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REVIEW ARTICLE

Small Intestinal Transplantation for Irreversible Intestinal Failure in Children

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Permanent intestinal failure, whether secondary to severe gastrointestinal tract dysfunction or short bowel syndrome, remains a challenging pediatric health problem that requires innovative therapeutic modalities. Steatorrhea and intractable diarrhea result in failure to thrive, hypovitaminosis, hypoproteinemia, electrolyte disturbance, and metabolic acidosis if parenteral alimentation (TPN) is begun too late. A variety of medical and surgical treatments have been devised to address each of the underlying causes of childhood intestinal failure. Nonetheless, a significant percentage of children with intestinal failure remain permanently bound to parenteral nutrition. While some of these children suffer minimal morbidity, others succumb to the life-threatening complications of TPN. Until recently they had no hope for survival, but within the past decade small intestinal transplantation has offered them an opportunity for prolonged life emancipated from the shackles of TPN.

In this review, we shall discuss in detail microvillus inclusion disease, intestinal pseudoobstruction, and short bowel syndrome, which are the most common causes of pediatric intestinal failure coming to intestinal transplantation. The factors facilitating intestinal adaptation or predisposing to irreversible liver disease in children with short bowel syndrome will be described. We shall also enumerate the indications for pediatric intestinal transplantation and outline the surgical techniques, postoperative management, and results of our experience to date at the University of Pittsburgh Transplantation Institute. Finally we shall recount recent scientific advances likely to improve patient survival in the future.

MICROVILLUS INCLUSION DISEASE AND INTESTINAL PSEUDOOBSTRUCTION

In 1978, Davidson et al described five Canadian infants with a specific form of intractable diarrhea (1). Four of the five had a positive family history of this disorder, and all five had specific histologic abnormalities. Light microscopy of their small intestines revealed villous atrophy but no crypt hyperplasia. Electron microscopy revealed cytoplasmic vesicles near the apical surface of enterocytes. The vesicles possessed microvilli and secretory granules. Four of the first five cases died in early infancy. A subsequent detailed account (2) of 23 cases surveyed from around the world indicated that the disorder had been seen in patients of Caucasian, Asian and Arab lineage; there was a 2:1 female predominance. Most patients presented with diarrhea in the first week of life, but rarely it was not recognized until 40–60 days of life. Diarrhea was profound, with most patients losing 200–500 cc of stool per kilogram of body weight per day. Malabsorption of all nutrients was evident. No pharmacologic intervention was especially effective, but parenteral somatostatin could reduce stool output by half. Eighty percent of the children died during infancy with the rest bound inextricably to TPN. It is notable that loss of venous access for only a few hours could lead to death from dehydration in these patients.

Chronic intestinal pseudoobstruction is characterized by the signs and symptoms of intestinal obstruc-

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tion without anatomic obstruction (3). Cases that are not secondary to hypothyroidism, scleroderma, amyloidosis, gastroschisis, Hirschsprung's disease, or other disorders are deemed idiopathic. The two major categories of idiopathic pseudoobstruction are the neuropathic and the myopathic forms. With either of the two types, symptoms begin at birth in 50% of patients and by age one year in 75%. Almost half the patients, regardless of type, have small bowel malrotation. Bilious vomiting, abdominal distension, and obstipation are almost universally present, but paradoxically, some patients develop secretory diarrhea. The severity of symptoms will wax and wane during the first several years of illness. Patients with the neuropathic form are more likely to have severe, incapacitating abdominal pain, and those with the myopathic form are at risk for spontaneous bowel perforation. Megacystis and megaureter are frequent accompaniments. The entire bowel may be involved or there may be selective involvement of the colon. In some cases the disorders seem to be acquired and may progress from isolated colonic involvement to total involvement of the alimentary canal. Manometric changes range from absent or decreased motility in the myopathic form to high-amplitude, nonpropogated clusters, retrograde propogation, or failure to produce a fed pattern in the neuropathic form. Some patients derive transient benefit from pharmacologic therapy with prokinetic drugs or somatostatin, and others can be fed by slow continuous enteral feeding through a jejunostomy or gastrostomy. The subset of these patients incapable of tolerating adequate enteral calories because of visceral pain, vomiting, or malabsorption is faced with the prospect of receiving TPN. When TPN complications become life-threatening, multivisceral transplantation is necessary.

SHORT BOWEL SYNDROME

Short bowel syndrome accounts for the majority of pediatric referrals for small intestinal transplantation (Table 1). The most common disorders requiring massive intestinal resection include necrotizing enterocolitis, midgut volvulus, gastroschisis, and congenital small bowel atresias.

Following resection, the length of the remaining bowel does not correlate perfectly with prognosis. One reason is that bowel length can not be measured very precisely. Measured length depends upon the extent of contraction or relaxation at any point in time. For example, 350 cm of bowel measured *in vivo* may expand to 600 cm in a postmortem examination

TABLE 1. CAUSES OF INTESTINAL FAILURE IN CHILDREN

Volvulus	10
Gastroschisis	8
Necrotizing enterocolitis	6
Intestinal atresia	7
Pseudoobstruction	4
Microvillus inclusion disease	3
Intestinal polyposis	1
Hirschsprung's disease	1
Total	41

(4). Additionally, inflamed bowel undergoes shortening postoperatively.

