the hepatic hilus, or inferior vena cava.[19]

The venous drainage clamps are removed only after complete perfusion of the organs, allowing bleeding to occur from the superior mesenteric vein (isolated small bowel graft) or from the infrahepatic vena cava (liver/small bowel or multivisceral graft). Reconstruction of the gastrointestinal tract is performed using conventional techniques. A proximal tube jejunostomy is performed to drain the proximal intestine, and can be used subsequently for enteral nutrition. Biliary reconstruction is required only in the liver/small bowel recipients and is performed to the most proximal end of the transplanted jejunum. Figure 11.2 outlines the basic procedures described above. The potential to transplant the entire gastrointestinal tract without the liver (stomach, duodenum, pancreas, small bowel and colon) has already been realized recently in a patient with multiple familial polyposis, the details of which however will not be described in this report.

IMMUNOSUPPRESSION

FK506 (0.15–0.2 mg/kg/day) is given by continuous intravenous infusion immediately after graft revascularization, targeting levels at between 2 and 3 ng/ml. Oral FK506 is started once intestinal motility is present and integrity of the intestinal anastomosis' is confirmed by contrast barium studies. Since FK506 absorption is independent of biliary enterohepatic circulation, maintenance of adequate levels on oral dosage alone is possible early in the postoperative course.[20] One gram of intravenous Hydrocortisone (children) or methylprednisolone (adults) is given intraoperatively. A steroid taper of methylprednisolone is started at a dose of 100 mg (children) or 200 mg (adults) and reduced over a period of 5 days to 10 mg (children) or 20 mg (adults) per day. Prostaglandin E_1 (Prostin) is administered at 0.003 to 0.009 micrograms/kg/minute intraoperatively and then continued for 5 days. This is given less for its immunosuppressive properties than for the beneficial effect upon FK506 nephrotoxicity.[21]

Graft rejection (liver and or small bowel) is treated initially with steroid therapy (intravenous hydrocortisone or methylprednisolone) as a bolus alone in cases of mild rejection, and with a steroid taper in cases of moderate to severe rejection. Optimization of FK506 trough levels should be performed by either increasing the baseline oral FK506 dose or using supplemental intravenous FK506. Rejection of the small bowel can alter FK506 absorption. The use of OKT3 is the next line of therapy when rejection has progressed on a steroid taper, however, this should be considered earlier if there is evidence of impending mucosal exfoliation (Fig. 11.3). Azathioprine is used to supplement baseline immunosuppression in cases of recurrent rejection, and where reduction of the FK506 dose is necessary because of nephrotoxicity.

