PAPER

Outcome After Intestinal Transplantation

Results From One Center's 9-Year Experience

Douglas G. Farmer, MD; Suzanne V. McDiarmid, MD; Hasan Yersiz, MD; Galen Cortina, MD; Farin Amersi, MD; Jorge Vargas, MD; George Gershman, MD; Marvin Ament, MD; Ronald W. Busuttil, MD, PhD

Hypothesis: Outcomes after intestinal transplantation have improved during the past decade with refinements in surgical techniques as well as advances in immunosuppression and antimicrobial therapy.

Design: Retrospective analysis.

Setting: Tertiary care medical center, August 1991 through December 2000.

Patients: Adult (5) and pediatric (12) patients with intestinal failure. All developed complications from long-term total parenteral nutrition therapy. Median age was 8.6 years and median weight was 22 kg.

Interventions: Primary intestinal transplantation with (n=14) or without (n=3) the liver.

Main Outcome Measures: Patient and graft survival, viral infections, rejection, and nutritional autonomy.

Results: Twenty-one intestinal grafts were transplanted into the 17 recipients. All donors were cadaveric and were matched by ABO blood group and size. Patient survival at 1 and 3 years was 63% and 55%, respectively. Death-censored graft survival at 1 and 3 years was 73% and 55%, respectively. There were 1.5 acute cellular rejection episodes per graft and 3 grafts were lost to rejection. Incidences of infection with the Epstein-Barr virus and cytomegalovirus were negligible with aggressive prophylaxis and preemptive therapy. Nutritional autonomy was achieved in 69% of grafts surviving more than 30 days after intestinal transplantation.

Conclusions: Intestinal transplantation is now the standard of therapy for patients with intestinal failure and complications resulting from total parenteral nutrition. Outcomes have markedly improved since initiation of the program. Aggressive immunosuppression as well as prophylaxis and preemptive antiviral therapy have led to low incidences of acute cellular rejection, Epstein-Barr virus, and cytomegalovirus. Finally, nutritional autonomy can be achieved after successful intestinal transplantation.

Arch Surg. 2001;136:1027-1032

From the Departments of Surgery (Drs Farmer, Yersiz, Amersi, and Busuttil); Pediatrics (Drs McDiarmid, Vargas, Gershman, and Ament); and Pathology (Dr Cortina), University of California, Los Angeles, UCLA School of Medicine, Los Angeles.

INTESTINAL transplantation (IT) has emerged as a clinical reality during the 1990s owing primarily to the clinical application of the potent immunosuppressant tacrolimus as well as the standardization of surgical techniques.[1-11] Still, outcomes lag behind those seen in other solid organ transplantations, limiting the widespread application of this procedure. Owing to the complexity of the procedure and postoperative care, few centers worldwide have initiated IT programs, leaving the bulk of the clinical experience restricted to a small number of specialized centers. Ours was one of the initial centers to develop a comprehensive program of IT,[12,13] and this article reviews our experience to date.

RESULTS

Seventeen patients underwent primary transplantations involving the intestine (**Table 1**). Most recipients were children aged 13.2±13.1 years and weighed 36.7±26 kg. Recipients had been dependent on TPN for 68%±43% of their lifetimes. The etiology of short-bowel syndrome includes trauma, jejunoileal atresia, necrotizing enterocolitis, gastroschisis, and inflammatory bowel disease (**Figure 1**). The estimated length of remnant intestine was 53.7±93.5 cm.

The manifestations of IF are presented in **Table 2**. Most patients had advanced liver disease with TPN as the

PATIENTS AND METHODS

In September 1991, an IT program was initiated at the Dumont-UCLA Transplant Center (Los Angeles). A retrospective analysis of all patients undergoing transplantation involving the intestine was undertaken. Data sources included medical center and transplant center records. No patient was lost to follow-up and the study was concluded on December 31, 2000.

Candidates were selected using a multidisciplinary approach. The indications for IT were irreversible intestinal failure (IF) associated with 1 or more life-threatening complications that included liver disease, loss of central venous access sites, frequent central venous catheter infections, and major fluid/electrolyte imbalances associated with proximal gastrointestinal stomas or fistulas.

Donors were selected based on quality, blood group match, hemodynamic stability, and size. ABO blood group compatible donors were accepted. A donor approximately half the size of the recipient was ideal. The donor procurement was altered slightly from that described elsewhere.[14,15] En bloc retrieval of the liver and small intestine on a vascular pedical including the superior mesenteric and celiac arteries was performed. For isolated ITs, the entire jejunoileum was procured on its vascular pedical, consisting of the superior mesenteric artery and vein.