Other factors influencing the prognosis of short bowel syndrome include the gestational age of a newborn at the time of small bowel resection, the postnatal age of the patient at the time of resection, the remaining length of small bowel after resection, the site of remaining small bowel, the presence or absence of an ileocecal valve, the remaining length of colon after resection, and the amount of damage incurred by the remaining gastrointestinal tract at the time of initial insult (5).

Duodenal resection leads to disproportionate malabsorption of minerals and folic acid. Jejunal resection disproportionately impairs protein and carbohydrate absorption (6), which can be partially overcome if ileal length is adequate. However, jejunectomy also results in decreased production of cholecystokinin and secretin, which in turn leads to gallbladder stasis and decreased exocrine pancreatic secretion. Inadequate jejunal production of gastric inhibitory polypeptide (GIP) and vasoactive intestinal polypeptide (VIP) combined with reduced gastrin catabolism result in increased serum gastrin and gastric hypersecretion (7).

Massive ileal resection not only decreases overall intestinal absorptive surface area but also disrupts the enterohepatic circulation of bile salts, leading to either a depleted bile salt pool and steatorrhea, or bile salt-mediated diarrhea (8). Absorption of vitamin B_{12} may also be inadequate following extensive resection of the terminal ileum (9). Resection of the ileocecal valve shortens intestinal transit time and permits colonic contents to regurgitate into the small bowel, resulting in small bowel bacterial overgrowth syndrome (10).

Disaccharide intolerance frequently accompanies short bowel syndrome and other types of intestinal failure. Malabsorbed carbohydrates are fermented by colonic flora to produce short-chain fatty acids such as acetate, butyrate, and propionate (11, 12).

Among patients with steatorrhea, luminal ionized calcium is saponified by fatty acids, resulting in excessive free oxalate presented to the colon. Increased colonic absorption of free oxalate leads to hyperoxalurea, placing patients at risk for oxalate urolithiasis (13).

INTESTINAL ADAPTATION

The capacity for intestinal adaptation following massive small bowel resection is governed by a variety of factors. In general, children seem to be more capable of adapting than are adults (14–19). Successful adaptation is also facilitated by the presence of the ileocecal valve. In his classic treatise, Wilmore (14) showed that survival was possible among infants left with 15 cm of jejunum and ileocecal valve. Forty centimeters of jejunum were necessary for survival if the ileocecal valve had been sacrificed. More recent publications (15–18) have described survival among children with as little as 10 cm of remaining bowel, but an intact ileocecal valve remains an important determinant of survival.

Adaptation results in increased villous height, intestinal length, and intestinal diameter. Individual cellular absorptive capacity does not improve, but the number of cells per unit of surface area increases (19). In unfed animals, disuse villus atrophy occurs within three days of a resection, but early institution of enteral feeding promotes recovery and enhances intestinal adaptation.

Enterocytes, which have the greatest energy requirements of all types, utilize glutamine in preference to glucose (20). This observation has led investigators to study the effects of parenteral or enteral glutamine supplementation upon the small bowel mucosa when the gastrointestinal tract is stressed and the muscle glutamine pool is likely to be depleted. Wilmore's group has shown that TPN-induced mucosal atrophy in rats can be partially corrected by glutamine enrichment of parenteral aminoacids (21). An isonitrogenous quantity of glycine will have comparable effects when delivered at 1 g/100 ml but not at 2 g/100 ml. In an animal model of short bowel syndrome, this same group showed that altering the dietary compositions of an elimental diet such that glutamine comprised 25% of the total amino acids resulted in significantly improved adaptation (22). Human studies by this group suggested that substitution of other amino acids with an isonitrogenous quantity of oral glutamine combined with pharmacologic parenteral doses of growth hormone could improve caloric absorption by about 20% and reduce stool output by about 25% in the limited number of adults with short bowel syndrome who were tested (23). Animal studies by Vanderhoof and colleagues cast some doubt upon the salutary effect of enteral glutamine insofar as substitution of glycine or glucose for glutamine in isocaloric quantities led to comparable or better adaptation following 80% bowel resection (24, 25).

Problematic patients are those whose small bowel never adapts, those who develop cholestasis and subsequent end-stage liver disease associated with TPN, those with multiple technical line complications, those who develop severe infectious and metabolic complications of TPN, and those who experience an unsatisfactory quality of life secondary to their underlying intestinal disorder.

TPN-ASSOCIATED LIVER DISEASE

A variety of liver disorders may beset patients bound to TPN. Fatty liver and hepatic fibrosis are common in adults and older children receiving TPN. Those changes are linked to the delivery of excessive carbohydrate calories (26). In contrast, cholestasis is commonly observed among infants and younger children (27, 28). Both exogenous (TPN-related) factors and individual host factors place patients at risk for cholestasis. The TPN-related factors (28) most often implicated include provision of excessive protein; provision of excessive glycine, alanine, and tryptophan; provision of flavinoids, which are photooxidized to toxic products; or provision of insufficient antioxidants such as selenium or tocopherol. Finally, relative taurine deficiency may be instrumental in the cholestatic process.

