

REVIEW ARTICLE

CURRENT CONCEPTS

Intestinal Transplantation

Thomas M. Fishbein, M.D.

From the Georgetown Transplant Institute, Georgetown University Hospital, Washington, DC. Address reprint requests to Dr. Fishbein at the Georgetown Transplant Institute, 2 Main, Georgetown University Hospital, 3800 Reservoir Rd. NW, Washington, DC 20007, or at tmf8@gunet.georgetown.edu.

This article (10.1056/NEJMra0804605) was last updated on September 4, 2009, at NEJM.org.

N Engl J Med 2009;361:998-1008.
Copyright © 2009 Massachusetts Medical Society.

THE RESULTS OF INTESTINAL TRANSPLANTATION HAVE IMPROVED OVER the past decade. During this period, the number of intestinal transplant procedures performed in North America has increased by a factor of three.¹ In 2008, a total of 185 intestinal transplantations were performed in the United States, and 221 patients were registered on the waiting list as of June 2009 (<http://optn.transplant.hrsa.gov>). Early attempts at transplantation were hindered by technical and immunologic complications that led to graft failure or death. As a result of recent surgical advances, control of acute cellular rejection, and a decrease in lethal infections, the rate of patient survival at 1 year now exceeds 90% at experienced centers. Although long-term follow-up data are still lacking, the role of intestinal transplantation in the treatment of patients with gut failure is becoming clearer.

Parenteral nutrition is currently the primary maintenance therapy for patients in whom intestinal absorptive function has failed. Transplantation is offered to patients with irreversible gut failure who have one of three problems: complications of parenteral nutrition, an inability to adapt to the quality-of-life limitations posed by intestinal failure, or a high risk of death if the native gut is not removed (as in the case of unresectable mesenteric tumors or chronic intestinal obstruction). However, there is still controversy about exactly which patients should continue to receive parenteral nutrition and which should receive an intestinal transplant.

This article explores the current indications for intestinal transplantation, the surgical procedures involved, our current understanding of the immunology of intestinal transplantation, the detection and treatment of complications, postoperative outcomes, and future applications.

INTESTINAL FAILURE

Intestinal failure refers to actual or impending loss of nutritional autonomy due to gut dysfunction. The condition is initially managed by parenteral delivery of nutrition.^{2,3} Many patients, particularly those with the short-bowel syndrome, require only temporary parenteral support while the injured intestine is given time to adapt, and the support can eventually be discontinued. However, this process is unpredictable. In some patients, adaptation is rapid, whereas in others, it takes years or is never achieved. Table 1 lists the clinical factors that influence the outcome of treatment with parenteral nutrition.^{2,4-14} Markers of intestinal epithelial biomass, such as the level of plasma citrulline, may also predict the likelihood of nutritional rehabilitation. Patients in whom nutritional autonomy cannot be achieved have irreversible intestinal failure, and which of these patients ultimately undergo transplantation depends on the success or failure of their adaptation to parenteral nutrition.

DISEASE STATES

Intestinal transplantations are performed in both children and adults (Table 2). The majority of children who require transplants have the short-bowel syndrome, usually

after surgical resection; a smaller proportion has congenital enterocyte disorders that cause infantile diarrhea, disturbances of motility, or malabsorption due to polyposis.¹⁵

Most adult candidates for transplantation also have the short-bowel syndrome, and in the majority of cases the cause is Crohn's disease, mesenteric vascular accidents, trauma, volvulus, or surgical complications. Complications of surgery for obesity are increasingly being encountered. Sometimes the only treatment option for locally advanced benign mesenteric tumors is exenteration and intestinal transplantation. Multivisceral transplants have also been used to treat complications of portal hypertension when splanchnic venous thrombosis precludes liver transplantation alone.¹⁶

UNSUCCESSFUL PARENTERAL NUTRITION

The 1-year rate of survival for patients treated with parenteral nutrition is approximately 90% in experienced centers, which is similar to the rate achieved with intestinal transplantation.^{3,7} However, long-term therapy is often associated with complications. The rates of survival at 3 years and at 5 years remain 70% and 63%, respectively, in various series.^{3,4,6,9,10,17,18} Liver disease is widely recognized as the most deadly complication of parenteral nutrition. It eventually develops in half the adults and children who receive continuous therapy^{13,19,20}; if detected early, this complication sometimes responds to cycling of the infusion, a reduction in the lipid or dextrose load, oral administration of ursodiol, alteration of the lipid emulsion, or the addition of antibiotics.^{21,22} A new lipid preparation not yet approved for use in the United States shows promise as a way of decreasing the incidence of this complication, if the initial data are borne out by further study.²³ However, liver disease currently leads to death within a year of its onset in the majority of patients in whom it persists.^{5,24,25}

Thrombosis at the site of central catheter insertion, recurrent episodes of catheter-related sepsis, dehydration, formation of renal calculi, and electrolyte disorders are other common complications.²⁶ Unfortunately, randomized or case-control studies comparing outcomes of transplantation with those of parenteral nutrition in similar patient populations are not available, so there is considerable controversy about which patients should be referred for transplantation. Studies evaluating the relative risk of a poor outcome in

association with clinical features, patient characteristics, or complications of parenteral therapy in intestinal failure might be helpful for the future.

CANDIDATES FOR TRANSPLANTATION

The complications of parenteral nutrition summarized above account for the majority of indications for intestinal transplantation accepted by the Centers for Medicare and Medicaid Services (Table 3). Specifically, patients should be considered for a transplant if they have recurrent episodes of sepsis, two or more episodes of loss of central venous access, early cholestatic liver disease, evidence of portal hypertension, or repeated episodes of dehydration.^{21,27} As the outcomes of transplantation improve, these indications may be broadened.²⁸ Our increasing ability to predict the failure of parenteral nutrition allows earlier transplantation (with patients admitted directly from home, before they require hospitalization for complications), which is associated with improved survival.¹⁵ Other characteristics associated with an increased risk of death during parenteral nutrition therapy include specific disease states (primary motility disorders, extremely short bowel [defined as less than 50 cm of jejunoleum], chronic obstruction, or radiation injury), end-jejunosomy without colon, and abdominal-wall defects in older adults and in children (Table 1).²⁹ In such patients referral for a transplant is much less controversial. The high

Table 1. Factors Adversely Influencing the Outcome of Long-Term Parenteral Nutrition Therapy.*

Factor	Source of Data
Affecting survival	
Age >60 yr at institution of therapy	Messing et al. ⁴
Jejunoleal length <50 cm	Messing et al., ⁴ Chan et al. ⁵
Dysmotility	Scolapio et al. ⁶
Radiation enteritis	Howard and Malone ⁷
More severe obstruction	Messing et al. ⁴
Longer treatment	Howard and Malone ⁷
Affecting rehabilitation	
Jejunoleal length <50 cm	Wilmore et al. ²
Absence of ileocecal valve	Wilmore et al. ²
Mucosal disease	Wilmore et al. ²
Dysmotility	Scolapio et al. ⁶
Abdominal-wall defect in children	Thakur et al. ⁸

* Data are from the Intestinal Transplant Registry (www.intestinaltransplant.org).