The conduct of the recipient operation has been described previously.[12] For combined liver and IT, the grafts were placed in the orthotopic position with retention of the recipient infrahepatic vena cava ("piggyback technique") in all but the first 2 transplants. Arterial inflow was via a supraceliac aortic conduit with venous outflow via the donor vena cava. The recipient portal vein was anastomosed to the side of the donor portal vein except in 2 cases in which ligation was required. Intestinal continuity was restored using a proximal enterojejunostomy and a distal ileocolostomy. An ileostomy was also constructed for monitoring purposes. Biliary continuity was restored with a choledochojejunostomy using the transplanted jejunum as a defunctionalized limb. For isolated IT, the bowel was placed in the orthotopic position with arterial inflow from the infrarenal aorta and venous outflow into either the portomesenteric system (preferred) or the infrarenal vena cava. Intestinal continuity was as described for the combined liver-intestinal grafts.

Immunosuppressive regimens varied during the study period. The current regimen is tacrolimus-based and includes induction with an interleukin 2 receptor antagonist and maintenance with mycophenolate mofetil and steroids. Endoscopic graft surveillance was undertaken at predetermined intervals as well as when clinically indicated. Acute cellular rejection (ACR) was diagnosed using standard histopathologic and clinical criteria and was treated with pulsed steroids as the first line of therapy. Muromonab-CD3 was given for steroid-resistant episodes.

Enteral nutrition was initiated with the return of allograft function. Feeding was accomplished via a surgically place tube in the allograft jejunum using elemental formulas. Total parenteral nutrition (TPN) was discontinued once all caloric needs were met using the enteral route.

Data regarding the donor and recipient cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection status as well as the incidence of posttransplantation viremia and tissue infection were also analyzed. Since 1996, an aggressive protocol against CMV and EBV using prophylactic and preemptive therapy with ganciclovir and CMV immune globulin has been instituted.[16] Frequent patient monitoring for viremia has been accomplished using peripheral blood polymerase chain reaction testing for viral DNA.[17,18]

Survival was calculated using the method of Kaplan and Meier. Comparison between means and medians of the variables was accomplished using the unpaired 2-tailed *t* test and the Wilcoxon rank-sum test, respectively. Categorical variables were compared using the Pearson χ^2 test. Statistical significance was defined as $P \leq .05$. Data are reported as mean ± SD unless otherwise specified.

Table 1. Recipient Demographics*

Parameter	
M/F ratio	9:8
Adult-child ratio	5:12
Age, y	13.2 ± 13.1
Weight, kg	36.7 ± 26.0
Receiving TPN (% of lifetime)	68 ± 43
Estimated remnant, cm	53.7 ± 93.5
ICV present, No. (%)	3/17 (18)
Prior abdominal operations per patient	4 ± 2.7

*N = 17. Data are given as mean ± SD unless otherwise indicated.
TPN indicates total parenteral nutrition; ICV, ileocecal valve.

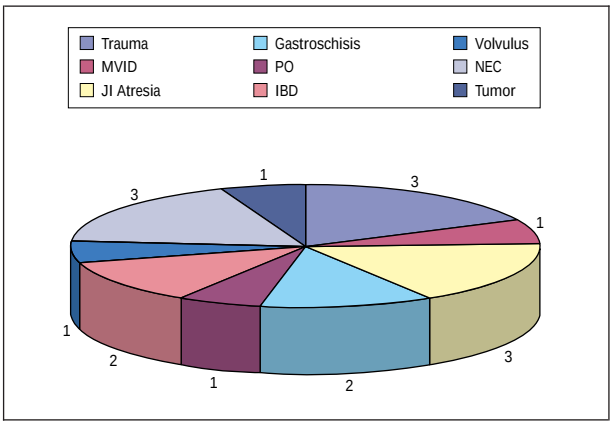

Figure 1. The etiology of short-bowel syndrome in 17 patients undergoing intestinal transplantation. MVID indicates microvillus inclusion disease; JI, jejunoileal; PO, pseudo-obstruction; IBD, inflammatory bowel disease; and NEC, necrotizing enterocolitis.

primary cause. Secondary causes included hepatitis C, hepatitis B, secondary hemochromatosis, and sclerosing cholangitis. The preoperative bilirubin level and prothrombin time in these patients were 30.1±13.8 mg/dL (515±236 µmol/L) and 14.1±4.1 seconds, respectively. There were 3 patients with early or insignificant liver injury related to TPN. The other major manifestations of IF included recurrent central venous catheter infections, limited vascular access, and nonreconstructible gastrointestinal tracts.