It is well recognized that cholestasis begins earlier and is more severe among infants receiving more than 2 g protein/kg body weight/day by the parenteral route as compared with counterparts receiving ≤2 g/kg/day (29). Furthermore, glycine and alanine will produce a significant cholestatic effect when perfused into isolated, perfused rat liver (30). The sulfated amino acid tryptophan is also cholestatic, but its cholestatic effect is enhanced by photooxidation to tryptophan sulfoxide (31). Riboflavin seems not only to facilitate the photooxidation of tryptophan but also become photooxidized to a potential hepatotoxin itself (32). Taurine is a provisionally essential amino acid in premature infants, malnourished patients, or cirrhotic patients who do not possess enough cystathionine synthetase or *S*-adenosylmethionine synthetase to permit taurine synthesis by *trans* sulfura-

tion of methionine. In the case of taurine deficiency, monohydroxy bile acids are preferentially conjugated with glycine, rendering them more hepatotoxic than their taurine-conjugated counterparts (33).

Host-related factors (34) playing a role in cholestasis are a reduction in bile acid pool due to prematurity or intestinal bile acid wasting, the development of biliary sludge due to prolonged fasting or insufficient cholecystokinin production, the loss of portal hepatotrophic factors in the absence of enteral feeding, excessive portal vein concentrations of endotoxin leading to reduced bile flow, or the damaging effects of bacterial cell wall glycoproteins upon hepatic function after bacterial translocation across the intestine.

Liver abnormalities can be reversed if intestinal function permits early initiation of enteral nutrition, minimizing the need for TPN. Cycling of parenteral nutrition, protecting solution from light (32), supplementing with taurine (33), and judiciously employing oral antibiotics for selective bowel decontamination (35) are all accepted therapeutic strategies. More recently animal studies have suggested that prophylaxis with intravenous ursodeoxycholic acid prevents TPN cholestasis (36). Pilot human studies (37, 38) suggest that oral ursodeoxycholic acid may actually reverse cholestasis in TPN-bound patients. However, a subset of patients with irreversible bowel dysfunction may develop irreversible liver damage within months or years after TPN is started. Isolated orthotopic liver transplantation may be an unwise option for them because the need for TPN will persist, with subsequent damage to the new liver. Additionally, the short segment of remaining bowel may not permit satisfactory Roux-en-Y biliary drainage of the allograft liver, and a duct-to-duct biliary anastomosis may be technically impossible.

INDICATIONS FOR SMALL BOWEL TRANSPLANTATION

In order to qualify for combined small bowel–liver transplantation, the patient must be plagued by irreversible intestinal failure, TPN dependency, and end-stage liver disease (39, 40). Patients without end-stage liver disease but with severe hepatic fibrosis or cirrhosis are more problematic. In this group, it may be difficult to judge the amount of functioning liver necessary to withstand the insult of portal diversion during small intestinal transplantation. It is also possible that a persistent need for TPN during the first few posttransplant weeks might lead to irreversible hepatic damage. Thus, all such patients are listed for a combined small bowel-liver transplant; however, the final decision of allograft type will likely be made in the operating room after assessing for evidence of portal hypertension and judging the severity of cirrhosis at the time an organ becomes available.

TPN-dependent patients without liver disease must also satisfy rigorous criteria before being considered active candidates for isolated intestinal transplantation. Their intestinal disease must be irreversible, and they must be TPN-dependent. Additionally, at least one of the following criteria must be met: inadequate venous access must imperil the ability to administer TPN, the risk for fatal TPN complications (such as recurrent sepsis) must be substantial, or the underlying disease process (such as microvillus inclusion disease or diffuse juvenile polyposis) must be life-threatening.

SURGICAL TECHNIQUE

The abdominal viscera are analogous to a cluster of grapes and each of the organs (the grapes) may be transplanted singly or in groups (41). Two central stems (the celiac axis and the superior mesenteric artery) supply arterial blood. These arteries can be anastomosed to the infrarenal or supraceliac aorta. Venous drainage of the small bowel–liver allograft is into the confluence of the recipient hepatic veins, whereas the isolated small bowel allograft can be drained into the recipient portal vein, splenic vein, or inferior vena cava (as a permanent mesocaval shunt).

The donor ileocecal valve and colon can be included in the graft to enhance water and electrolyte absorption.

Figure 1 illustrates isolated small intestinal transplant. Figure 2 describes small bowel transplantation in conjunction with a liver graft. A multivisceral graft is shown in Figure 3.

POSTOPERATIVE CARE

Induction and maintenance immunosuppression are achieved using the macrolide immunosuppressant agent, tacrolimus (30, 31), which is not only 100 times more potent than cyclosporine A, but is also absorbed quite well in the upper gastrointestinal tract in the absence of intraluminal bile acids. This agent functions like cyclosporine to inhibit T-cell production of interleukins 2, 3, and 4 as well as granulocyte stimulatory factor and interferon-α (42). It produces somewhat less hypertension and markedly less hirsutism and gingival hyperplasia than does cyclosporine (43).

