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Post-operative care of small bowel transplant recipients

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A clinical trial of intestinal transplantation was initiated at the University of Pittsburgh in May of 1990. A total of 34 patients received either a combined liver/small bowel graft (n=20), an isolated small bowel graft (n=10), or a multivisceral graft (n=4). Induction as well as maintenance immunosuppression was with FK506 and steroids. Sixteen patients were male and 18 were female, with ages ranging between 4 months and 50 years. There were 7 deaths, which were attributed to graft-versus-host disease (n=1) post transplant lymphoproliferative disease (n=1), and sepsis (n=5). Transplantation of the intestine has evolved into a feasible operation with satisfactory results. Overall patient survival of 79%, and overall graft survival of 73% has been achieved. These survivors are free of TPN; the majority are home. Though this endeavour has required significant human and economic resources, the encouraging results justify further clinical trials.

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Prior to the introduction of total parenteral nutrition (TPN), the prognosis of patients with intestinal failure (short gut syndrome) was dependent upon adaptation of the remaining bowel [1]. The use of TPN has improved the long-term outcome, [2] (65% - 80% 3 year survival) and is the accepted therapeutic modality. Complications from this therapy, however, are frequent. Liver failure secondary to TPN, and venous access complications (infection and thrombosis) are the most incapacitating. The care of these patients is perhaps one of the most difficult challenges in the field of transplantation today.

Transplantation of the small bowel was first reported experimentally as an isolated organ graft by Lillehei in 1959 [3]. One year later Starzl included the small bowel as part of a multivisceral graft in dogs [4]. The clinical applicability of small bowel transplantation did not, however, enjoy the rapid expansion experienced by liver and kidney transplantation during the same period after the introduction of cyclosporin A. This was attributed to a high incidence of graft loss from rejection, infections, and technical complications [5].

We report here the experience accumulated with intestinal transplantation in 34 patients transplanted at the University of Pittsburgh between May 1990 to January 1993. Highlights of the evaluation process, donor and recipient operation, and post-operative care will be reviewed.

PRE-TRANSPLANT CONSIDERATIONS

The indications for intestinal transplantation at the University of Pittsburgh are listed in TABLE 1. Hepatic integrity is assessed by standard liver transplant protocols looking for jaundice, degree of synthetic dysfunction and the presence of portal hypertension. Of the 34 patients reported in this series, 22 presented with liver dysfunction as evidenced by total bilirubin levels ranging between 2.3 and 50 mg/dl and signs of portal hypertension. The severity of fibrotic changes on liver biopsy has also been helpful when associated with hepatosplenomegaly, ascites, and esophageal varices. These patients are candidates for replacement of the liver and transplantation of the small bowel.

Necrotizing Enterocolitis	Malrotation
Gastroschisis	Crohn's Disease
Volvulus	Thrombolytic Disorder
Pseudo-obstruction	Trauma
Hirschsprung's Disease	Radiation Enteritis
Intestinal Atresia	Desmoid Tumor
Microvillus Inclusion Disease	Familial Polyposis

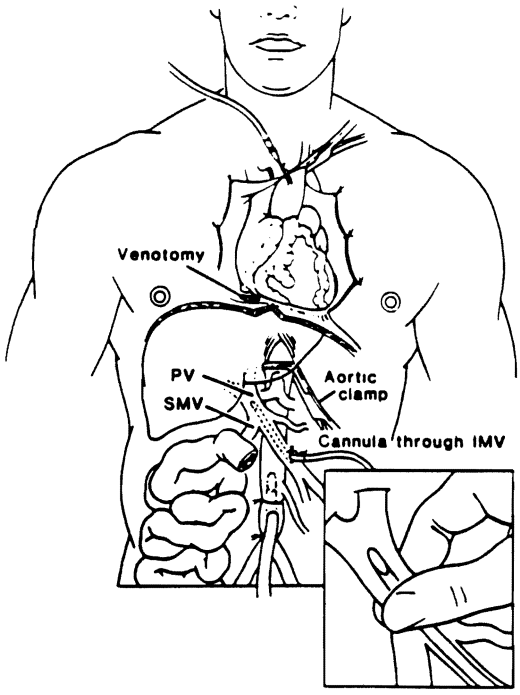
TABLE 1. Indications for small intestinal transplantation.