Table 2. Manifestations of Intestinal Failure*

Parameter	Result
ESLD, No. (%)	14 (82.4)
Etiology, No. of patients	
TPN	9
TPN + HCV	2
TPN + HBV	1
TPN + Fe	1
TPN + other	1
	None (3)
Mean ± SD preoperative total bilirubin, mg/dL	30.1 ± 13.8
Mean ± SD preoperative PT, s	14.1 ± 4.1
Line infection, No. (%) of patients	9 (52.3)
Vascular access, No. (%) of patients	8/17 (47.1)
Nonreconstructable, No. (%) of patients	5 (29.4)

*ESLD indicates end-stage liver disease; TPN, total parenteral nutrition; HCV, hepatitis C virus; HBV, hepatitis B virus; and PT, prothrombin time.

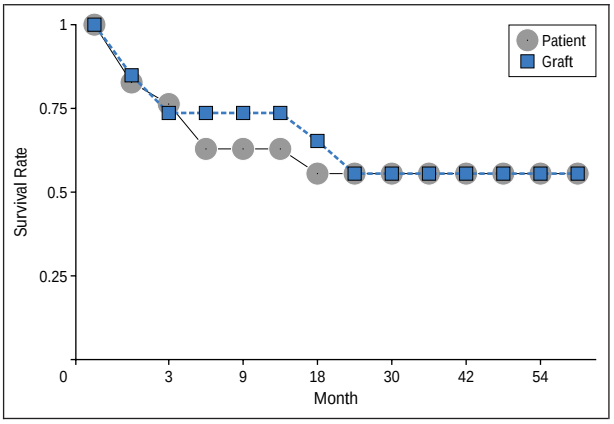

Figure 2. Patient and graft survival. The actuarial patient and death-censored graft survival vs month after intestinal transplantation is shown for all 17 patients undergoing transplantation.

The waiting time for suitable donor organs after listing was 76.1±62.4 days. Forty-one percent of the recipients were intensive care unit-bound prior to transplantation while another 41% were hospital-bound prior to IT. Four patients required retransplantation a median of 107 days (range, 5-669 days) after the primary IT. Unless otherwise specified, the retransplanted grafts are not included in the analysis.

There were 21 donors used for the 17 primary and 4 secondary ITs. Donors were aged 13.3±8.4 years. The weight ratio between the donor and recipient was 0.95±0.5. ABO blood group matching of the donor and recipient was either identical (85.7%) or compatible (14.3%). HLA matching was random.

Combined liver and intestinal grafts were required in 14 patients while 2 patients received isolated intestinal grafts and 1 received an en bloc intestine plus pancreas graft. Retransplantation was performed using the combined liver and intestinal graft (3 patients) or isolated intestine (1). The lengths of operative and ischemic times were 9:06±1:35 hours:minutes and 6:09±1:42 hours:minutes, respectively. Blood loss during the procedure as estimated by the volume of packed red blood cells transfused was 3.8±4.8 L.

The patient and graft survival after primary IT is shown in **Figure 2**. The patient survival at 1 year and 3 years after IT was 63% and 55%. Sepsis accounted for 63% of all patient deaths. For the same time points, the death-censored graft survival was 73% and 55% for the total group. The most common cause of graft loss was ACR (3 patients), primary nonfunction (1), and hepatic artery thrombosis (2). Three patients died with a functioning allograft.

Rejection of the 16 grafts functioning more than 30 days after IT was reported as the mean time to first ACR and was 44±26 days. No graft was lost to rejection before postoperative day 30. There were a total of 20 separate episodes of ACR after IT for an incidence of 1.5±1.1 episodes per graft. Fourteen ACR episodes (70%) responded to adjustment in the primary immunosuppression regimen or the addition of pulsed tapered steroids. Three ACR episodes (15%) required muromonab-CD3 therapy for resolution and 3 episodes (15%) required enterectomy.

Enteral tube feedings were initiated 9.6±4.3 days after IT. Independence from TPN was achieved in 81.3% of the 16 grafts surviving more than 30 days after IT. Remarkably, all (3/3) of the grafts surviving more than 30 days after retransplantation achieved TPN independence. At 1 year after IT, patients demonstrated a 20%±14% weight gain above the pretransplantation weight. The serum prealbumin level at 1 year was 23.5±7.3 mg/dL (reference range, 19.0-38.4 mg/dL).