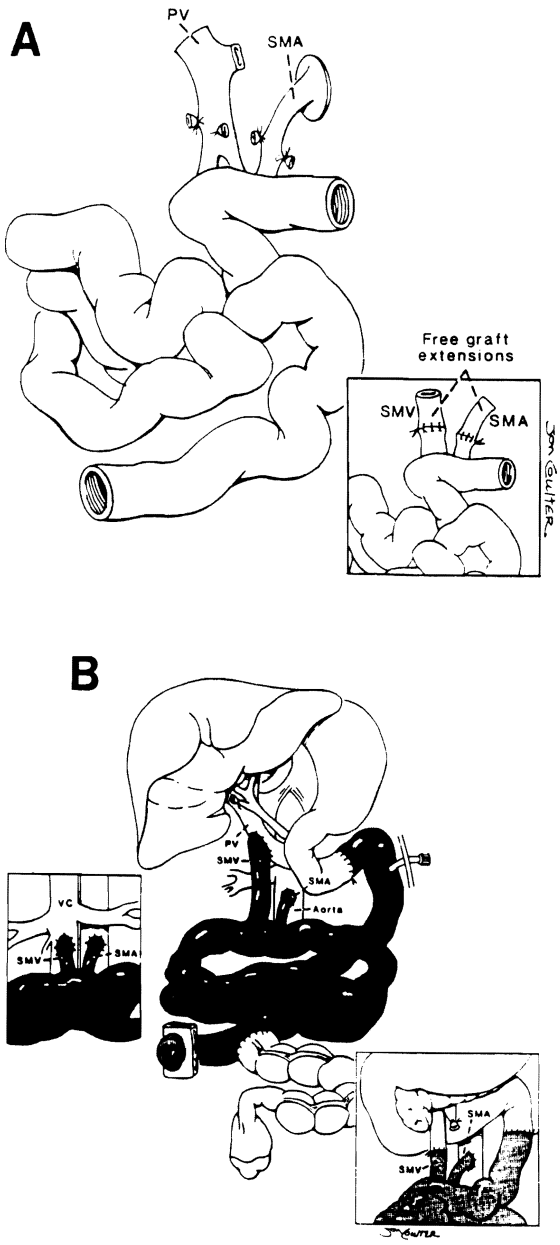

Fig 1. Isolated small bowel transplantation: (A) Donor operation; full-length vascular pedicle of the superior mesenteric artery (SMA) with Carrel patch and superior mesenteric vein (SMV), are divided more distally, they can be lengthened on the back table with arterial and venous grafts (insert). (B) Recipient operation. Anastomosis of the full length of SMA to the aorta and the angled end of the SMV to the portal vein. In an alternative method the SMV is anastomosed to the recipient SMV inferior to the pancreas (lower insert). Option of SMV drainage into the inferior vena cava is shown in upper insert.

The dose used is 0.1 mg/kg/day by continuous intravenous infusion, beginning immediately after reperfusion of the allograft. A whole blood level of 15–20 ng/ml is desirable. As soon as postoperative ileus resolves, oral tacrolimus is started at a dose of 0.2 mg/kg/day and overlapped with intravenous tacrolimus for a day or two to ensure therapeutic plasma levels.

Adjuvant steroid therapy is initiated during the operation and customarily eliminated within a few weeks based on the patient's clinical condition. Patients usually receive an intraoperative parenteral bolus of intravenous hydrocortisone (300–500 mg for children weighing less than 20 kg, 500–1000 mg for children weighing more than 20 kg) followed a day later by a methylprednisolone taper administered intravenously, beginning at approximately 5 mg/kg/day. Within 5 days the dose is tapered to a baseline of 1 mg/kg/day by mouth. The baseline dose is maintained for the shortest possible period before being discontinued. Prostaglandin E_1 is administered as a continuous infusion for five days at a dose of 0.003–0.009 μg/kg/hr to augment immunosuppression (44). Azathioprine is provided at a dose of 1–2 mg/kg/day. It is initially given intravenously and later by mouth. Table 2 outlines the immunosuppression regimen currently employed at the University of Pittsburgh.

MONITORING OF REJECTION

Serum liver enzyme levels are measured frequently, and liver biopsies are performed periodically. Liver allograft rejection is monitored just as it would be for patients who have undergone isolated liver transplantation. Rejection of the gastrointestinal tract is suspected anytime the patient's clinical picture deteriorates, stomal output increases or decreases, endoscopic examination becomes abnormal, or histologic features of rejection appear. Endoscopic biopsies can be obtained by esophagogastroduodenoscopy, stomal endoscopy, or colonoscopy. These are performed as frequently as twice a week initially or whenever the index of suspicion for rejection is high. Clinical findings prompting endoscopic evaluation are fever, ileus, increased stoma output, or gastrointestinal bleeding.

Endoscopically, early signs of rejection are edema, erythema, friability, and aperistalsis. Progression to aphthoid ulcers and ultimately, broad-based ulcers with overlying pseudomembrane occurs when immunosuppression is inadequate (45, 46).

Histologic characteristics (Figure 4) of intestinal acute cellular rejection are activated lymphocytes attacking crypt epithelium and patchy epithelial apoptosis (47). Severe rejection may progress to desquamation and diffuse pseudomembranous enterocolitis.