Table 2. Distribution of Disease States among Recipients of Intestinal Transplants.*

Disease State	Children (N=1031)	Adults (N=733)
	percent	
Short bowel syndrome		
Volvulus	17	7
Gastroschisis	21	1
Trauma	2	8
Necrotizing enterocolitis	13	1
Ischemia	1	25
Crohn's disease	0	12
Intestinal atresia	8	0
Other	2	8
Malabsorption (mucosal defect)		
Microvillus inclusion	6	0
Secretory diarrhea	0	0
Autoimmune enteritis	0	0
Other	2	0
Motility disorder		
Pseudo-obstruction	9	9
Aganglionosis		
Hirschsprung's disease	8	0
Other	1	0
Tumors	1	15
Retransplantation	8	7
Other	2	5

* Data are from the Intestinal Transplant Registry (www.intestinaltransplant.org).

mortality among patients awaiting intestinal transplants — up to one third of patients in some age groups — exceeds that among candidates for other solid-organ transplants, making early referral of patients with such risk factors important.³⁰

For patients who will have lifelong dependency on parenteral nutrition but have not had complications and are seeking to improve their quality of life, the decision about transplantation is more controversial. Such patients often thrive after transplantation, but centers vary considerably in how they define candidacy for preemptive transplantation. The limited data available corroborate improved quality-of-life indicators among patients who have undergone preemptive transplantation, as compared retrospectively with those who receive parenteral nutrition therapy before the transplantation.²⁸

TYPES OF TRANSPLANTS

The defining component of any intestinal transplant is the small intestine (jejunioileum). When this part of the gut is transplanted alone, it is referred to as an isolated intestinal transplant (Fig. 1A). Commonly, however, other organs are transplanted simultaneously from the same donor. When advanced liver disease is present, the liver is replaced as well (Fig. 1B). This can be accomplished with a composite allograft or with organs implanted separately from the same donor. The pancreas and duodenum are often included along with these organs to facilitate en bloc engraftment and to obviate biliary reconstruction, particularly in small children.³¹ The exact extent of liver disease associated with parenteral nutrition that would indicate the need for a liver transplant remains a matter of judgment. After successful engraftment of an isolated intestinal transplant, early liver disease may regress with the cessation of parenteral therapy.^{32,33} However, liver function that is preserved at the time of intestinal resection often deteriorates rapidly in small children,³⁴ accounting for the relatively larger proportion of children who receive combined organ transplants.^{13,35}

Some patients require replacement of the entire gastrointestinal tract because of coexisting intestinal disorders or disease of other organs. For example, some have had their colon removed (Crohn's colitis), some have had stomach surgery (gastric bypass), some have chronic pancreatitis (related to parenteral nutrition), some have renal failure (because of oxalic acid stones or hypertension), and some have had a host of other possible complications related to intestinal failure or parenteral nutrition. In such cases, the transplant team makes an individual determination regarding whether to include other organs. Transplants that include the stomach along with the small bowel are frequently referred to as multivisceral (composite visceral or multiorgan) transplants. Exenteration of the entire native gastrointestinal tract makes room for the en bloc organ graft (Fig. 1C). Transplantation of the colon along with the intestinal allograft was previously avoided because of the risk of infection,³⁶ but it is now sometimes carried out.³⁷ Although technical refinements continue to be made, these operations still roughly resemble those first described by Starzl over 40 years ago in dogs.³⁸⁻⁴⁰

After the operation, a feeding tube is inserted to provide early enteral nutrition, after which the patient is transitioned to oral feeding. Small ba-

Table 3. Failure of Parenteral Nutrition, as Defined by the Centers for Medicare and Medicaid Services.*

Impending or overt liver failure due to TPN-induced liver injury
Thrombosis of two or more central veins
Two or more episodes per year of catheter-related systemic sepsis that requires hospitalization
A single episode of line-related fungemia, septic shock, or acute respiratory distress syndrome
Frequent episodes of severe dehydration despite intravenous fluid supplementation in addition to TPN

* TPN denotes total parenteral nutrition.

bies often must acquire feeding skills if they had not been learned before the operation. An ileostomy is constructed during the transplantation procedure to allow surveillance biopsies of the intestinal mucosa in order to help direct medical therapy. Graft rejection and most infections can be diagnosed histologically. Several months after transplantation, when graft function has become stable, the ileostomy is reversed in patients who retain a functional colon or received one as part of the allograft.

IMMUNOLOGIC FEATURES OF INTESTINAL TRANSPLANTATION

Transplantation of the intestine presents a greater immunologic challenge than does that of other solid organs. Approximately 80% of immune cells normally reside in the gut, and they are repopulated after transplantation with recipient cells, whereas the genotype of the epithelium remains largely that of the donor, making the organ highly chimeric and immunogenic.⁴¹⁻⁴³ Although most transplanted organs are sterile, the gut relies on barrier and other immunologic mechanisms, such as the production of antimicrobial peptides, to provide protection against invasion by extensive commensal flora. Breach of this ileal barrier by ischemia or reperfusion injury, by recipient immune cells, or by defects such as impaired microbial control mechanisms results in inflammation and tissue damage and increases the likelihood of infection. This loss of immunologic protection makes the augmented immunosuppression required to treat rejection particularly dangerous.