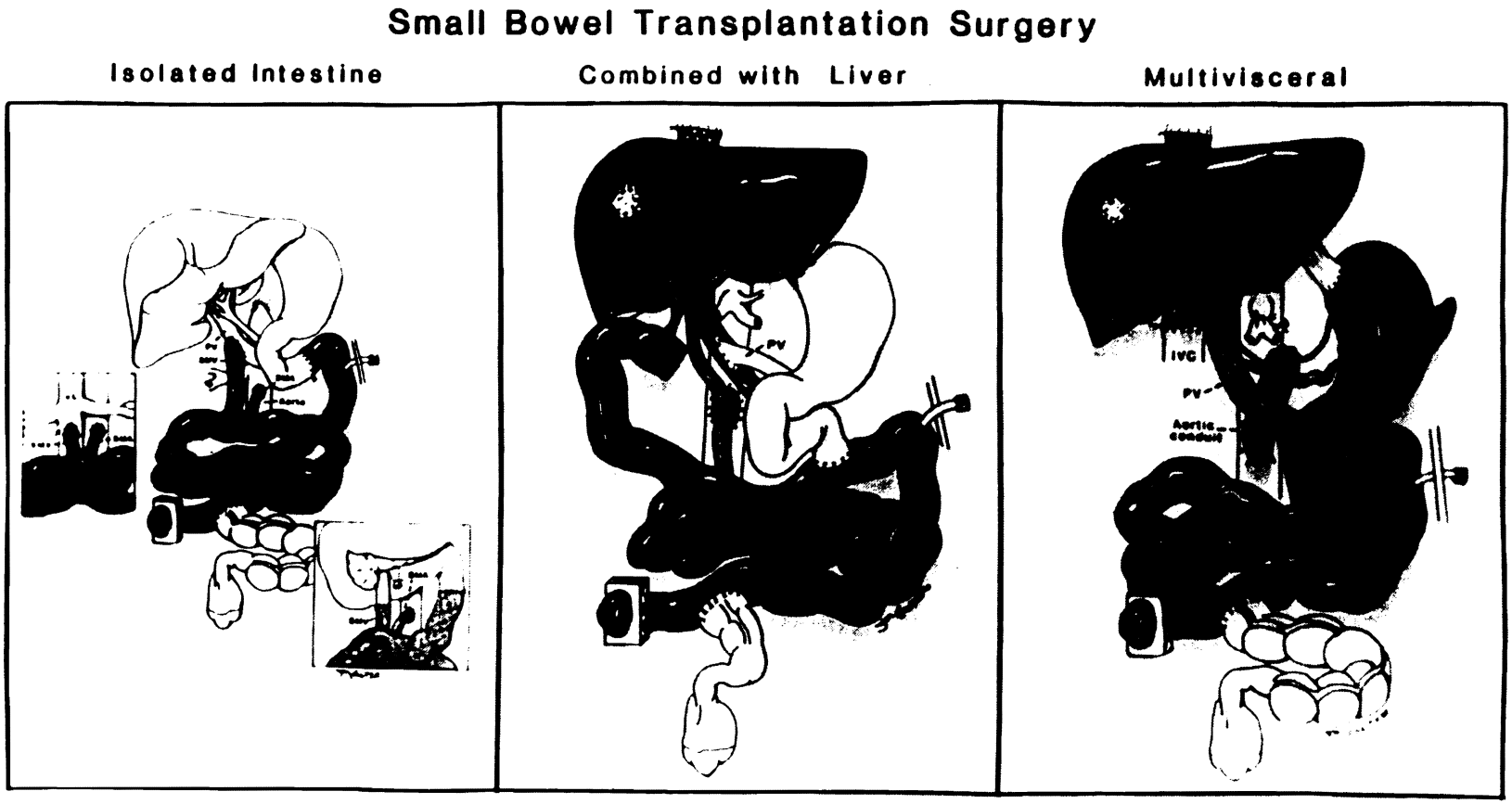


Fig. 11.2. The three basic operations performed on the 34 recipients here reported. The last 4 patients have also received the colon. Reprinted with permission from Todo S. Intestinal transplantation in composite visceral grafts or alone. Annals Surg 1992. © J. B. Lippincott Co.

Long term immunosuppressive management has entailed reduction of FK506 dose (independent of the level), and stopping steroid therapy if the patient is clinically well and with a normally functioning graft. Although cocktail therapy is used for induction, most pediatric patients can be managed eventually by monotherapy with FK506.

POSTOPERATIVE CARE AND RESULTS

The results reported herein pertain to 34 patients who received intestinal transplants. There were 18 female and 16 male patients, with ages ranging between 6 months and 50 years. Twenty patients had combined liver/intestine transplants, 10 patients had isolated intestine transplants, and 4 patients had multivisceral transplants. The followup time ranged between 5 months and 3 years. The specifics of this patient population with their outcome is detailed in Table 11.3.

Patients receiving a combined liver/small bowel graft are usually in significant liver failure and demand the same level of intensive care as a liver transplant recipient. They usually require a more prolonged period of ventilatory support and consequently an extended intensive care unit stay.

Broad spectrum intravenous antibiotics are given to the recipient for a period of 5 days postoperatively. If there is a history of nosocomial infections just prior to transplant (bacterial and fungal), appropriate prophylaxis should be given. Assessment of pulmonary status, infection surveillance, liver graft function, and general preservation of homeostasis is as per routine post liver transplant protocols.

Monitoring of the intestinal graft focuses on multiple daily clinical evaluations, noting the character of the intestinal graft stoma for texture,

Clinical SBTX
Treatment of Rejection

Histological Grade	Treatment
Mild	None
	FK 506, increase
	Steroids, bolus
Moderate	FK 506, increase
	Steroids, recycle
Severe	FK 506, increase
	Steroids, bolus/recycle
	OKT3

Fig. 11.3. The treatment of intestinal allograft rejection according to severity has been successful, however overlap and rapid evolution of severity is not uncommon.