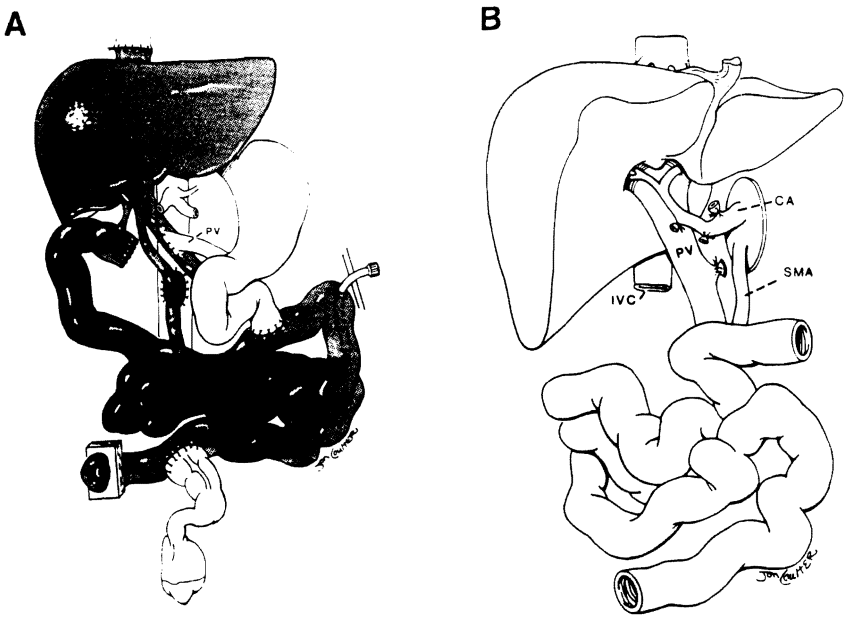

Fig 2. (A) Small bowel–liver allograft. Note the continuity of donor portal vein. (B) Recipient operation. Carrel patch containing the origin of the SMA and the celiac axis is anastomosed to the aorta. Ideally, the venous return from residual splanchnic viscera of the recipient is routed by vascular anastomosis into the graft portal vein. Numerous options of graft rearterialization and venous drainage have been described elsewhere.

Regeneration may occur in such instances but usually after long, intensive courses of immunosuppression (48). Of our eight pediatric patients experiencing severe exfoliative rejection, three underwent graft enterectomy, with one being subsequently successfully retransplanted. Yet a fourth underwent imme-

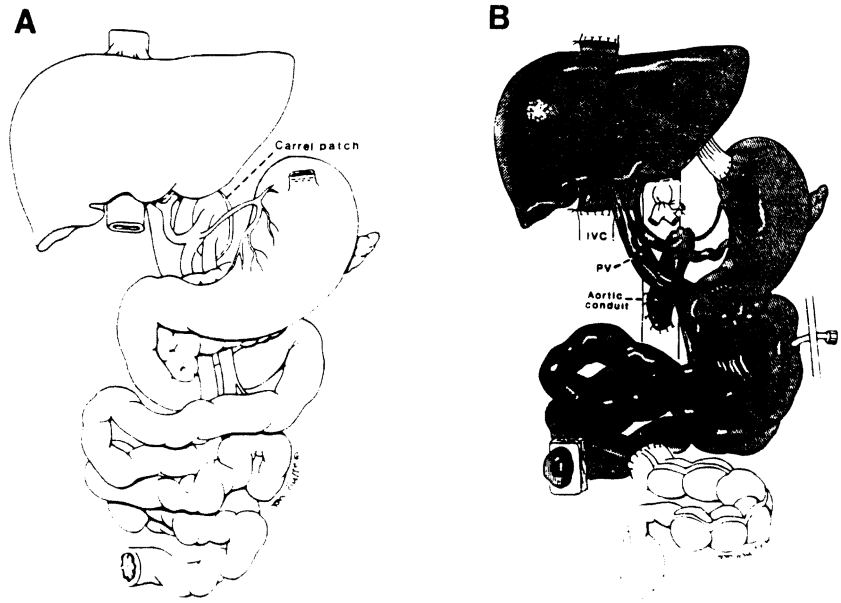

Fig 3. Multivisceral allograft (A) before and (B) after transplantation. Splenectomy is performed on the back table. In this case the Carrel patch with the superior mesenteric artery and celiac axis origins has been used to cap a free graft of donor thoracic aorta that has been used as a conduit. This is only one of the several options that the operator should be prepared to exercise.

TABLE 2. IMMUNOSUPPRESSION REGIMEN FOR PEDIATRIC SMALL BOWEL TRANSPLANTATION

I. Corticosteroid
  A. Initial
    1. Hydrocortisone
      a. 300–500 mg IV if weight <20 kg
      b. 500–1000 mg IV if weight >20 kg
    2. Steroid cycle with methylprednisolone
      a. 5 mg/kg IV during first postoperative day
      b. Reduce by 1 mg/kg/day to baseline of 1 mg/kg IV by postoperative day 5
  B. Long-term
    1. Switch to oral methylprednisolone 1 mg/kg when tolerating oral alimentation
    2. Attempt further tapers and discontinuing within 4–6 weeks if rejection is under control
II. Tacrolimus
  A. Initial
    1. 0.1 mg/kg by continuous IV infusion
    2. Overlap oral with IV for 1 or 2 days; as levels climb, discontinue IV tacrolimus
III. Azathioprine
    1. 1–2 mg/kg/day IV until tolerating oral alimentation, then switch to oral
IV. Prostaglandin E
    1. 0.003–0.009 μg/kg/hr by continuous IV infusion for 5 days

diate liver–small bowel retransplantation but died after a disseminated adenovirus infection.

Endoscopic and histologic changes may involve small bowel, stomach, and colon simultaneously or changes may be confined to one anatomic area (49). Usually the ileum is the most severely damaged region, but occasionally the jejunum is preferentially affected.