The incidence of viral infection was analyzed in the 13 patients who received transplants after 1996—the year in which preemptive and prophylactic therapies were introduced. The donor-recipient (D/R) pretransplantation CMV status (+, positive; –, negative) was: D+/R+ (6 patients), D+/R– (2), D–/R+ (3) and D–/R– (2). Viremia occurred 6 times in 4 patients (incidence, 30.7%). Two tissue-invasive infections (incidence, 15.4%)—recipient bowel (1) and allograft (1)—occurred, both of which were associated with viremia. All episodes of viremia were successfully treated medically with no patient or graft lost to CMV disease.

The D/R pretransplant EBV status was D+/R+ (5), $D_{unknown}$/R+ (5), D+/R– (1), D–/R+ (1), and D–/R– (1). Viremia occurred in 6 patients (incidence, 46.2%). Only 1 episode (incidence, 7.7%) of tissue involvement was found in which an allograft biopsy stained positive for EBV after treatment of an episode of ACR with muromonab-CD3. Complete resolution was achieved using medical therapy and no episodes of frank EBV-driven lymphoma have been seen to date.

COMMENT

Intestinal transplantation has evolved into a clinical reality since 1990, largely driven by a few specialized transplant centers.[6,8,10] This report, representing one of the larger series of IT recipients published to date, reflects many of the advances that have been made during the past decade.

The development of clear indications for IT has been a major advancement in this field. Today, IT should be considered only for patients with IF and 1 or more TPN-related, life-threatening complications, such as liver disease, loss of central venous access sites, recurrent catheter infections, or major fluid and electrolyte imbalances.[19] These patients have a poor chance for long-term sur-

vival when receiving TPN, and therefore the outcomes after IT demonstrated by many centers[20] including this one, offer improved prognosis. Conversely, most patients receiving long-term TPN therapy do not develop life-threatening complications and therefore, have a prognosis superior to that offered by IT at this time. This latter group would not benefit from IT.

Early referral for IT is crucial for improvement in outcomes as advanced organ failure coupled with long wait times for transplantation undoubtedly limit outcome.[21,22] Although some progress in this regard has been seen, candidates will often have advanced manifestations of IF on initial examination, as indicated by the high percentage of recipients requiring hospitalization prior to IT in this series. Furthermore, wait-list mortality rates, reported to be as high as 50% for IT candidates in other centers,[23,24] are compounded by the long waiting times caused by critical shortages in donor organs. Therefore, early referral for evaluation is crucial to obtaining suitable donor organs prior to recipient deterioration.

Restricted donor selection has traditionally limited donor availability. Donor-recipient size matching is critical and we continue to target a donor size that is approximately half that of the recipient to allow optimal positioning of organs in the recipient. The preferential use of the CMV/EBV-negative donor, although championed by other centers,[6] has not been necessary in our experience because of the effective prophylaxis against and treatment for these viruses. The role of HLA typing and histocompatibility testing in this population is not known, although with the known immunogenicity of the intestine, it is logical to assume that a closely matched organ may have some immunological advantage. These practices certainly limit potential donors and we therefore do not seek to HLA match or tissue type except for recipients of isolated intestinal grafts with high preformed antibody levels.[25]

Outcomes after IT have markedly improved. Ten years ago, success was measured by the sporadic survivor reported in the literature.[26-30] Today, survival rates similar to those reported herein are found in the literature in large series of patients. Two major areas of progress have contributed to these improvements in outcome. First, although the immunogenicity of the intestine is still a limiting factor, the use of tacrolimus-based immunosuppression regimens has enabled immunologic success. This is particularly evident in this series by the relatively low incidence of ACR compared with other series on IT. Still, the incidences of ACR after IT are much higher than those reported after other solid organ transplantations such as the liver or kidney, indicating that the optimal immunosuppressive regimen for IT is not known.

The second major area contributing to improved outcomes after IT is the control of CMV and EBV disease, which have been reported to have high incidences after IT, frequently leading to patient death and/or graft loss.[3,30] In our experience, as a result of the initiation of aggressive prophylaxis and preemptive antiviral protocols, not only have low incidences of CMV and EBV disease been seen but all episodes of viremia and tissue infection have resolved with therapy, thereby eliminating graft loss to these viruses.