Table 11.3. Postoperative results in small bowel transplantation

PT	AGE	SEX	DIAGNOSIS	GRAFT	SURVIVAL	TPN
1	3.2	F	NEC	SB/L	> 966	Free
2	4.3	M	Gastroschisis	SB/L	> 843	Free
3	2.8	M	Intestinal atresia	SB/L	385	Died/LP
4	0.6	F	Intestinal atresia	SB/L	23	Died/GVHD
5	1.1	F	Volvulus	SB/L	> 584	Free
6	1.7	F	Volvulus	SB/L	> 582	Free
7	2.5	F	Microvillus inclusion	SB	> 502	Free
8	1.3	M	Intestinal atresia	SB	> 447	Free
9	10.2	F	Pseudoobstruction	SB	> 375	Free
10	1.5	M	NEC	SB/L	70	Died/MOF
11	4.2	F	Gastroschisis	SB/L	> 279	Free
12	1.4	M	Gastroschisis	SB/L	29	Died/Sepsis
13	0.8	M	Microvillus Inclusion	SB/L	> 238	Free
14	0.5	M	Gastroschisis	SB/L	> 232	Free
15	4.0	F	Pseudoobstruction	MV	> 134	Free
16	3.6	M	NEC	SB/L	97	Died/Sepsis
17	0.9	F	Gastroschisis	SB/L	> 92	Free
18	15.5	M	Volvulus	SB/L	> 71	Free
19	31	M	Gunshot wound	SB	776	Died/Sepsis*
20	26	F	SMA thrombosis	SB/L	> 956	Free
21	21	M	Traffic accident	SB/L	> 573	Partial
22	32	M	CA & SMA thrombosis	MV	> 519	Partial
23	50	F	Crohn's disease	SB	> 444	Free
24	34	F	Desmoid tumor	SB	> 407	Total**
25	38	M	Crohn's disease	SB	376	Died/Sepsis
26	22	F	Crohn's disease	SB	> 369	Free
27	25	M	Crohn's disease	SB/L	> 353	Free
28	29	F	Desmoid tumor	SB/L	> 295	Free
29	24	M	CA & SMA thrombosis	MV	> 292	Free
30	20	F	Traffic accident	SB	> 282	Free
31	32	F	CA & SMA thrombosis	MV	> 217	Free
32	19	M	Traffic accident	SB/L	> 214	Free
33	44	F	SMA thrombosis	SB/L	> 190	Free
34	37	F	Familial polyposis	SB	> 109	Free

* Retransplantation at 22 months ** Graft removed at 8 months

color, and friability. The stomal output is assessed for volume, consistency, and the presence of reducing substances as tested by pH and clinitest (reflecting possible rejection, viral/bacterial infections, or malabsorption), and the presence of blood (seen with rejection or infections). Endoscopic evaluations are performed through the transplant ileostomy and also with upper endoscopy to assess the proximal transplanted bowel. This is performed twice a week for the first month and whenever clinically indicated thereafter; mucosal biopsies should be a minimum of 5 samples.[22]

Intestinal allograft rejection may be asymptomatic, but generally presents with a combination of fever, abdominal pain and distention, nausea or vomiting, and a sudden increase in stomal output. Severe rejection can progress to graft ileus and absence of stomal output, as well as intestinal

bleeding from mucosal sloughing. Translocation of bacteria through the injured epithelium can precipitate a septic shock picture. This represents one of the few situations in transplantation where treatment entails aggressive infectious and immunologic work-up focusing treatment on the specific infectious etiology, but more importantly additional immunosuppression for the treatment of graft rejection. Intestinal decontamination is continued (or reinstituted) during episodes of rejection.

Graft Rejection

Acute rejection of the intestinal graft is suspected by endoscopic observations of mucosal edema, erythema, and friability as evidenced by increased bleeding upon biopsy. The mucosa can loose its fine velvety appearance and go on to become ischemic or dusky, with focal ulcerations. Severe rejection can present a granular mucosal pattern with diffuse ulcerations, or sloughing of large areas of mucosa, accompanied by a loss of peristalsis.