We have identified "chronic intestinal rejection" in one adult patient but among none of our pediatric recipients (50). That patient, who stopped his immunosuppression months after transplantation, developed a "wasting disorder" characterized by steatorrhea. Small bowel endoscopy was normal, but patchy villous atrophy was present histologically. More impressive than mucosal abnormalities were submucosal changes, including smooth muscle hypertrophy and vascular obliteration, which would have been missed with mucosal biopsy. Superior mesenteric arteriography revealed segmental narrowing of jejunal and ileal arteries. Either full-thickness biopsy or angiography is thus required to establish the diagnosis of chronic rejection.

CONTROL OF REJECTION

This is achieved by modulating immunosuppressive agents to achieve optimal levels (39, 40). The tacrolimus dose may be increased, a steroid bolus may be given, or a steroid "recycle" may be initiated. OKT3 may be used in severe or refractory acute cellular rejection.

INFECTION SURVEILLANCE AND TREATMENT

Infection control plays a key role in success of small bowel transplantation (39, 40). The mucosal barriers of native bowel permit very little translocation of bacteria or yeast into mesenteric lymphatics, but once there, gut organisms are transported by macrophages to regional mesenteric lymph nodes for immunologic recognition and surveillance. In the transplanted bowel, this orderly process may be impaired by immunosuppression, luminal microbial overgrowth, dysfunction of gut-associated lymphocytes during graft repopulation by recipient cells, and acute cellular rejection. Increased numbers of gram-negative aerobes such as *E. coli*, *Klebsiella*, and *Pseudomonas* can translocate from gut lumen directly into the portal circulation, leading to life-threatening sepsis. Hence judicious postoperative use of antimicrobial agents is imperative.

Intravenous, broad-spectrum antibiotics are given for five days postoperatively and for 24 hr following endoscopic procedures. Oral, nonabsorbable antibiotics (including amphotericin and an aminoglycoside) are given for several weeks routinely and subsequently whenever stomal gram-negative microbial counts exceed 10^8 colony forming units per milliliter in an effort to selectively decontaminate the bowel. The purpose of selective decontamination is to reduce numbers of intraluminal, gram-negative aerobes, thereby permitting anaerobes (which are less likely to induce septicemia) to proliferate (51).

Pneumocystis, cytomegalovirus, and herpes prophylaxis are accomplished with prophylactic trimethoprim-sulfa, ganciclovir, and acyclovir, respectively.

POSTOPERATIVE NUTRITIONAL SUPPORT

As soon as postoperative ileus resolves, jejunostomy feeding is begun as a continuous, low-volume infusion of age-appropriate semielemental formulas. During the first six years of the program, patients were generally started on formulas containing thermally or enzymatically hydrolyzed cow's milk protein. More recent transplant recipients have initially received Tolerex, which contains glutamine. Because mesenteric lymphatics compromised at the time of transplantation may require several weeks to recanalize, this low-fat formula is usually well tolerated.