Autonomy from TPN is also a requisite for successful IT. The fact that 81% of patients in this series discontinued TPN substantiates this indicator. In fact, the only patients not weaning completely off TPN were the few that lived more than 30 days but died prior to hospital discharge. Similar findings have been reported by other centers.[8,31] We advocate long-term systematic evaluation of nutritional autonomy, including anthropometric measurements, serum nutritional parameters, and absorptive testing.

This series has demonstrated the progress made in IT. Standardization of indications and identification of recipients who can benefit from this procedure have been crucial developments. Early referral for evaluation should also help improve outcomes. Future progress will most likely result from optimization of immunosuppression protocols in an effort to reduce toxicity while improving efficacy.

Presented at the 72nd Annual Meeting of the Pacific Coast Surgical Association, Banff, Canada, February 18, 2001.

This study was supported in part through the generosity of the Dumont Foundation, Los Angeles, Calif.

We would like to acknowledge Natalie Amos, RN, Gregg Kunder, RN, A. J. Maxfield, RN, Beth Vandenbogaart, RN, and Laurie Reyen, RN, for their dedicated service to patient care; and Lena Ting, MS, for her statistical expertise.

Corresponding author: Douglas G. Farmer, MD, Dumont-UCLA Transplant Center, Room 77-120 CHS, Box 957054, Los Angeles, CA 90095-7054 (e-mail: dgfarmer@mednet.ucla.edu).

REFERENCES

1. Todo S, Tzakis A, Abu-Elmagd K, et al. Intestinal transplantation in composite visceral grafts or alone. *Ann Surg.* 1992;216:223-234.
2. Abu-Elmagd K, Todo S, Tzakis A, et al. Three years clinical experience with intestinal transplantation. *J Am Coll Surg.* 1994;179:385-400.
3. Todo S, Reyes J, Furukawa H, et al. Outcome analysis of 71 clinical intestinal transplantations. *Ann Surg.* 1995;222:270-282.
4. Todo S, Tzakis A, Abu-Elmagd K, et al. Abdominal multivisceral transplantation. *Transplantation.* 1995;59:234-240.
5. Kocoshis SA, Reyes J, Todo S, et al. Small intestine transplantation for irreversible intestinal failure in children. *Dig Dis Sci.* 1997;42:1997-2008.
6. Abu-Elmagd K, Reyes J, Todo S, et al. Clinical intestinal transplantation. *J Am Coll Surg.* 1998;186:512-527.
7. Farmer DG, McDiarmid SV, Smith C, et al. Experience with combined liver-small intestine transplantation at the University of California, Los Angeles. *Transplant Proc.* 1998;30:2533-2534.
8. Langnas AN, Shaw BW Jr, Antonson DL, et al. Preliminary experience with intestinal transplantation in infants and children. *Pediatrics.* 1998;97:443-448.
9. Jan D, Michel JL, Goulet O, et al. Up-to-date evolution of small bowel transplantation in children with intestinal failure. *J Pediatr Surg.* 1999;34:841-844.
10. Pinna AD, Weppler D, Nery J, et al. Intestinal transplantation at the University of Miami—five years of experience. *Transplant Proc.* 2000;32:1226-1227.
11. Farmer DG, McDiarmid SV, Yersiz H, et al. Improved outcome after intestinal transplantation. *Transplant Proc.* 2000;32:1233-1234.
12. Busuttil RW, Farmer DG, Shaked A, et al. Successful combined liver and small intestine transplantation for short gut syndrome and liver failure. *West J Med.* 1993;158:184-188.
13. Farmer DG, Shaked A, McDiarmid SV, et al. Small intestine transplantation (SIT) at the University of California, Los Angeles (UCLA). *Transplant Proc.* 1996;28:2746-2747.
14. Casavilla A, Selby R, Abu-Elmagd K, et al. Logistics and technique for combined hepatic-intestinal retrieval. *Ann Surg.* 1992;216:605-609.
15. Sindhi R, Fox IJ, Heffron T, et al. Procurement and preparation of human isolated small intestinal grafts for transplantation. *Transplantation.* 1995;60:771-773.
16. Winston DJ, Wirin D, Shaked A, et al. Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet.* 1995;346(8967):69-74.
17. Humar A, Gregson D, Caliendo AM, et al. Clinical utility of quantitative cytomegalovirus viral load determinations for predicting cytomegalovirus disease in liver transplant recipients. *Transplantation.* 1999;68:1305-1311.
18. Kenagy DN, Schlesinger Y, Weck K, et al. Epstein-Barr Virus DNA in peripheral