Figure 2 summarizes our current understanding of the immunologic characteristics of intestinal transplantation. Maintenance treatment with tacrolimus, which inhibits signal-1 activation of T lymphocytes through the inhibition of calcineurin, is the basis of current intestinal transplant immunosuppression. Signal 1 is one of three sig-

nals required for the activation of T lymphocytes. The recent addition of induction agents acting at signal 3, including interleukin-2 monoclonal antibodies, rabbit antithymocyte globulin (Thymoglobulin, Genzyme), and sirolimus (also known as rapamycin), have all decreased acute cellular rejection at different centers. Although some form of antilymphocyte antibodies — that is, competitive inhibitors, such as the monoclonal interleukin-2 blockers, or depleting antibodies, such as antithymocyte globulin or alemtuzumab (Campath-1H, Genzyme) — has been associated with decreased early rejection rates, such therapy may result in a globally increased level of immune suppression and may increase the risk of infection. Tacrolimus with low-dose corticosteroids, either alone or in combination with sirolimus (rapamycin), remains the most effective and reliable long-term regimen. The main complication of tacrolimus is chronic renal damage, which in rare cases may even require renal-replacement therapy.

A new fusion protein that is specific for CD80 and CD86 is now being used in trials of renal transplantation and would be the first approved agent for use in inhibiting signal-2 activation.⁴⁴ A single regimen has yet to be proved superior, so transplantation centers currently individualize immunosuppression. Ideally, future strategies will target mechanisms of mucosal injury that are specific to the ileum.

COMPLICATIONS

SURGICAL COMPLICATIONS

Early outcomes of intestinal transplantation have improved, reflecting the increase in surgical experience over the past decade. The rates of graft thrombosis, ischemia, and technical failure have all decreased, and graft losses are now more commonly attributable to medical and immunologic causes. This change probably reflects the greater experience of the teams at several centers that per-

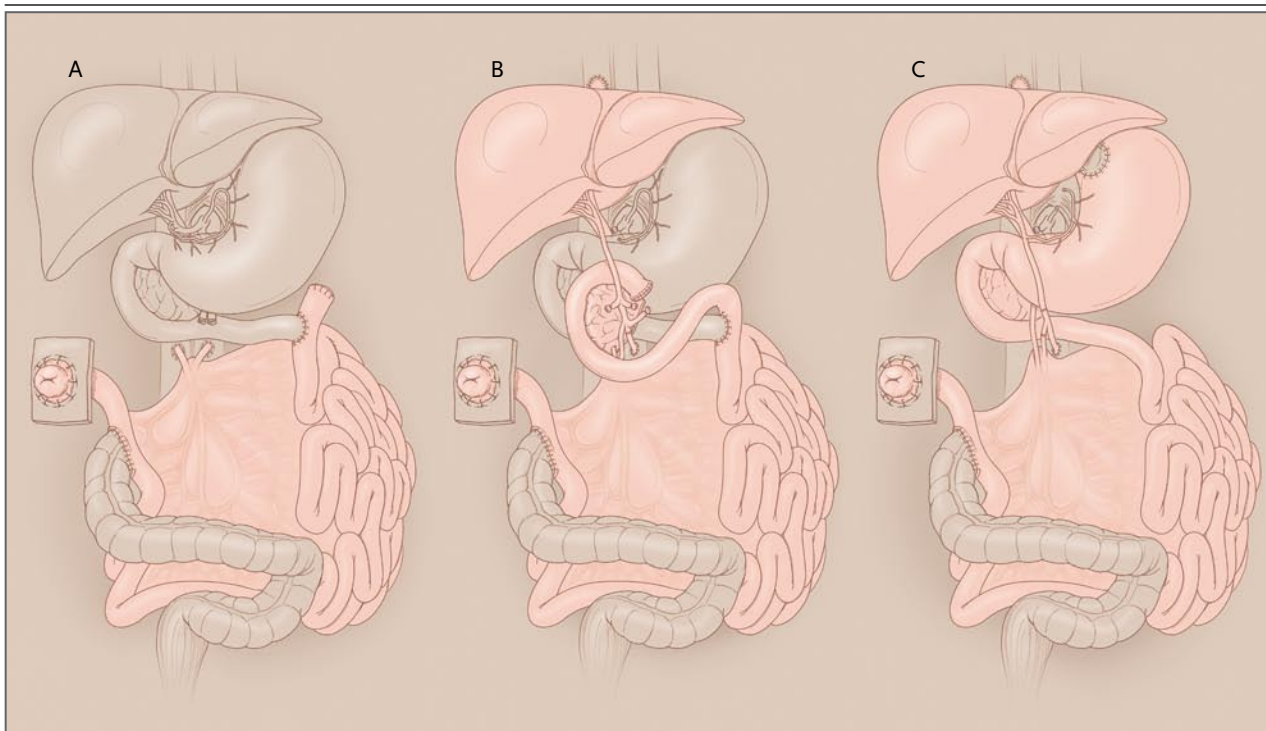


Figure 1. Three Types of Transplants in Intestinal Failure.

When the small intestine (jejunioileum) is transplanted alone, it is referred to as an isolated intestinal transplant (Panel A), with systemic drainage to the vena cava. A composite liver and intestinal transplant usually includes the duodenum and an intact biliary system and portal circulation, with the native foregut preserved (Panel B). In a multivisceral transplant, which involves the liver, stomach, duodenum, pancreas, and small intestine, the foregut is removed and a new stomach is transplanted (Panel C). This type of transplant sometimes includes the colon, kidney, or both. The transplanted organs are shown in pink, and the native organs or structures are shown in light brown.

form most of the transplantations. Transplantation of the isolated intestine before the onset of liver failure improves early outcomes, decreases the length of hospitalization, and allows more rapid conversion to a full enteral diet, as compared with multiorgan transplantation.⁴⁵ The advantage of single-organ over multiorgan transplantation with respect to long-term survival has yet to be proved. However, in the case of life-threatening complications, an isolated intestinal graft may be removed and parenteral nutrition temporarily reinstated while the patient awaits repeat transplantation.²⁷ Earlier referral and prioritized allocation of pediatric transplants to children in need of multiorgan grafts have also decreased the number of deaths among children on the waiting list.⁴⁶

GRAFT REJECTION

Graft failure and death after transplantation are most closely related to the development of rejection.