Due to the availability of alternative therapy (TPN), candidates selected for isolated transplantation of the small bowel have been limited to those patients with intestinal failure who are totally dependent on TPN for their survival, but, however are presenting complications of this therapy. Evidence of persistent liver function test abnormalities (no synthetic dysfunction), a history of multiple septic episodes from catheter infection, and progressive thrombosis of access sites should all be considered.

The present sophistication of multivisceral organ harvesting and graft acceptance can provide for the transplantation of organs such as the liver, stomach, duodenum, small bowel, pancreas, and colon. The graft composite will vary according to the anatomic and functional integrity of the recipient's remaining gastrointestinal tract, and the presence of abnormalities in other organs.

THE OPERATION

The donor is always of the same ABO blood group as the recipient and is usually of similar or smaller size. There is no functional assessment of the intestine prior to donation: a history of normal intestinal function in a referral for potential liver donation is sufficient. Highlights of the technique and donor preparation are



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

FIGURE 1. The multivisceral harvest should allow 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. (By permission of SURGERY, Gynecology & Obstetrics, Starzl TE et al. [4]).

as outlined in FIGURE 1, and the reader is referred to the bibliography for a more detailed description [4,5].

The early stages of the recipient operation focus on the status of the native liver, and the preservation of the remaining bowel. The final decision as to the needs of the patient as far as organs are concerned, is made at this time. If the liver is to be excised it 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) [6]. A portacaval shunt is performed for decompression of the remaining splanchnic organs (stomach, duodenum, pancreas, spleen)[7]. This is not required in recipients of a complete multivisceral or isolated small bowel graft.

Vascular inflow to the multivisceral or liver small bowel graft uses a "carrel patch" containing the coeliac and superior mesenteric arteries, which is anastomosed to the recipient infrarenal aorta (with or without an interposition graft of donor thoracic or abdominal aorta). The venous drainage of the graft is into the hepatic veins of the recipient or by replacement of the retrohepatic vena cava. The portacaval shunt can be taken down and a recipient portal vein to donor portal vein anastomosis performed. In the isolated small bowel graft the superior mesenteric artery is anastomosed directly to the infrarenal aorta. The venous drainage of the isolated small bowel graft can be into the native superior mesenteric vein, the portal vein at the level of the hepatic hilus, or inferior vena cava [8].

The graft is reperfused 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). This allows for drainage of the potassium rich preservation solution. The gastrointestinal tract is reconstructed with a proximal and distal anastomosis to the native intestine in a standard fashion. A proximal tube jejunostomy and a gastrostomy is performed to drain the proximal bowel. Biliary reconstruction is required only in recipients of a liver/small bowel graft, and is performed to the most proximal end of the transplanted jejunum (FIGURE 2).

IMMUNOSUPPRESSION

One gram of intravenous hydrocortisone (children) or methylprednisolone (adults) is given immediately after graft reperfusion. FK506* (0.15 - 0.2 mg/kg/day) is then begun by continuous intravenous infusion, targeting levels at between 2 and 3 ng/ml. Oral FK506 is initiated once intestinal motility is present. 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. Prostoglandin E_1 (Prostin) is administered at 0.003 to 0.009 µ/kg/min intraoperatively and then continued for 5 days. This is given for the beneficial effect on FK506 nephrotoxicity [9]. Azathioprine is used to supplement baseline immunosuppression in cases of recurrent rejection or FK506 nephrotoxicity.

Although induction therapy requires multiple drugs, the long term management entails reduction of FK506 and stopping steroid therapy if the patient is clinically well. Most paediatric patients can be managed by monotherapy with FK506.

* FK506 is a novel new immunosuppressant which has similar actions to cyclosporin A and is currently undergoing extensive evaluation.