blood leukocytes of patients with posttransplant lymphoproliferative disease. *Transplantation.* 1995;60:547-554.
19. Kaufman S, Atkinson JB, Bianchi A, et al. Indications for intestinal transplantation. *Pediatr Transplant.* 2001;5:80-87.
20. Grant D. Intestinal transplantation. *Transplantation.* 1999;67:1061-1064.
21. Cacciarelli TV, Dvorchik I, Mazariegos GV, et al. An analysis of pretransplantation variables associated with long-term allograft outcome in pediatric liver transplant recipients receiving primary tacrolimus (FK506) therapy. *Transplantation.* 1999;68:650-655.
22. Eckhoff DE, Pirsch JD, D'Alessandro AM, et al. Pretransplant status and patient survival following liver transplantation. *Transplantation.* 1995;60:920-925.
23. Atkison P, Chatzipetrou M, Tsaroucha A, et al. Small bowel transplantation in children. *Pediatr Transplant.* 1997;1:111-118.
24. Beath SV, Protheroe SP, Brook GA, et al. Early experience of pediatric intestinal transplantation in the United Kingdom, 1993 to 1999. *Transplant Proc.* 2000; 32:1225.
25. Bond G, Reyes J, Mazariegos G, et al. The impact of positive T-cell lymphocytotoxic crossmatch on intestinal allograft rejection and survival. *Transplant Proc.* 2000;32:1197-1198.
26. Goulet O, Revillon Y, Cerf-Bensussan N, et al. Small intestinal transplantation in a child using cyclosporine. *Transplant Proc.* 1988;20(suppl 3):288-296.
27. Starzl TE, Rowe MI, Todo S, et al. Transplantation of multiple abdominal viscera. *JAMA.* 1989;261:1449-1457.
28. Williams JW, Sankary HN, Foster P, et al. Splanchnic transplantation. *JAMA.* 1989; 261:1458-1462.
29. Deltz E, Schroeder P, Gebhardt H, et al. Successful clinical small bowel transplantation: report of a case. *Clin Transplant.* 1989;3:89-91.
30. Grant D, Wall W, Mimeault R, et al. Successful small-bowel/liver transplantation. *Lancet.* 1990;335:181-184.
31. Nour B, Reyes J, Tzakis A, et al. Intestinal transplantation with or without other abdominal organs. *Transplant Proc.* 1994;26:1432-1433.

DISCUSSION

Christopher R. Shackleton, MD, Los Angeles, Calif: Intestinal transplantation remains an ongoing challenge in the realm of abdominal organ transplantation. To put this into some perspective, it is worth noting that whereas there are now approximately 22 000 solid organ transplants performed annually in the United States, fewer than 100 of these are intestinal, either alone or in combination with other organs. Moreover, whereas there are some 272 kidney transplant centers and 131 liver centers registered with the United Network for Organ Sharing, there are but 26 intestinal transplant centers and of these, only 5 have performed 10 or more such procedures. As evidenced by their report here today, the UCLA team is among this select group.

The age distribution of recipients of intestinal transplants is bimodal: approximately one half are under the age of 5 years with a second peak constituting about one third of recipients in the 18- to 49-year age range. Fully 2 thirds of all recipients are under the age of 18 years. That the majority of recipients of these grafts are pediatric only accentuates the donor availability issues and the recipient technical challenges of an already daunting operation. The UCLA group's extensive experience in pediatric liver transplantation no doubt contributes significantly to their intestinal transplant initiative.

At any one time there are approximately 100 individuals awaiting intestinal transplantation in the US. Despite this comparatively small number, the death rate for those on the waiting list is the highest of any solid organ and is approximately double that of the second-highest risk group (lung recipient candidates) and nearly 4 times that of liver recipient candidates. Indeed, the annual mortality of parenteral nutrition–dependent patients approaches 25%. Moreover, about half of infants receiving parenteral nutrition for intestinal failure develop liver disease. While noncirrhotic liver dysfunction, including mild degrees of fibrosis, may reverse following isolated intestinal transplantation, the onset of advanced liver disease necessitating combined liver-small bowel transplantation is associated with a marked increase in wait-list mortality as compared to those awaiting isolated intestinal grafts. Moreover, the results of the combined operation tend to be inferior to those achieved with isolated intestinal transplantation, no doubt reflecting the more debilitated state of the recipients and the increased complexity of the procedure and its posttransplant management.

Of those who receive an intestinal transplant, just over half (56%) wait for less than 1 year, with the remainder waiting longer. Of intestinal transplants done, about one half are isolated bowel transplants, one third are combined liver-intestinal grafts, and the remainder are clusters of other organ combinations.