The histologic criteria for the diagnosis of acute intestinal allograft rejection includes edema of the lamina propria with mononuclear cell infiltrates (small and/or blastic lymphocytes), villous blunting and cryptitis. Neutrophils, eosinophils, and macrophages may be seen traversing the muscularis mucosa.[23] The degree of epithelial cell necrosis was variable according to the severity of rejection; necrosis and regeneration are necessary components for the diagnosis of rejection. Complete mucosal and crypt destruction are seen in patients with severe rejection. The mucosal surface can be replaced by granulation tissue and inflammatory pseudomembranes.

Chronic rejection has been seen in two patients after severe acute rejection, and is characterized by villous blunting, focal ulcerations, and epithelial metaplasia. Clinically there is chronic weight loss, with intermittent diarrhea, fever and blood loss. Mesenteric angiography in one such patient has revealed segmental narrowing of the mesenteric arteries.[24]

The incidence of acute intestinal allograft rejection has been reported to be 80% in the isolated small bowel recipients, and 77% in the liver/small bowel recipients; the incidence of acute liver allograft rejection in the liver/small bowel recipients was 55%.[23]

Nutritional Support

Nutritional support was accomplished initially by using standard TPN solutions which was tapered gradually as oral or enteral feedings (via the jejunal tube) were tolerated. Feeding was started after upper gastrointestinal barium studies confirmed a satisfactory intestinal anastomosis and good motility. Enteral feeding is the rule after intestinal transplantation since most patients do not voluntarily ingest an adequate amount of calories early on. This has been particularly important in pediatric recipients since they characteristically have poor or no oral intake. The specifics of this eating disorder is still under evaluation, however, factors such as never having been fed before (and thus never learning), a hyper-gag reflex from lack of eating, and the association of a noxious feeling with the act of eating are important factors. Tube feedings were commenced using Peptamen, which is an isotonic dipeptide formula containing medium chain triglycerides and glutamine. Peptamen was later converted in children to Complete B which is a lactose gluten free diet containing dietary fibers to promote normalization of intestinal motility and function.