POST-OPERATIVE CARE

Recipients of a combined liver/small bowel graft or a complete multivisceral graft are commonly in liver failure, therefore the care with respect to pulmonary function, infection surveillance, and liver graft function is similar to a routine post liver transplant recipient. The intensive care unit stay and total hospital stay however, are significantly longer. Early on there is a significant capillary leak, with "third spacing" of fluid into the interstitial tissues. Renal function may be impaired due to the extensive surgery, blood transfusion requirements, intraoperative

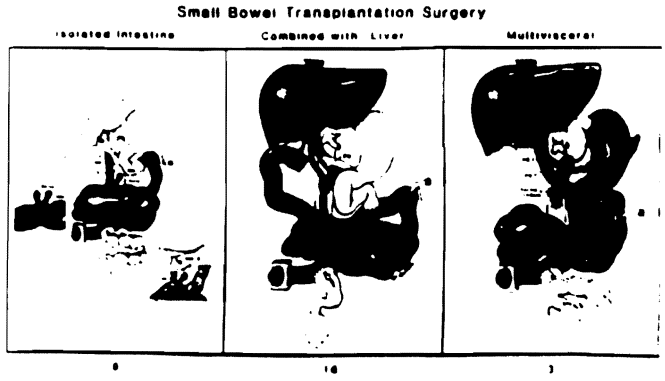


FIGURE 2. The three basic operations performed on the 34 recipients here reported.

Recipients of liver/small bowel grafts have usually required a mean of 60 days to become independent of TPN, whereas isolated small bowel graft recipients have become independent of TPN at approximately 30 days post-transplant. Weight and height increase between transplant and latest follow up have been consistently good in the children, however some adults have lost weight after transplantation (FIGURE 4). 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 pre-transplant in others [ ].

COMPLICATIONS

Graft dysfunction

Rarely, intestinal allograft rejection may be asymptomatic. More commonly a combination of fever, abdominal pain and distension, nausea and vomiting, and a sudden increase in stomal output occurs. The stoma may become oedematous, pale or erythematous, and friable. Gastrointestinal bleeding can be seen with passage of dark burgundy to tarry stools in cases of severe rejection in which there are ulcerations and or sloughing of the intestinal mucosa. Translocation of bacteria through the injured epithelium is common and can occur with bacteria and fungi. Intestinal decontamination must be instituted during these episodes [ ].

Endoscopically the transplanted intestinal mucosa loses its fine velvety appearance and may initially become ischaemic or dusky, with focal ulcerations. Severe rejection will present with increased erythema, friability, with a granular mucosal pattern and diffuse ulcerations. Loss of peristalsis is common.

Histologically there is oedema of the lamina propria with mononuclear cell infiltrates (small and/or blastic lymphocytes), villous blunting and cryptitis. Neurotrophils, eosinophils, and macrophages may be seen traversing the muscularis mucosa [ ]. The degree of epithelial cell necrosis varies with the severity of rejection. Complete mucosal and crypt destruction are seen in patients with severe rejection. The mucosal surface is replaced by granulation tissue and inflammatory pseudomembranes.

Chronic rejection has been seen in 2 patients after severe acute rejection. Clinically there is chronic weight loss with intermittent diarrhoea, fever, and bleeding. Histologically there is villous blunting, focal ulcerations, and epithelial metaplasia [ ].

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% [ ].

Graft rejection may be treated initially with bolus steroid therapy (intravenous hydrocortisone or methylprednisolone) in cases of mild rejection, and with a steroid taper in cases of moderate to severe rejection. The FK506 trough levels should be optimised by either the oral or intravenous routes. 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, or there is significant FK506 nephro or neurotoxicity.

** OKT3 is a murine monoclonal antibody directed against human T cells. It is used for induction of immunosuppression and treatment of severe rejection.

Post-operative haemorrhage

Intra-abdominal bleeding is a common complication since most patients have had many previous abdominal procedures which leave extensive raw peritoneal surfaces. If the recipient also has significant liver disease the coagulopathy and portal hypertension may make intraoperative bleeding difficult to control. The temporary portacaval shunt is a significant aid in the performance of haemostasis. Immediate postoperative bleeding is usually from a vascular anastomosis, abdominal wound, or retroperitoneal surfaces.