Among 922 recipients of intestinal transplants between 2002 and 2007, rejection was strongly associated with both graft loss and patient death (Grant D, Intestinal Transplant Registry). Multiple factors have led to a decrease in the rates of rejection. Early diagnosis is critical for successful reversal of the rejection process. Despite considerable effort to find one, no minimally invasive marker reliably predicts rejection. Endoscopic surveillance biopsy remains the standard for diagnosing this problem (Fig. 3). The standardized histologic grading of rejection has allowed more consistent early diagnosis and has helped to discriminate graft rejection from viral infection.⁴⁷ Several centers have reported decreases in the rate and severity of early acute rejection with the use of newer medications, including monoclonal interleukin-2 antagonists, polyclonal antithymocyte antibodies, and sirolimus.⁴⁸⁻⁵⁰ Acute cellular rejection in the first 90 days, which previously oc-

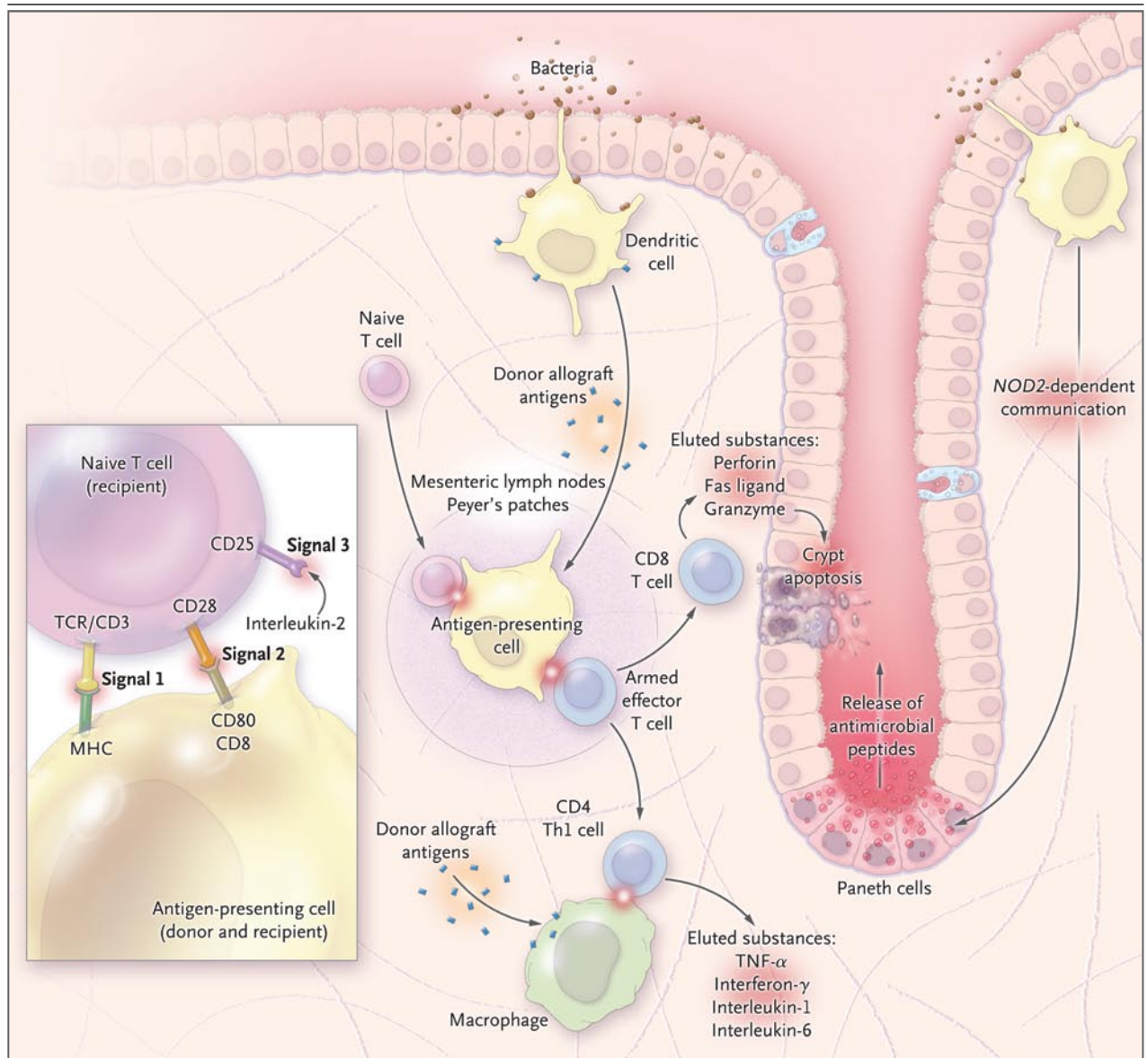


Figure 2. Immunologic Response to the Donor Allograft in Intestinal Transplantation.

The immunologic response involves six steps, some of which may occur simultaneously. Naive T cells infiltrate the allograft and undergo priming and activation in the donor mesenteric lymph nodes and Peyer's patches. In other solid organs, such priming occurs primarily in recipient lymphoid tissues. Donor antigen-presenting cells, such as dendritic cells, then ingest and display the "foreign" graft antigens in association with class I and II molecules of the major histocompatibility complex (MHC) (see inset). Antigen-presenting cells are stimulated to express costimulatory effectors required to "arm" naive CD8⁺ cytotoxic T cells and predominantly CD4⁺ type 1 helper T cells (Th1 cells). The CD8⁺ cytotoxic T cells attack certain donor-cell targets and produce substances, including perforin, granzyme, and Fas ligand, that lead to crypt-cell apoptosis. Armed Th1 cells provoke an inflammatory state driven by the production of cytokines, including interferon- γ . The dendritic cell also maintains immune defenses of the epithelium by regulating secretion of the antimicrobial peptide human defensin 5 from Paneth cells by means of *NOD2*-dependent circuits. Recipients with mutations in the *NOD2* gene are at significantly increased risk for immunologic graft loss, possibly owing to inadequate antimicrobial defense, which results in epithelial damage, bacterial invasion, and a secondary inflammatory response. The inset shows the signals involved in the immune response involving the recipient naive T cell and antigen-presenting cells. Tacrolimus interferes with signal 1. To date, no inhibitors to block signal 2 have been approved for use in humans. Interleukin-2 monoclonal antibodies and sirolimus (rapamycin) inhibit signal 3. TCR denotes T-cell receptor, and TNF tumor necrosis factor.