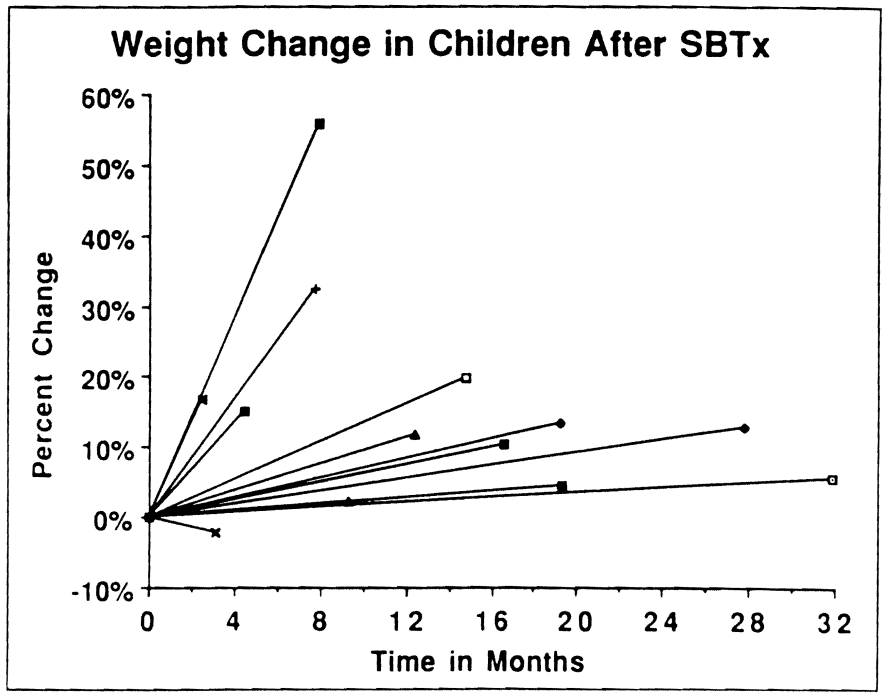
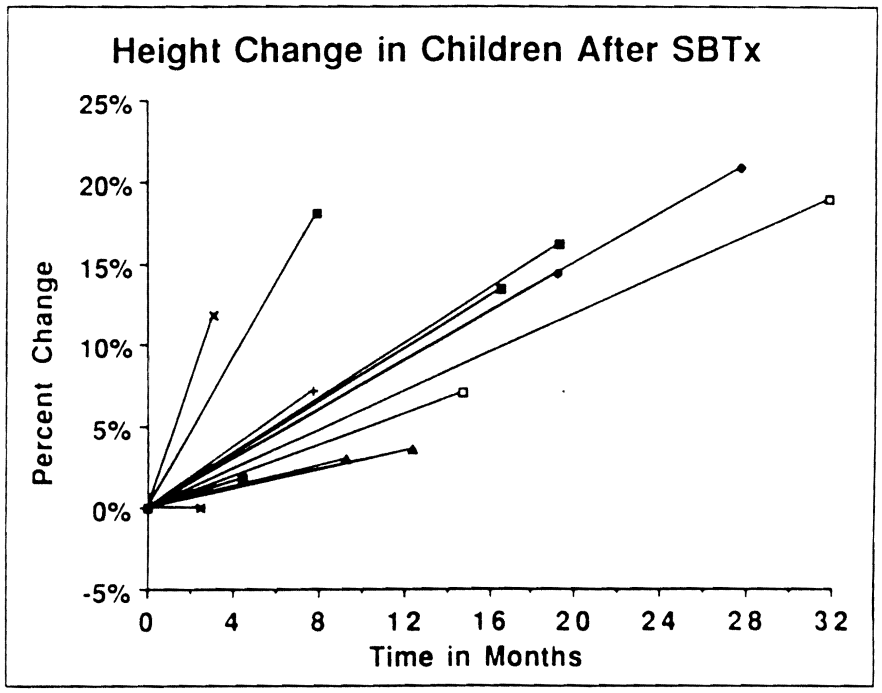


Fig. 11.4A

Fig. 11.4B



Figs. 11.4 A - 11.4B. Weight and height has been consistently good in the pediatric patients after intestinal transplantation, the percentile increases in height are a better index of patient well being.

Continuous feedings can be given by either a nasogastric or nasoduodenal tube, gastrostomy tube (with extension tube past the pylorus), or jejunostomy tube (into the transplanted bowel). The stomal output is assessed for volume pH and the presence of reducing substances as well as for quantitative bacterial cultures. Recipients of liver/small bowel grafts usually require a mean of 60 days to become independent of TPN, whereas isolated small bowel allograft recipients have become independent of TPN 30 days posttransplant. Weight and height increases between transplant and latest followup have been consistently good in the children (Figs 11.4A and 11.4B), however some adults have lost weight after transplantation (Fig. 11.5). This has been due to a lesser adaptability to oral intake in some multivisceral recipients, and also to the presence of mild to moderate obesity pretransplant in others.[25]

Function has been assessed through the absorption of D-xylose and FK506, as well as the quantitation of fat in the stool. Most patients present satisfactory absorption curves for D-xylose, with values ranging between 15 to 20 ng/dl within the first postoperative month. Absorption has increased over time as the transplanted bowel recovered motility and enteral feedings were advanced. Abnormal results were associated with increased stomal outputs and dysmotility; this has always prompted an aggressive search for rejection.

Though the excretion of fat in the stool has been abnormal in almost all patients, there have been no clinical implications to this phenomenon.