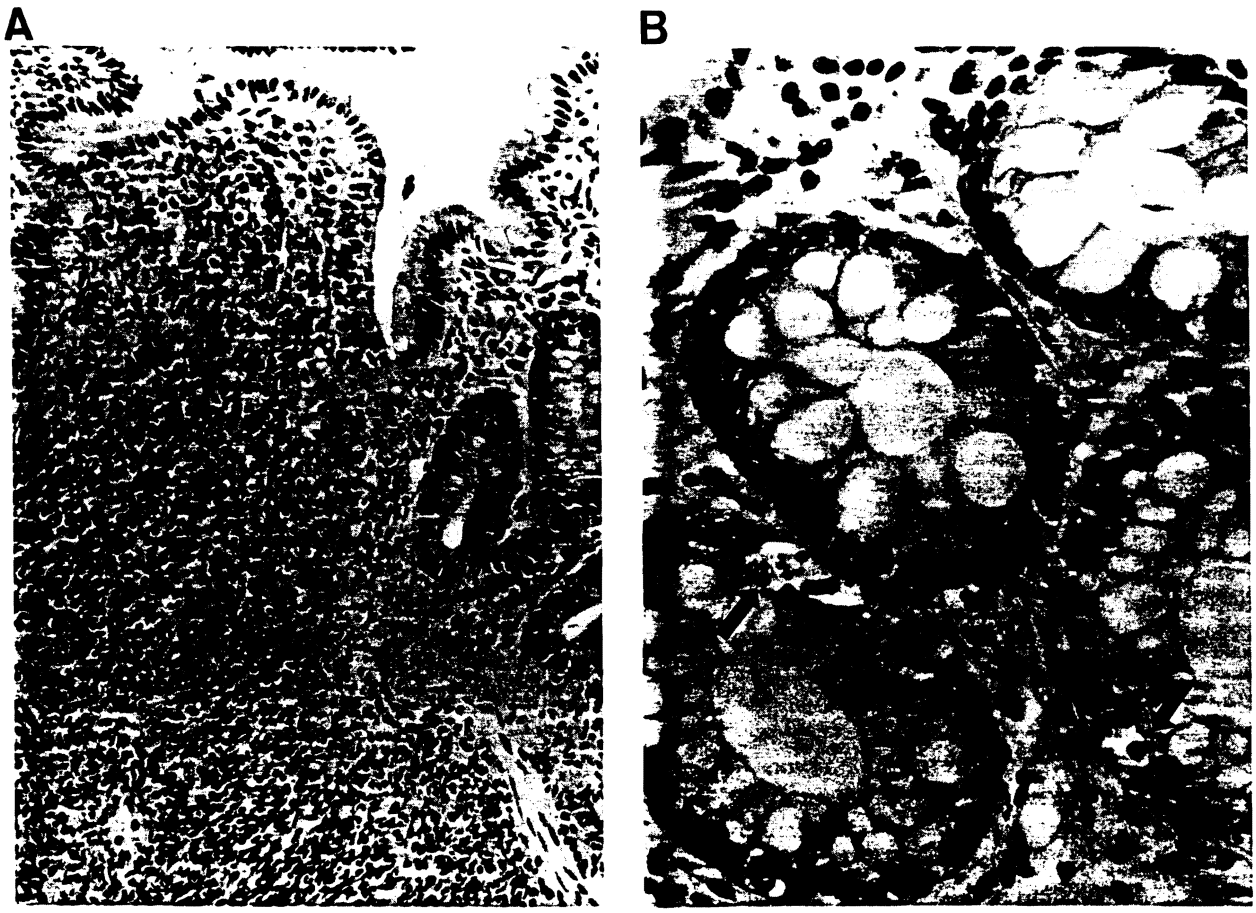

Fig 4. Focus of activated lymphocytes within lamina propria (A) in a patient experiencing acute cellular rejection of the small intestine (hematoxylin and eosin, 40×). High power view of acute cellular rejection (B) showing apoptotic crypt epithelial cells (arrows) adjacent to normal epithelial cells (hematoxylin and eosin, 250×).

After two or three weeks, fat is provided as a mixture of long-chain fats and medium-chain triglycerides that can be absorbed directly into the portal circulation. However, essential fatty acids are provided intravenously and (to some extent) enterally to prevent deficiency. The carbohydrate given is a mixture of oligosaccharides and glucose. If elemental formula is tolerated for several weeks, nutritionally defined formulas such as Pediasure or Peptamin Jr are delivered orally or by continuous nocturnal intragastric infusion. Patients are also fed general diets *ad libitum*.

Parenteral nutrition, which is begun during the early postoperative period, is continued until such time as the allograft absorptive capacity is adequate to sustain life. Notably, we have not seen significant TPN-associated hepatic dysfunction in any patients who are also receiving enteral nutrition.

ASSESSMENT OF ALLOGRAFT ABSORPTIVE FUNCTION

Hematologic and biochemical blood tests are performed to assess the state of hydration and renal function. Stomal output, urine output, and daily body weights are meticulously recorded and serve to guide fluid and electrolyte balance.

Stomal absorption testing is performed periodically to assess absorption of nutrients. Seventy-two-hour fecal fat balance is conducted as soon as the diet contains substantial quantities of long-chain fats. Fat-soluble vitamin levels are measured several weeks after weaning from parenteral nutrition. A stable or a rising serum albumin level and improved anthropometric measurements and growth velocity indicate satisfactory absorption of proteins. Daily measurement of reducing sugars in stomal effluent as well as

periodic measurement of D-xylose absorption are means of assessing carbohydrate and monosaccharide absorption. Serum calcium, phosphorus, magnesium, iron, trace element levels, and tacrolimus levels while the patient is off parenteral supplements are also markers of graft function.

OUTCOME

Between May 1990 and June 1995, 44 small bowel grafts were transplanted into 41 pediatric patients aged 6 months to 18 years at the University of Pittsburgh Medical Center. Table 1 enumerates the causes of intestinal failure in these patients. Organs transplanted were an isolated small bowel graft in 10 and small bowel with liver in 27. Multivisceral transplants including stomach and pancreas were performed in six, and one patient received a multivisceral transplant without the liver. Between January and June 1995, five of the transplant recipients received simultaneous bone marrow infusions to enhance the establishment of chimerism. Twenty-four children are still alive from two months to five years postoperatively. Four of the five receiving bone marrow have survived for three to six months. As of June 1995, 21 of the 24 living children were off TPN and exclusively on enteral feeding.

The pediatric deaths were due to sepsis in four patients, respiratory syncitial virus (RSV) pneumonia in two, GVHD in one, and posttransplant lymphoproliferative disease (PTLD) in three, cerebral infarction in one, rejection in four, iatrogenic salt toxicity in one, and respiratory failure after line insertion in one.

OBSTACLES TO SUCCESSFUL INTESTINAL TRANSPLANTATION

The successful intestinal transplant requires careful attention to detail. The transplant team should not only possess the technical expertise to perform the surgery but also the willingness to provide meticulous postoperative care to the transplant recipient. Any successful management strategy must include recognition and anticipation of potential obstacles to success. A few of those obstacles will be discussed individually.

Fluid and Electrolyte Imbalance

Patients receiving a small intestinal transplant undergo ileostomy to permit easy endoscopic monitoring for rejection. They are thus subject to high output ileostomy drainage until such time as absorption matures. Fluids and electrolytes are initially provided intravenously but as intestinal function matures, they may be delivered enterally via a feeding jejunostomy. Not only is the sodium requirement quite substantial, but calcium and magnesium levels must be monitored closely and daily supplements of each must be provided for several weeks.

Rejection

Almost all patients experience rejection at least once during the postoperative period, but the spectrum of severity is quite broad. Rejection may be severe and intractable, beginning with the first postoperative week and progressing to death or enterectomy despite an intensive course of immunosuppression. Conversely, some patients experience only mild, episodic asymptomatic histologic rejection that, if left untreated, may become clinically apparent.