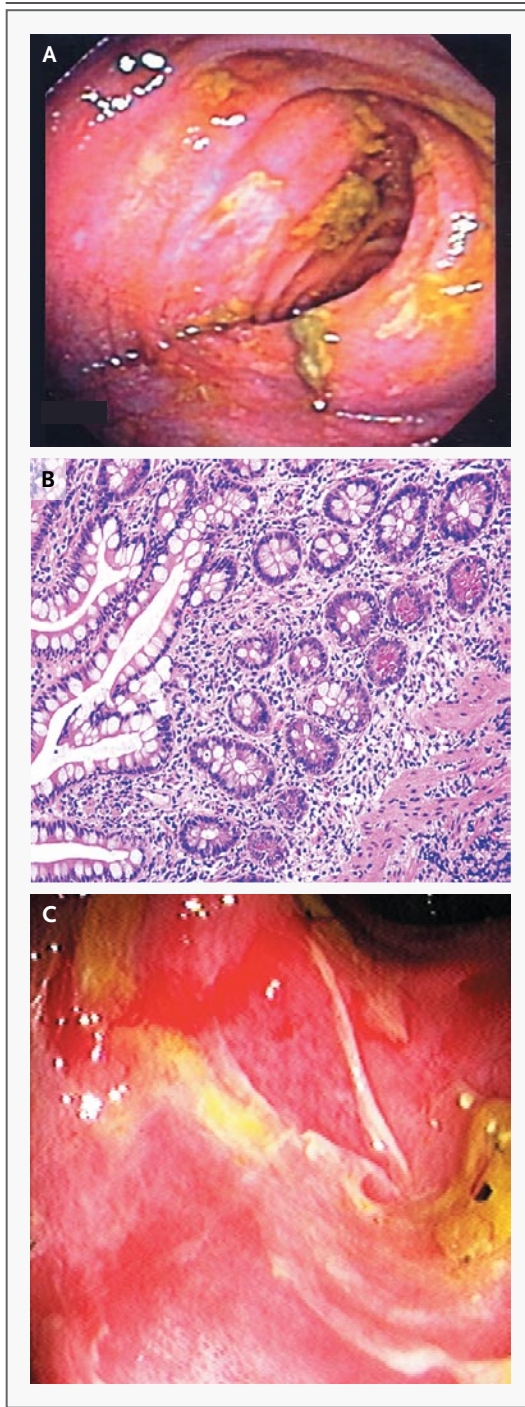


Figure 3. Endoscopic Views and Biopsy Specimen with Evolving Rejection of an Ileal Allograft.

Edema and erythema are evident in this endoscopic view of graft rejection after ileal transplantation (Panel A). A histologic specimen from the endoscopic biopsy reveals increased destruction of crypt cells, apoptosis, and a lamina propria infiltrate of mixed cellularity, findings that are characteristic of evolving rejection (Panel B, hematoxylin and eosin). If untreated, the rejection process progresses to erosions and eventually mucosal dissolution (Panel C).

in specimens from surveillance biopsies correlates with late graft loss suggests that early intervention in such cases could further improve survival.⁵¹ The effect of other conditions, such as mutations of *NOD2* (the gene encoding nucleotide-binding oligomerization domain–containing 2) that are associated with Crohn's disease, is just now being recognized as a cause of increased immunologic risk.^{52–54}

INFECTION

Infections remain common after transplantation.⁴⁶ In the medical management of intestinal-transplant recipients, it is essential to distinguish viral or bacterial enteritis from rejection. Both conditions may be characterized by diarrhea, and endoscopic evaluation of the graft mucosa is warranted if they are suspected at any interval after transplantation. Adenovirus, calicivirus, *Clostridium difficile*, and cytomegalovirus infections may all masquerade as rejection, and biopsy evaluation by a pathologist experienced with intestinal transplants is necessary.^{55,56} Only recently has the number of misdiagnoses been decreased by sufficient experience and detailed descriptions of the differences in biopsy specimens between infection with these pathogens and graft rejection. Whereas augmented immunosuppression is the treatment for rejection, it may have disastrous consequences in the presence of viral infection. Post-transplantation lymphoproliferative disorder, driven by Epstein–Barr virus, was initially common after pediatric intestinal transplantation, occurring in 20% of patients in 1992 but decreasing to only 7% by 2007. With early detection of viremia by a quantitative polymerase-chain-reaction assay and treatment with rituximab, a monoclonal antibody against the B-lymphocyte CD20 receptor, this problem is now managed much more effectively.

occurred in 70 to 90% of transplant recipients, is now seen in only one third to one half of patients. Better control of rejection has improved early graft survival and can be expected to have an effect on long-term survival as experience increases. Some evidence that asymptomatic rejection as detected

GRAFT DYSFUNCTION

The common symptom in virtually all cases of allograft dysfunction is diarrhea, which may be caused by an infection, rejection, antibiotic use, or poor food choice. In the absence of known food allergy or rapid gastric emptying (the dumping syndrome), histologic examination is essential for an accurate diagnosis. Assessment for infectious agents is performed with the use of stool cultures, plasma assays (for adenovirus, Epstein–Barr virus, and norovirus), and immunohistochemical studies of graft-biopsy specimens (for cytomegalovirus, Epstein–Barr virus, norovirus, and adenovirus). Viral infections are more common in children and during the first 3 months after transplantation, when levels of immunosuppression are still high. Judicious withdrawal of immunosuppressive therapy is coupled with the administration of antiviral medication. Owing to the poorly understood, multifactorial nature of the diarrhea, the standard evaluations — that is, testing for fecal reducing substances and obtaining stool cultures to detect overgrowth — are rarely helpful. Bloody diarrhea is frequently a sign of severe rejection with mucosal erosion or sloughing. However, ileal ulcers near an anastomotic site may also cause chronic anemia; these ulcers sometimes respond to treatment with antibodies against tumor necrosis factor, but they often recur in the absence of any discernible cause, suggesting mechanisms similar to those causing other inflammatory bowel diseases.⁵⁴ The causes of such lesions remain poorly understood even today.

OUTCOMES

GRAFT AND PATIENT SURVIVAL

Marked improvements in survival have occurred over the past decade.^{15,33,57} The 1-year rate of graft survival for recipients of intestinal and multiorgan transplants in North America increased from 52% in 1997 to 75% in 2005.¹ Similarly, the 1-year rate of patient survival improved from 57% in 1997 to 80% in 2005.¹ Rates of patient survival at 3 and 5 years for transplantations performed between 1997 and 2000 have remained modest at 61% and 47%, respectively, according to pooled data (<http://optn.transplant.hrsa.gov>). Such large database outcomes are limited by variations in survival rates among centers and the changes in practice that have occurred over the past decade. More recent

results at centers where larger numbers of transplantations are performed include survival rates exceeding 90% at 1 year and should translate into improved long-term survival.^{33,57,58} Patients who have been admitted directly from home to undergo transplantation, younger patients, those who have received a first transplant, and those who receive antibody induction therapy or maintenance sirolimus are most likely to survive.^{15,19,54,59-79} These findings emphasize the importance of early referral of patients who are well enough to await transplantation at home and to tolerate aggressive induction immunosuppression.