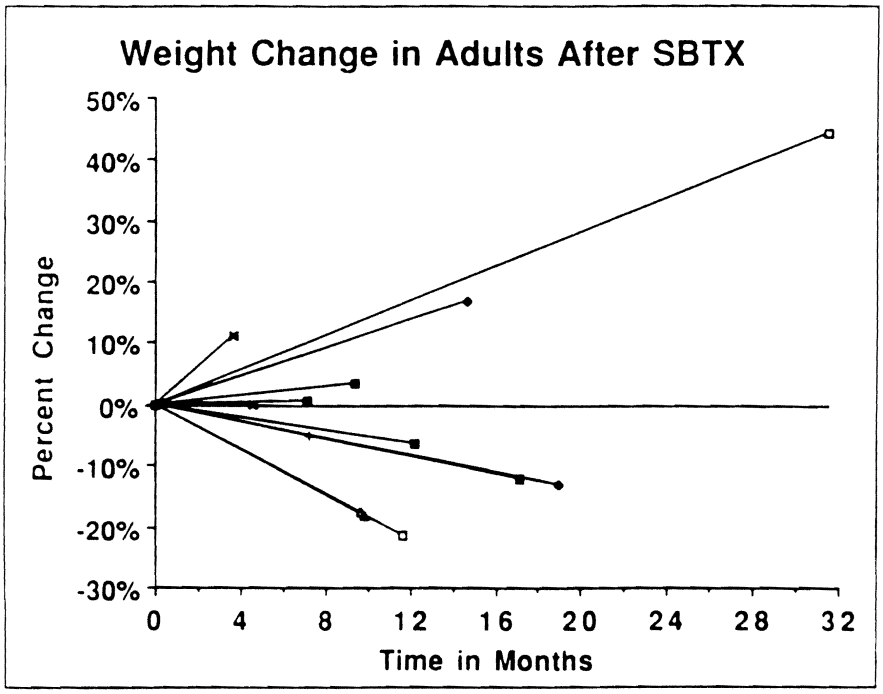


Fig. 11.5. Percentile weight changes in adults have varied, since there is a higher incidence of overweight patients on TPN. Also, multivisceral graft recipients have had a harder time maintaining weight.

Fat can be provided as mean chain triglycerides in the enteral feeds and thus not require intact lymphatics. The absorption of FK506 was assessed by the maintenance of satisfactory blood trough levels off intravenous therapy. This occurred at a mean of about 28 days postoperatively. Recipients of multivisceral transplants tended to remain on IV therapy longer, however, the difference is not significant. The dose required to maintain adequate FK506 trough levels has been similar to the standard liver transplant recipient. Total protein and albumin levels have improved in all surviving recipients.

Radiologic evaluations were valuable in assessing the mucosal pattern and motility (Fig. 11.6A). Some evidence of mucosal edema can be seen in the presence of intestinal graft rejection. Severe rejection with exfoliation of the mucosa will ablate the normal mucosal pattern and be visualized as segments of "tubulized" intestine with intermittent strictures (Fig. 11.6B). Transit times vary between 30 minutes to 5 hours with a mean of 2 hours in intestinal allografts that were recovering satisfactorily. Dysmotility either as rapid transit or ileus has been seen with rejection. Abnormalities of the