Biliary complications

Biliary leaks can occur only in recipients of the liver/small bowel graft. One such complication occurred in a paediatric recipient who presented leakage of biliary fluid through the abdominal wound, in a setting of candida peritonitis. The choledocojejunostomy was revised using a U-tube through the liver, however, the patient succumbed to infection 4 weeks later.

Vascular complications

Thrombosis of the hepatic artery has been seen in a paediatric recipient of a liver small bowel graft. The patient developed acute hepatic gangrene and required retransplantation of the hepatic component of the graft. The superior mesenteric artery and the intestinal component of the graft did not suffer thrombosis. The patient died of influenza B pneumonia 3 weeks later.

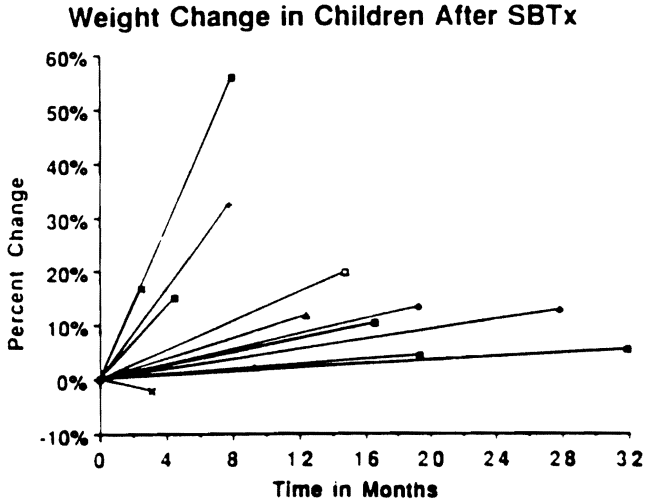


FIGURE 4A: Weight has been consistently good in the paediatric patients

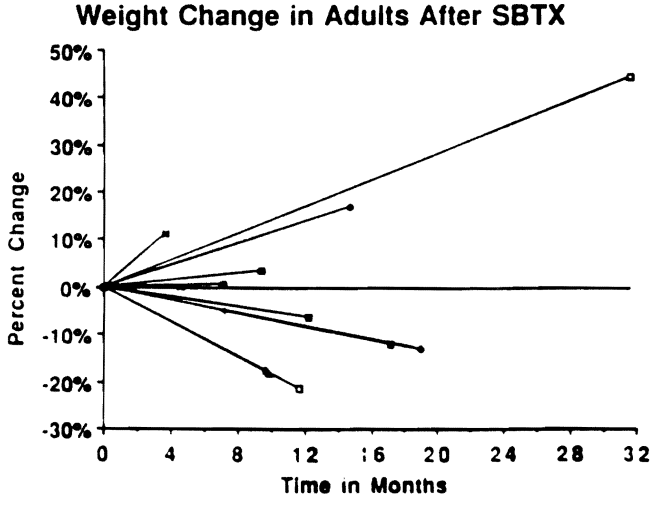


FIGURE 4B. Percentile weight changes in adults have varied, since there is a higher incidence of overweight on TPN. Also, multivisceral graft recipients have had a harder time maintaining weight.

FIGURE 3. Radiograph of intestinal allograft after severe exfoliative type rejection showing a "tubulised" pattern and strictures.

haemodynamic instability, and drug toxicities. Only one patient has required a kidney transplant postoperatively.

Ventilatory support is usually more prolonged in these patients. Muscle wasting and malnutrition, partial or complete paralysis of the right hemidiaphragm, and occasional discrepancies in donor/recipient size producing an increased intra-abdominal volume with compression of the thoracic cavity, are responsible factors. Four patients have required tracheostomies because of the need for prolonged ventilatory support.

Any history of recent nosocomial infections just prior to transplant should be addressed with appropriate specific antibiotics, otherwise broad spectrum intravenous antibiotic prophylaxis is acceptable and is given for a period of 5 days post-operatively. Intestinal decontamination in the recipient as illustrated in FIGURE 1 is performed for a period of 6 weeks, and during episodes of rejection.