It is fair to say that this series may more accurately be characterized as being that of the UCLA experience with combined liver-intestinal transplantation. As reported by UNOS [United Network for Organ Sharing], the 1- and 5-year cumulative patient survival for recipients of combined liver-small bowel transplants are 50% and 37%, respectively. The results of the series reported here today are substantially higher than this, both for the entire series and in particular for the late group (70% and 60% at 1 and 3 years, respectively). While there may be some advantage in reporting death-censored graft survival to isolate other causes of graft loss as was the case in the present study, it is more typical to calculate total cumulative graft survival and to include retransplant grafts, and these results are together probably of more value for comparative purposes. As the results of the present study can clearly hold their own against other published series, I would encourage the authors to revise their graft survival analysis accordingly. Moreover, as this series is predominantly that of combined liver-intestinal transplants and the survival results of combined liver-intestinal grafts tend to be inferior to those achieved in isolated intestinal transplants, the authors' results are all the more satisfactory.

It is now well appreciated that intestinal grafts are more immunostimulatory than those of other solid organs for reasons that are not entirely evident but may, in part, be related to the bowel's rich complement of immunocompetent cells. Acute rejection rates of 1 to 2 per graft within the first year are common so the incidence reported herein is not unexpected. In contrast, rates of ACR in renal and liver allografts are well under one half of this (about 30%-40% with the use of modern combination immunosuppression). I commend the authors for the application of prospective cross matching, as positive tests have been associated with accelerated, aggressive rejection in many series.

As pointed out by the authors, the advent of tacrolimus represented a quantum step in the clinical application of IT, but trough levels employed in IT are often considerably higher than those used in other solid organ transplants. The authors do not provide information on specific trough targets in the present report, but it is common practice to aim for trough levels that are approximately double those for liver transplantation and this, together with the use of poly or monoclonal antilymphocyte antibody preparations in the induction period, often sets the stage for the emergence of viral-mediated morbidity and dose-related drug toxicities in many series. That the UCLA series reported before our association had near 0 viral-mediated morbidity, including Epstein-Barr virus–mediated posttransplant lymphoproliferative disorder (PTLD, 10%-15% incidence in other series), despite their aggressive immunosuppression, represents one of the major triumphs of this presentation in my view and speaks to the effectiveness of the antiviral prophylactic strategies that have been developed by the UCLA group. Surely the ultimate goal of intestinal transplantation must be the attainment of nutritional autonomy together with normal growth and development in infants and children in particular. The results achieved in the present report constitute yet another significant step toward the attainment of this goal.

In summary, this presentation represents an incremental contribution to the field of intestinal transplantation, a challenging one in which, by its very nature, virtually all advances must be measured incrementally. Its seminal contributions, in addition to the survival and nutritional autonomy rates, are the low rates

of viral-mediated morbidity despite an acutely ill patient population and an aggressive immunosuppressive strategy. Further advances in intestinal transplantation will require perseverance both at the laboratory bench and in the clinic and through the collaborative pooling of information and prospective strategies among the pioneering centers. I encourage the UCLA team to press on; experience remains one of the greatest teachers.

How does one judge the quality of a potential intestinal donor graft in the absence of objective parameters that are commonly used in the case of other abdominal organs, such as liver function tests or serum creatinine concentration and urine flow, as might be applied to potential liver and kidney donors, respectively? What, if any, is the role for leukocyte depleting therapy of the donor as has been advocated by the University of Nebraska group? What are your target trough levels for tacrolimus, and what has been the impact of these levels on renal function in particular? Have you any experience with combination tacrolimus/rapamycin therapy, which has proven to be an effective rejection mitigating strategy in other solid organ transplants? What are your criteria for the diagnosis of acute rejection, and how do you distinguish it from viral-mediated enteropathies? Do you schedule protocol endoscopy/biopsy as advocated by other centers and, if so, how often? What is your schedule and/or criteria for CMV/EBV PCR (polymerase chain reaction) monitoring, and do you feel that the low yield of positive results reported today (2%-3% for CMV and 15% for EBV) justify the time-intensity and expense of such monitoring in light of the effectiveness of your antiviral strategies? Were there any instances of graft vs host disease? What do you see is the role for living donation as there have been a few such cases performed? What do you see as the next steps needed to further advance this transplant option?