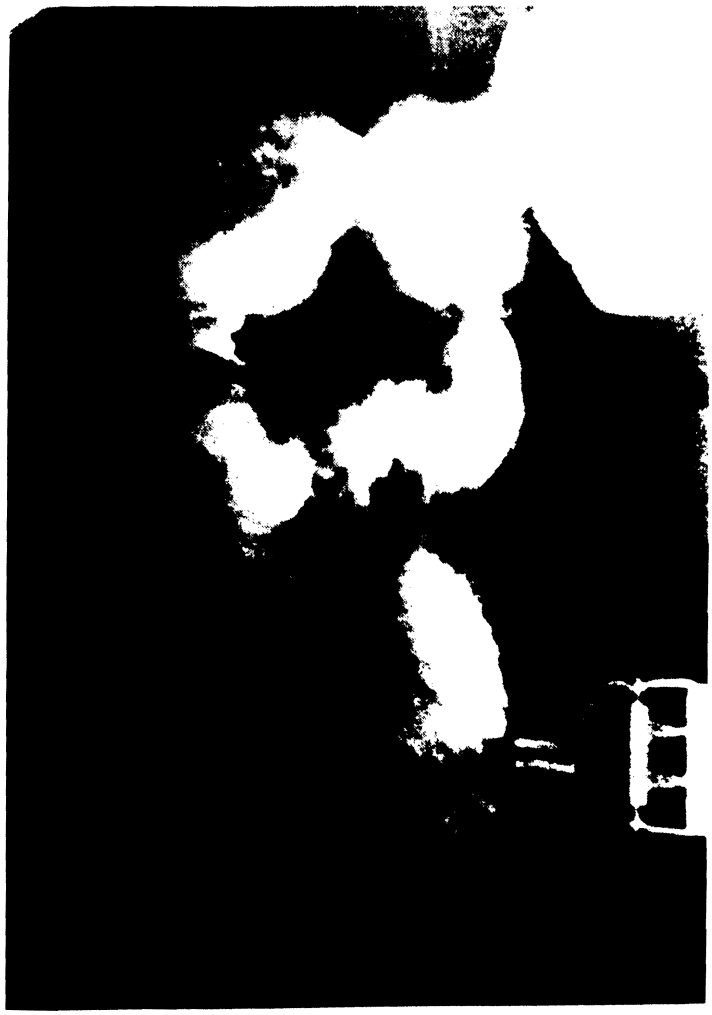


Fig. 11.6A. A normal appearing mucosal pattern in an intestinal allograft.

native (recipient) gastrointestinal tract (stomach, duodenum) can be seen early on, and resolve over time. This may require a more prolonged period of tube alimentation.

Complications

Patients who undergo the combined liver/small bowel transplant require longer intensive care unit stay as well as a longer total hospital stay. Candidates for a liver/small bowel graft are generally in end stage liver disease with many of its associated morbidities. Infections and technical complications have occurred almost exclusively in the recipients of the liver/small bowel graft.

Infections have included bacterial, fungal and viral organisms. These may manifest as primary pulmonary, peritoneal, or venous catheter infections, or be part of a translocation phenomenon in a graft damaged by rejection.[26] Most deaths which have occurred have been related to infections. One recipient of 2 isolated intestinal grafts died of infectious complications after retransplantation. One child died following a biliary leak and sepsis; two children suffered disruption of the proximal intestinal anastomosis and sepsis. One of these children also suffered hepatic artery thrombosis with fulminant hepatic gangrene, required a new liver graft, and eventually dyed of Influenza pneumonia; the other child presented a baseline immunodeficiency disorder and developed Pneumocystis Carrinii pneumonia and probable graft versus host disease.

Three patients have died of complications related to the treatment of their intestinal allograft rejection. One patient previously stated was an isolated small bowel recipient who died of infection after retransplant. Another isolated small bowel recipient died of candida sepsis after salvage for a severe exfoliative type intestinal allograft rejection. One pediatric recipient of a

Fig. 11.6B. Intestinal allograft after severe exfoliative type rejection showing a "tubulized" pattern and strictures.

liver/small bowel graft suffered severe rejection of the intestine requiring OKT3, and then went on to develop severe adenovirus hepatitis of the liver graft. Though the intestinal portion of the allograft recovered, the severity of liver injury from the adenovirus infection required a combined liver/small bowel retransplantation. The child then went on to severely reject the intestinal allograft and did not respond to OKT3. He died of enterococcal sepsis and intestinal bleeding.

Viral infections of most significance have included adenovirus and the Epstein-Barr virus in children and cytomegalovirus in the adults. One patient developed an unspecified viral encephalitis which required stopping the immunosuppression, then developed rejection of the intestinal allograft which required removal.

Posttransplant lymphoproliferative disease (PTLD) has been seen in 3 patients, all recipients of liver/small bowel grafts. These patients presented with multifocal disease and were treated with intravenous acyclovir or ganciclovir, as well as withholding of immunosuppression. One patient died of this complication. Two patients are presently recovering, however rejection of the intestinal allograft has occurred during the recovery phase, and has been treated successfully with steroids and reinstitution of FK506 immunosuppression.

CONCLUSION

Transplantation of the intestine has evolved into a feasible operation with satisfactory results. Overall patient survival is 79%, and overall graft survival is 73%. These survivors are free of TPN; the majority are home. Though this endeavor has required significant human and economic resources, the encouraging results justify further clinical trials.