QUALITY OF LIFE AND COST

Several studies confirm that the state of intestinal failure is associated with significant psychosocial disability, decreased quality of life, and increased narcotic dependence, all of which improve after successful transplantation.^{68,80,81} More than 80% of transplant recipients who survive attain freedom from parenteral nutritional support and can resume regular activities (with high Karnofsky performance scores).¹⁵ One study assessed the quality of life among adults who were receiving parenteral nutrition at home after intestinal transplantation. They were weaned from nutritional support at a median of 18 days after transplantation and reported improvements in quality-of-life indicators such as anxiety, depression, cognitive emotion, stress, parenting, digestive and urinary function, control of impulsiveness, medical compliance, quality of social relations, and leisure and recreation.²⁸ Dependence on narcotics decreased after transplantation. Responses on the Child Health Questionnaire were similar among children who had undergone transplantation 5 years earlier and healthy children, although the parents of the treated children perceived mild decreases in physical and psychosocial functioning.

Extensive data on costs are also lacking, but published information to date indicates that, like renal transplantation, intestinal transplantation becomes cost-effective after approximately 2 years.⁸²

NUTRITION

Intestinal function after transplantation is usually mildly abnormal, necessitating some dietary restrictions. Foods containing insoluble cellulose or high in simple carbohydrates (salad, citrus fruits,

refined sugars) may cause type 1 (early) dumping symptoms. Thus, the diet may be modified by an individual clinician and patient according to tolerance. In patients with a longer colonic remnant or a transplanted colon, function may improve, but the use of anti-diarrheal medications (e.g., diphenoxylate and atropine [Lomotil, Pfizer] or loperamide [Imodium, McNeil]) is common. Vitamin, mineral, and micronutrient absorption is generally good, and routine assessments are not necessary. Several studies in children have shown linear growth and development after a transition to enteral feeding⁸³⁻⁸⁶ but failed to show “catch up” from the depressed growth curves seen before transplantation in virtually all these patients.

FUTURE APPLICATIONS

Each year thousands of patients who have total intestinal infarction due to mesenteric ischemia, necrotizing enterocolitis, volvulus, or other disorders that lead to irreversible intestinal failure die from sepsis because a planned resection is canceled. This practice of aborting resection is changing as such patients are given the opportunity to have an acceptable quality of life through the de-

livery of home parenteral nutrition and transplantation, with the promise of an eventual return to normal life. Although the number of intestinal transplants remains relatively small nationally, the rapid improvement in outcomes seen over the past decade presages a substantial increase in volume as well as broader indications to include preemptive transplantation for patients at low risk for complications and lifesaving treatment in cases once considered to be terminal. Isolated intestinal transplantation before liver failure occurs and the use of multiorgan transplants are likely to increase as long-term outcomes improve. Internists, pediatricians, and surgeons on the front lines continue to incorporate these procedures into their practices. Further insights into the immunologic characteristics of intestinal transplantation, with its associated inflammation, should also continue to improve our understanding of intestinal inflammatory conditions in general.

No potential conflict of interest relevant to this article was reported.

I thank my clinical mentors, Dr. Charles Miller and Dr. Jorge Reyes, my scientific collaborators, Dr. Michael Zasloff and Dr. Kenneth Newell, and the patients whose contributions have helped further our knowledge and improve treatment for future patients.

REFERENCES

- Hanto DW, Fishbein TM, Pinson CW, et al. Liver and intestine transplantation: summary analysis, 1994-2003. *Am J Transplant* 2005;5:916-33.
- Wilmore DW, Lacey JM, Soultanakis RP, Bosch RL, Byrne TA. Factors predicting a successful outcome after pharmacologic bowel compensation. *Ann Surg* 1997; 226:288-92.
- Howard L, Ament M, Fleming CR, Shike M, Steiger E. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology* 1995;109:355-65.
- Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. *Gastroenterology* 1999;117:1043-50.
- Chan S, McCowen KC, Bistrain BR, et al. Incidence, prognosis, and etiology of end-stage liver disease in patients receiving home total parenteral nutrition. *Surgery* 1999;126:28-34.
- Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition-treated patients: 20 years of experience at the Mayo Clinic. *Mayo Clin Proc* 1999;74:217-22.
- Howard L, Malone M. Current status of home parenteral nutrition in the United States. *Transplant Proc* 1996;28:2691-5.
- Thakur A, Chiu C, Quiros-Tejiera RE, et al. Morbidity and mortality of short-bowel syndrome in infants with abdominal wall defects. *Am Surg* 2002;68:75-9.
- Van Gossum A, Vahedi K, Abdel-Malik M, et al. Clinical, social and rehabilitation status of long-term home parenteral nutrition patients: results of a European multicentre survey. *Clin Nutr* 2001;20:205-10.
- Casey L, Lee KH, Rosychuk R, Turner J, Huynh HQ. 10-Year review of pediatric intestinal failure: clinical factors associated with outcome. *Nutr Clin Pract* 2008;23: 436-42.
- Fishbein TM, Schiano T, LeLeiko N, et al. An integrated approach to intestinal failure: results of a new program with total parenteral nutrition, bowel rehabilitation, and transplantation. *J Gastrointest Surg* 2002;6:554-62.
- Quiros-Tejiera RE, Ament ME, Reyner L, et al. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. *J Pediatr* 2004;145:157-63.
- Sondheimer JM, Asturias E, Cadnapaphornchai M. Infection and cholestasis in neonates with intestinal resection and long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr* 1998;27:131-7.
- Carbonnel F, Cosnes J, Chevret S, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. *JPEN J Parenter Enteral Nutr* 1996;20:275-80.
- Grant D, Abu-Elmagd K, Reyes J, et al. 2003 Report of the intestine transplant registry: a new era has dawned. *Ann Surg* 2005;241:607-13.
- Florman SS, Fishbein TM, Schiano T, Letizia A, Fennelly E, DeSancho M. Multi-visceral transplantation for portal hypertension and diffuse mesenteric thrombosis caused by protein C deficiency. *Transplantation* 2002;74:406-7.
- Vargas JH, Ament ME, Berquist WE. Long-term home parenteral nutrition in pediatrics: ten years of experience in 102 patients. *J Pediatr Gastroenterol Nutr* 1987;6:24-32.
- Ricour C. Home TPN. *Nutrition* 1989; 5:345-6.
- Fecteau A, Atkinson P, Grant D. Early referral is essential for successful pediatric small bowel transplantation: the Canadian experience. *J Pediatr Surg* 2001;36:681-4.
- Sigalet DL. Short bowel syndrome in infants and children: an overview. *Semin Pediatr Surg* 2001;10:49-55.