Nutritional support is by standard TPN solutions which are tapered gradually as oral or enteral feedings (via gastric or jejunal tube) are advanced. Tube feedings are initiated using Peptamen, which is an isotonic dipeptide formula containing medium chain triglycerides and glutamine. This is later converted to Complete B which is a lactose gluten free diet containing dietary fibres to promote normalisation of intestinal motility and function. Most patients do not voluntarily eat adequate amounts early on. This has been particularly severe in paediatric recipients.

Assessment of small bowel function has been through the use of absorption studies of D-xylose, FK506, and the quantitation of fat in the stool. Most patients present satisfactory absorption curves for D-xylose within the first postoperative month, with absorption improving over time. Abnormal results should always prompt an aggressive search for rejection. The maintenance of satisfactory FK506 blood trough levels off intravenous therapy is used as the indicator of adequate absorption. This has occurred at a mean of 28 days post-transplant, and has tended to be longer in recipients of a multivisceral graft. The excretion of fat in the stool has been abnormal in almost all patients, however, there have been no clinical implications to this phenomenon.

Radiologic evaluations by standard barium gastrointestinal series are valuable in assessing mucosal pattern and motility. Intestinal graft rejection, when mild, can be suspected when there is evidence of mucosal oedema. Severe rejection, with exfoliation of the mucosa, will ablate the normal mucosal pattern and can be seen as segments of "tubulised" intestine and strictures (FIGURE 3).

Monitoring for intestinal graft rejection focuses on clinical evaluations and gross morphology of the intestine at the level of the stoma and at endoscopy. The stomal output is assessed for volume, consistency, and the presence of reducing substances, which can be seen in the event of rejection, bacterial overgrowth, or malabsorption. The presence of blood in the stool is always an ominous sign, and must be assumed to be rejection until proven otherwise. Endoscopic evaluations are performed routinely twice a week through the transplant ileostomy. Upper endoscopies are performed when indicated.

RESULTS

Thirty-four patients received intestinal transplants between May 1990 to January 1993. There were 16 male and 18 female patients, with ages ranging between 6 months to 50 years. Twenty patients had combined liver/small bowel transplants, 10 patients had isolated small bowel transplants and 4 patients had multivisceral transplants. The follow up time has ranged between 5 months and 3 years (TABLE 2).

INTESTINAL GRAFT RECIPIENTS
MAY 1990 - JANUARY 1993

AGE YEARS	SEX	DIAGNOSIS	GRAFT	SURVIVAL DAYS	TPN
3.2	F	Nec	SB/L	> 966	Free
4.3	M	Gastroschisis	SB/L	> 843	Free
2.8	M	Intestinal atresia	SB/L	385	Died/PTLD
0.6	F	Intestinal atresia	SB/L	23	Died/GVHD
1.1	F	Volvulus	SB/L	> 584	Free
1.7	F	Volvulus	SB/L	> 582	Free
2.5	F	Microvillus Inclusion	SB	> 502	Free
1.3	M	Intestinal atresia	SB	> 447	Free
10.2	F	Pseudoobstruction	SB	> 375	Free
1.5	M	NEC	SB/L	70	Died/Sepsis
4.2	F	Gastroschisis	SB/L	> 279	Free
1.4	M	Gastroschisis	SB/L	29	Died/Sepsis
0.8	M	Microvillus Inclusion	SB/L	> 238	Free
0.5	M	Gastroschisis	SB/L	> 232	Free
4.0	F	Pseudoobstruction	MV	> 134	Free
3.6	M	NEC	SB/L	97	Died/Sepsis
0.9	F	Gastroschisis	SB/L	> 92	Free
5.5	M	Volvulus	SB/L	> 71	Free
31	M	Gunshot wound	SB	776	Died/Sepsis*
26	F	SMA thrombosis	SB/L	> 956	Free
21	M	Traffic accident	SB/L	> 573	Partial
32	M	CA & SMA thrombosis	MV	> 519	Partial
50	F	Crohn's disease	SB	> 444	Free
34	F	Desmoid tumor	SB	> 407	Total**
38	M	Crohn's disease	SB	376	Died/Sepsis
22	F	Crohn's disease	SB	> 369	Free
25	M	Crohn's disease	SB/L	> 353	Free
29	F	Desmoid tumor	SB/L	> 295	Free
24	M	CA & SMA thrombosis	MV	> 292	Free
20	F	Traffic accident	SB	> 282	Free
32	F	CA & SMA thrombosis	MV	> 217	Free
19	M	Traffic accident	SB/L	> 214	Free
44	F	SMA thrombosis	SB/L	> 190	Free
37	F	Familial polyposis	SB	> 109	Free