REFERENCES

1. Wilmore DW, Groff DB, Bishop HC et al. Total parenteral nutrition in infants with catastrophic gastrointestinal anomalies. J Ped Surg 1969; 4(2):181-189.
2. Oasis, Home Nutrition Support Patient Registry Annual Report—1989 Data. The Oley Foundation Albany, NY 1991.
3. Howard L, Heaphey L, Fleming RC et al. Four years of North American registry home parenteral nutrition outcome data and their implications for patient management. J Paren Ent Nutr 1991; 15(4):384-393.
4. Lillehei RC, Goott B, Miller FA. The physiologic response of the small bowel of the dog to ischemia including prolonged in vitro preservation of the bowel with successful replacement and survival. Ann Surg 1959; 150:543.
5. Starzl TE, Kaupp Jr HA. Mass homotransplantation of abdominal organs in dogs. Surg Forum 1960; 11:28-30.
6. Grant D. Intestinal transplantation: Current status. Transplant Proc 1989; 21:2869-2871.
7. Starzl TE, Rowe M, Todo S et al. Transplantation of multiple abdominal viscera. JAMA 1989; 261:1449-1457.
8. Grant D, Wall W, Mimeault R et al. Successful small-bowel/liver transplantation. Lancet, 1990; 335:181-184.
9. Goulet OK, Revillon Y, Jan D et al. Small-bowel transplantation in children. Transplant Proc 1990; 22:2499.

10. Deltz E, Schroeder P, Gebhardt H et al. Successful clinical small bowel transplantation report of a case. Clin Transplant 1989; 3:89.
11. Grosfeld J, Rescoria FJ West KW. Short bowel syndrome in infancy and childhood: analysis of survival in 60 patients. Am J Surgery 1986; 151:41-46.
12. Wilmore DW. Factors correlating with a successful outcome following extensive intestinal resection in newborn infants. J Pediatric 1972; 80:88-95.
13. Casella JF, Lewis JH, Bontempo FA et al. Successful treatment for homozygous protein C deficiency by hepatic transplantation. Lancet 1988; 435-438.
14. Starzl TE, Todo S, Tzakis A et al. The many faces of multivisceral transplantation. Surg Gynecol Obstet (lead article) 1991; 172:335-344.
15. Starzl TE, Hakala TR, Shaw Jr BW et al. A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 1984; 158:223-230.
16. Casavilla A, Selby R, Abu-Elmagd K et al. Logistic and technique for combined hepatic-intestinal retrieval. Ann Surg 1992; 216:605-609.
17. Tzakis AG, Reyes J, Nour B et al. Temporary end-to-side portocaval shunt in orthotopic liver transplantation. Surg Gynecol Obstet 1993; 176:180-182.
18. Tzakis A, Todo S, Starzl TE. Piggyback orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg 1989; 210:699-652.
19. Tzakis AG, Todo S, Reyes J et al. Piggyback orthotopic intestinal transplantation. Surg Gynecol Obstet 1993; 176(3):297-298.
20. Venkataramanan R, Jain A, Warty VW et al. Pharmacokinetics of FK 506 following oral administration: A comparison of FK 506 and cyclosporine. Transplant Proc 1991; 23:931-933.
21. Takaya S, Iwaki Y, Starzl TE. Liver transplantation in positive cytotoxic crossmatch cases using FK 506, high dose steroids, and prostaglandin E_1. Transplantation 1992; 54:927-929.
22. Abu-Elmagd K, Tzakis A, Todo S et al. Monitoring and treatment of intestinal allograft rejection in humans. Transplant Proc 1993; 25:1202-1203.
23. Nakamura K, Abu-Elmagd K, Todo S et al. Pathology of human small intestinal transplantation: Alone or in combination with the liver. Gastroenterology (Submitted).
24. Abu-Elmagd KM, Todo S, Tzakis A et al. An isolated complete intestinal transplantation in an adult: A complicated postoperative course. Transplantation Science 1992; 2:23-27.
25. Reyes J, Tzakis AG, Todo S et al. Nutritional management of intestinal transplant recipients. Transplant Proc 1993; 25(1):1200-1201.
26. Reyes J, Abu-Elmagd K, Tzakis A et al. Infectious complications after human small bowel transplantation. Transplant Proc 1992; 24:1249-1250.