21. Beath S, Pironi L, Gabe S, et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. *Transplantation* 2008;85:1378-84.
22. Buchman AL, Iyer K, Fryer J. Parenteral nutrition-associated liver disease and the role for isolated intestine and intestine/liver transplantation. *Hepatology* 2006;43:9-19.
23. Gura KM, Duggan CP, Collier SB, et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. *Pediatrics* 2006;118(1):e197-e201.
24. Fleming CR. Hepatobiliary complications in adults receiving nutrition support. *Dig Dis* 1994;12:191-8.
25. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000;132:525-32.
26. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology* 2003;124:1111-34.
27. Fishbein TM, Matsumoto CS. Intestinal replacement therapy: timing and indications for referral of patients to an intestinal rehabilitation and transplant program. *Gastroenterology* 2006;130:Suppl 1:S147-S151.
28. O'Keefe SJ, Emerling M, Koritsky D, et al. Nutrition and quality of life following small intestinal transplantation. *Am J Gastroenterol* 2007;102:1093-100.
29. Howard L. Home parenteral nutrition: survival, cost, and quality of life. *Gastroenterology* 2006;130:Suppl 1:S52-S59.
30. Fryer J, Pellar S, Ormond D, Koffron A, Abecassis M. Mortality in candidates waiting for combined liver-intestine transplants exceeds that for other candidates waiting for liver transplants. *Liver Transpl* 2003;9:748-53.
31. Sudan DL, Iyer KR, Deroover A, et al. A new technique for combined liver/small intestinal transplantation. *Transplantation* 2001;72:1846-8.
32. Fiel MI, Sauter B, Wu HS, et al. Regression of hepatic fibrosis after intestinal transplantation in total parenteral nutrition liver disease. *Clin Gastroenterol Hepatol* 2008;6:926-33.
33. Fishbein TM, Kaufman SS, Florman SS, et al. Isolated intestinal transplantation: proof of clinical efficacy. *Transplantation* 2003;76:636-40.
34. Chung C, Buchman AL. Postoperative jaundice and total parenteral nutrition-associated hepatic dysfunction. *Clin Liver Dis* 2002;6:1067-84.
35. Salvia G, Guarino A, Terrin G, et al. Neonatal onset intestinal failure: an Italian multicenter study. *J Pediatr* 2008;153:674-6.
36. Todo S, Tzakis A, Reyes J, et al. Small intestinal transplantation in humans with or without the colon. *Transplantation* 1994;57:840-8.
37. Kato T, Selvaggi G, Gaynor JJ, et al. Inclusion of donor colon and ileocecal valve in intestinal transplantation. *Transplantation* 2008;86:293-7.
38. Matsumoto CS, Fishbein TM. Modified multivisceral transplantation with splenopancreatic preservation. *Transplantation* 2007;83:234-6.
39. Starzl TE, Kaupp HA Jr, Brock DR, Butz GW Jr, Linman JW. Homotransplantation of multiple visceral organs. *Am J Surg* 1962;103:219-29.
40. Todo S, Tzakis AG, Abu-Elmagd K, et al. Intestinal transplantation in composite visceral grafts or alone. *Ann Surg* 1992;216:223-33.
41. Mayer L. Mucosal immunity and gastrointestinal antigen processing. *J Pediatr Gastroenterol Nutr* 2000;30:Suppl:S4-S12.
42. Iwaki Y, Starzl TE, Yagihashi A, et al. Replacement of donor lymphoid tissue in small-bowel transplants. *Lancet* 1991;337:818-9.
43. Newell KA. Transplantation of the intestine: is it truly different? *Am J Transplant* 2003;3:1-2.
44. Vincenti F, Larsen C, Durrbach A, et al. Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005;353:770-81.
45. Kato T, Mittal N, Nishida S, et al. The role of intestinal transplantation in the management of babies with extensive gut resections. *J Pediatr Surg* 2003;38:145-9.
46. Guaraldi G, Cocchi S, Codeluppi M, et al. Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. *Transplantation* 2005;80:1742-8.
47. Ruiz P, Bagni A, Brown R, et al. Histological criteria for the identification of acute cellular rejection in human small bowel allografts: results of the pathology workshop at the VIII International Small Bowel Transplant Symposium. *Transplant Proc* 2004;36:335-7.
48. Tzakis AG, Kato T, Nishida S, et al. Preliminary experience with campath 1H (C1H) in intestinal and liver transplantation. *Transplantation* 2003;75:1227-31.
49. Sudan DL, Chinnakotla S, Horslen S, et al. Basiliximab decreases the incidence of acute rejection after intestinal transplantation. *Transplant Proc* 2002;34:940-1.
50. Fishbein TM, Florman S, Gondolesi G, et al. Intestinal transplantation before and after the introduction of sirolimus. *Transplantation* 2002;73:1538-42.
51. Takahashi H, Kato T, Selvaggi G, et al. Subclinical rejection in the initial postoperative period in small intestinal transplantation: a negative influence on graft survival. *Transplantation* 2007;84:689-96.
52. Fishbein T, Novitskiy G, Mishra L, et al. NOD2-expressing bone marrow-derived cells appear to regulate epithelial innate immunity of the transplanted human small intestine. *Gut* 2008;57:323-30.
53. Sarkar S, Selvaggi G, Mittal N, et al. Gastrointestinal tract ulcers in pediatric intestinal transplantation patients: etiology and management. *Pediatr Transplant* 2006;10:162-7.
54. Turner D, Martin S, Ngan BY, Grant D, Sherman PM. Anastomotic ulceration following small bowel transplantation. *Am J Transplant* 2006;6:236-40.
55. Bueno J, Green M, Kocoshis S, et al. Cytomegalovirus infection after intestinal transplantation in children. *Clin Infect Dis* 1997;25:1078-83.
56. Kaufman SS, Magid MS, Tschernia A, LeLeiko NS, Fishbein TM. Discrimination between acute rejection and adenoviral enteritis in intestinal transplant recipients. *Transplant Proc* 2002;34:943-5.
57. Sudan DL, Kaufman SS, Shaw BW Jr, et al. Isolated intestinal transplantation for intestinal failure. *Am J Gastroenterol* 2000;95:1506-15.
58. Reyes J, Mazariegos GV, Bond GM, et al. Pediatric intestinal transplantation: historical notes, principles and controversies. *Pediatr Transplant* 2002;6:193-207.
59. Andres AM, Thompson J, Grant W, et al. Repeat surgical bowel lengthening with the STEP procedure. *Transplantation* 2008;85:1294-9.
60. Florescu DE, Hill LA, McCartan MA, Grant W. Two cases of Norwalk virus enteritis following small bowel transplantation treated with oral human serum immunoglobulin. *Pediatr Transplant* 2008;12:372-5.
61. Lopushinsky SR, Fowler RA, Kulkarni GS, Fecteau AH, Grant DR, Wales PW. The optimal timing of intestinal transplantation for children with intestinal failure: a Markov analysis. *Ann Surg* 2007;246:1092-9.
62. Sudan D, Thompson J, Botha J, et al. Comparison of intestinal lengthening procedures for patients with short bowel syndrome. *Ann Surg* 2007;246:593-601.
63. Torres C, Sudan D, Vanderhoof J, et al. Role of an intestinal rehabilitation program in the treatment of advanced intestinal failure. *J Pediatr Gastroenterol Nutr* 2007;45:204-12.
64. Botha JF, Grant WJ, Torres C, et al. Isolated liver transplantation in infants with end-stage liver disease due to short bowel syndrome. *Liver Transpl* 2006;12:1062-6.
65. Diamond IR, Wales PW, Grant DR, Fecteau A. Isolated liver transplantation in pediatric short bowel syndrome: is there a role? *J Pediatr Surg* 2006;41:955-9.
66. Sudan D, DiBiase J, Torres C, et al.