* Retransplantation at 22 months
** Graft removed at 8 months.
SB - Small bowel only
SB/L - Small bowel/liver
MV - Multivisceral
PTLD - Post-transplant lymphoproliferative disease
GVHD - Graft-versus-host disease (possible)

TABLE 2. Data on the 34 intestinal graft recipients

Gastrointestinal complications

The most common intestinal complication after small bowel transplantation is leakage through either the proximal or distal gastrointestinal anastomosis. Also, there have been leaks from native duodenal and colonic stumps, as well as gastrostomy sites. Surgical revision of these leaks and aggressive treatment of peritoneal soilage with frequent laparotomies and appropriate antibiotic therapy have been performed.

Gastrointestinal motility disorders have occurred in both native and transplanted intestine. Gastric atony with pylorospasm has been common and self limiting. Hypermotility of the allograft intestine is frequently found early after transplantation, and can be controlled with agents such as paregoric, loperamide, immodium, pectin, or somatostatin. Sudden increases or decreases in transit time should initiate a search for rejection.

Gastrointestinal bleeding has occurred almost exclusively with rejection of the allograft intestine. Management strategy must focus on endoscopic evaluation and treatment of the rejection episode.

Infections

Infections remain the most significant cause of morbidity and mortality after intestinal transplantation. Predisposing factors include the severity of liver failure, as well as the presence of intra-abdominal, pulmonary, or line sepsis prior to transplant. Technically more difficult transplant procedures with increased operative time, increased blood transfusions, and increased likelihood of re-explorations are significant risk factors.

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. All deaths after intestinal transplantation have had severe related infections. One recipient of two 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 (requiring a new liver graft) and eventually died of influenza B pneumonia; the other child presented a baseline immunodeficiency disorder and developed *Pneumocystis carinii* pneumonia and probable graft versus host disease.

The most frequent bacterial pathogens have been staphylococci and enterococci. Viral agents that have been significant include adenovirus, cytomegalovirus, parainfluenza, influenza B, and RSV. Post-transplant lymphoproliferative disease associated with the Epstein-Barr virus has occurred in 3 children, and resulted in one fatality. These patients presented with multifocal disease and were treated with intravenous acyclovir or ganciclovir, as well as withholding of immunosuppression. Rejection of the intestinal allograft may occur during the recovery phase and should be treated with steroids and reinstitution of FK506 immunosuppression. Patients who have died of complications related to treatment of intestinal allograft rejection include the following: 1 recipient of an isolated small bowel died of infection after retransplantation for chronic rejection. Another isolated small bowel recipient died of candida sepsis after salvage for a severe exfoliative type intestinal allograft rejection. One paediatric recipient of a liver/small bowel graft severely rejected the intestine and required OKT3. He then went on to develop severe adenovirus hepatitis and subsequently developed liver failure. The intestinal portion of the allograft recovered, however, the severity of liver injury from the adenovirus infection required a combined liver/small bowel retransplantation. Severe rejection of the intestinal allograft ensued and the child did not respond to OKT3. He died of enterococcal sepsis and intestinal bleeding.

CONCLUSION

Success with intestinal transplantation has required technical and clinical management modifications. The most important factor, however, remains the maintenance of adequate immunosuppression with FK506. Most complications or management difficulties will hinge around maintaining an intact, normally functioning allograft intestine; all other concerns remain secondary.

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