Therefore, close endoscopic and histologic monitoring is imperative. It has been our policy to perform surveillance ileoscopy twice weekly or at the first sign of clinical deterioration. Notably, gram-negative sepsis often accompanies rejection. Thus, signs of sepsis should not lull the clinician into excluding rejection as a cause of symptoms (52). Rejection is patchy in distribution, usually involving the ileum, but occasionally preferentially involving the proximal small intestine (49).

After several postoperative months, patients are usually quite stable and the risk for rejection declines. However, viral enteritis occurring months or years after transplantation may result in malabsorption of tacrolimus resulting in late-onset rejection. Hence, a sense of vigilance must be maintained indefinitely.

Viral Infections

Invasive cytomegalovirus (CMV) infections continue to plague pediatric small bowel transplant recipients. As with liver transplantation, infections appear most frequently in CMV-negative recipients who have received a CMV-positive grafts. Infections are characterized by hepatitis and by hemorrhagic enterocolitis. Fortunately, the use of prophylactic ganciclovir during the first two postoperative weeks seems to be associated with a reduced risk for infection (53). Furthermore, active infection can be successfully treated without appreciably reducing immunosuppression by using a several week course of parenteral gancyclovir (54).

In contrast, Epstein-Barr virus (EBV) infections are more difficult to treat. Like recipients of solid organs, intestinal transplant recipients are prone to develop EBV-associated posttransplant lymphopro-

liferative disease (PTLD), which straddles the border between infection and neoplasia (55). These lymphoid tumors are characterized by destructive lymphoid infiltrates, gross tumors, clonal proliferation of lymphocytes, and (frequently) progression to neoplasia. No effective antiviral agent exists for PTLD. PTLD may appear among immunosuppressed organ recipients either as a primary infection or reactivation of remotely acquired disease. Children, who are more likely to develop primary EBV infections, seem to be at greater risk than are adults for PTLD. The risk is also enhanced among children who have had rejection severe enough to require high doses of tacrolimus, multiple steroid recycles, and OKT3. Splenectomy appears to be an independent risk factor (56). Antiviral strategies such as treatment with acyclovir, ganciclovir, and interferon-α have been disappointingly unsuccessful (42). Like liver transplant recipients with PTLD, small bowel transplant recipients with PTLD should undergo reduction in immunosuppressive doses. However, unlike liver transplant recipients, they can not rely upon tumor anergy to protect against rejection if immunosuppression is discontinued. Therapy of concommitant PTLD and rejection has been characterized as "a therapeutic tightrope" whereby aggressive treatment of rejection leads to progression of PTLD and aggressive reduction in immunosuppression results in severe rejection.

Graft-versus-Host Disease (GVHD)

The use of tacrolimus, steroids, and azathioprine has rendered groundless the concern that GVHD would be a major clinical problem among small bowel transplant recipients. In the Pittsburgh series, GVHD was observed only in rare and unusual circumstances. One patient with jejunal atresia and common variable immune deficiency developed GVHD soon after transplantation. Another, who experienced severe rejection, underwent removal of the allograft. Transient GVHD induced by residual dendritic (antigen presenting) cells developed only after removal of the allograft and cessation of immunosuppression.

Intestinal Dysmotility

A small subset of intestinal transplant recipients have undergone formal manometric testing (57). In those patients examined during fasting periods, antral waves were of reduced amplitude and frequency. Migrating myoelectric complexes (MMCs) originated in the stomachs only when stomach and small bowel were transplanted in continuity. When isolated small bowel transplant was performed, MMCs originated in the allograft and could be retrograde, antegrade, or simultaneous. No patient had a normal fed pattern. Denervation of the bowel and use of tacrolimus, which may itself effect motility, were undoubtedly contributory factors. Regardless of these abnormalities, all patients tolerated oral and enteral nutrition.

FUTURE TRENDS IN TRANSPLANTATION

Even though transplantation has progressed greatly since its inception in 1959, the mortality rate remains quite high and the degree of immunosuppression required remains worrisome. Until newer, more refined immunosuppression becomes available, an effective approach may be the enhancement of systemic chimerism (58).

Chimerism is known to occur following intestinal transplantation. Epithelium of the allograft is donor-derived, but Peyer's patches become populated by recipient lymphocytes. Additionally, donor dendritic cells are commonly engrafted into distant organs of the recipient. The model best explaining this phenomenon is the two-way mixed lymphocyte reaction, which can also occur after bone marrow transplantation if recipient marrow is not cytoablated. It has been shown that immunologic tolerance can be conferred after solid organ transplantation if chimeric environment is enhanced by simultaneous bone marrow transplantation (58). This rationale has governed our performance of simultaneous bone marrow infusion and intestinal transplantation in five of our most recent six intestinal transplants. It is too early to judge the beneficial effect of this strategy, but the early outcome in our small series of patients receiving bone marrow–intestinal transplants has been quite favorable.

The need for immunosuppression in the first postoperative weeks has not been excessive, and it is anticipated that the need for long-term immunosuppression will be reduced after a period of time. While the techniques for producing donor–recipient immunologic balance are far from perfect, we remain optimistic that enhancement of chimerism will successfully minimize the need for pharmacologic immunosuppression as well as its numerous undesirable side effects.

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