- A multidisciplinary approach to the treatment of intestinal failure. *J Gastrointest Surg* 2005;9:165-76.
67. Chaney M. Financial considerations insurance and coverage issues in intestinal transplantation. *Prog Transplant* 2004;14:312-20.
68. Sudan D, Horslen S, Botha J, et al. Quality of life after pediatric intestinal transplantation: the perception of pediatric recipients and their parents. *Am J Transplant* 2004;4:407-13.
69. Kaila B, Grant D, Pettigrew N, Greenberg H, Bernstein CN. Crohn's disease recurrence in a small bowel transplant. *Am J Gastroenterol* 2004;99:158-62.
70. Kellersmann R, Lazarovits A, Grant D, et al. Monoclonal antibody against beta7 integrins, but not beta7 deficiency, attenuates intestinal allograft rejection in mice. *Transplantation* 2002;74:1327-34.
71. Sudan D, Grant W, Iyer K, Shaw B, Horslen S, Langnas A. Oral beclomethasone therapy for recurrent small bowel allograft rejection and intestinal graft-versus-host disease. *Transplant Proc* 2002;34:938-9.
72. Kiyochi H, Zhang Z, Jiang J, et al. Histologic comparison of small bowel, heart, and kidney xenografts in a rat to mouse model. *Transplant Proc* 2000;32:964.
73. Atkison P, Chatzipetrou M, Tsaroucha A, Lehmann R, Tzakis A, Grant D. Small bowel transplantation in children. *Pediatr Transplant* 1997;1:111-8.
74. Ozcay N, Fryer J, Grant D, Freeman D, Garcia B, Zhong R. Budesonide, a locally acting steroid, prevents graft rejection in a rat model of intestinal transplantation. *Transplantation* 1997;63:1220-5.
75. Zhang Z, Zhu L, Quan D, et al. Pattern of liver, kidney, heart, and intestine allograft rejection in different mouse strain combinations. *Transplantation* 1996;62:1267-72.
76. Fryer J, Jiang J, Zhong R, et al. Influence of macrophage depletion on bacterial translocation and rejection in small bowel transplantation. *Transplant Proc* 1996;28:2660.
77. Zhang Z, Zhu L, Garcia B, et al. Organ-specific differences in the pattern of allograft rejection in the mouse. *Transplant Proc* 1996;28:2487.
78. Quan D, Zhang Z, Zhong R, Jevnikar A, Garcia B, Grant D. Intestinal allograft rejection in lipopolysaccharide-hyporesponsive mice. *Transplant Proc* 1996;28:2460-1.
79. Fryer J, Grant D, Jiang J, et al. Influence of macrophage depletion on bacterial translocation and rejection in small bowel transplantation. *Transplantation* 1996;62:553-9.
80. Rovera GM, DiMartini A, Schoen RE, Rakela J, Abu-Elmagd K, Graham TO. Quality of life of patients after intestinal transplantation. *Transplantation* 1998;66:1141-5.
81. DiMartini A, Rovera GM, Graham TO, et al. Quality of life after small intestinal transplantation and among home parenteral nutrition patients. *JPEN J Parenter Enteral Nutr* 1998;22:357-62.
82. Sudan D. Cost and quality of life after intestinal transplantation. *Gastroenterology* 2006;130:Suppl 1:S158-S162.
83. Ueno T, Kato T, Revas K, et al. Growth after intestinal transplant in children. *Transplant Proc* 2006;38:1702-4.
84. Nucci AM, Barksdale EM Jr, Beserock N, et al. Long-term nutritional outcome after pediatric intestinal transplantation. *J Pediatr Surg* 2002;37:460-3.
85. Iyer K, Horslen S, Iverson A, et al. Nutritional outcome and growth of children after intestinal transplantation. *J Pediatr Surg* 2002;37:464-6.
86. Porubsky M, Testa G, John E, Holterman M, Tsou M, Benedetti E. Pattern of growth after pediatric living-donor small bowel transplantation. *Pediatr Transplant* 2006;10:701-6.

Copyright © 2009 Massachusetts Medical Society.



Mt. Emei, China

Ira Kirschenbaum, M.D.

CORRECTION

Intestinal Transplantation

Intestinal Transplantation . In Table 2 (page 1000), the heading above the first column of data should have read "Children (N=1031)," and the heading above the second column should have read "Adults (N=733)." The article has been corrected at NEJM.org.