Sources: *2000 Annual Report of the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data: 1990-1999*. Rockville, Md: US Dept of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation; 2000.
Sudan DL, Kaufman SS, Shaw BW Jr, et al. Isolated intestinal transplantation for intestinal failure. *Am J Gastroenterol*. 2000;95:1506-1515.

Bruce M. Wolfe, MD, Sacramento, Calif: Eighteen years ago I had the honor of presenting to this Association our initial experience with long-term parenteral nutrition, which was regarded as somewhat of an accomplishment at the time. Unfortunately over the last 18 years, progress in the management of the patients with short-bowel syndrome has primarily been improvement in enteral feeding such that we can wean patients off of parenteral nutrition. The patients who remain TPN-dependent, face the constant threat of life-threatening complications. The results reported here are remarkably good when one considers the size of the UCLA home TPN program and the relatively small number of patients who have been transplanted. In fact, the patients all faced desperate circumstances in their care before selection for transplant.

Could you comment on the doses of immunosuppressives required due to the high rejection propensity of small intestine and the long-term implications that result from these higher doses that are required?

James W. Holcroft, MD, Sacramento: Could you describe your management with respect to your postoperative enteral feeding? I ask in part because I am curious about how that is done in transplant patients, but I also ask because it might have generalizable implications for all of us who are managing postoperative patients. As an example, where do the feedings have to be delivered? Do you insist that they be delivered in the postpyloric part of the bowel, or are you willing to accept the stomach? Do you use growth factors such as growth hormone to perhaps allow the gut to adapt better to the feedings? Do you add nutrients to your regimen that might not ordinarily be used? Do you use glutamine or argenine?

Dr Busuttil: Dr Shackleton, you really presented me with a litany of questions. I don't know if I will be able to get through all of them. Intestinal transplantation is really a last-ditch effort for somebody who has failed TPN. In no way is this operation indicated for somebody who could be maintained on TPN and, as you know, 85% of people on TPN can do very well for 5 years or more. So these are patients who have failed TPN and are dying, and that is when we do this operation. In regards to how we judge the quality of the graft, the procurement, basically we visualize the graft. If the liver graft is usually good, in most cases the intestinal graft is good. There are no specific tests that we really do. We try to keep the sodium less than 160, but basically the parameters that we use for a liver graft are pertinent for an intestinal graft.

Leukocyte depletion has been abandoned. I know that Nebraska does it but we did it early on in our series. But probably there is a deleterious effect to leukocyte depletion and it was found certainly in Pittsburgh that the majority of these patients who had that had a much higher incidence of LPD (lymphoproliferative disease), so we have totally abandoned that. Furthermore, there is probably a deleterious effect in that you don't have the advantage of the microchimerism that occurs if you deplete the lymphocytes from the graft.

Our FK target levels are a little bit higher than they are for livers. Usually with livers we are about 5 to 8. In the intestinal transplants we are usually above 10. In relation to Dr Wolfe's question, this indeed does create somewhat of a problem because there is a higher incidence of nephrotoxicity that we see when we keep the levels greater than 10 and in addition, the combination of immunosuppressive therapy that is required for intestinal transplantation, the interleukin 2 blockers, MNF, tacrolimus, and a longer course of steroids clearly results in a greater incidence of toxicity and a greater incidence of infection. You will have to remember that when we do liver transplants, by and large we only use dual immunosuppressive therapy, low-dose FK, and steroids. So there is no question that we are paying a penalty for the higher immunosuppression with the small-bowel transplant patients.

Dr Shackleton, I don't have any information regarding rapamicin plus FK. Our regimen is basically anecdotal and we have had only a few patients with that but we are using more and more rapamicin, even with our liver transplant patients. Thank you for your comments regarding the EBV and CMV prophylactic regimens because I too agree. That is one of the most important contributions that our series has illustrated. These are lessons that we learned from our liver transplant experience when we were very very aggressive in treating preemptively against CMV, and then in the intestinal transplant population this is indeed translated into a very very low incidence of disease with either CMV and EBV. Most importantly there has been really no increased incidence of PTLD lymphoma, which was seen prior to the initiation of this regimen.

Living donation has been done. We have considered it, but I think we have not really found a recipient who we thought would be suitable, but this has clearly been done several times with success.

Dr Holcroft asked questions about the nutritional management. Basically, as Doug illustrated in the talk, we start enteral management as soon as we possibly can and that is usually within the first week to 2 weeks after transplantation. We use an elemental Vivonex formula. We instill it through the jejunum. All of these patients have a jejunostomy placed at the time of operation and we augment this with glutamine and then as these patients tolerate it, we advance them to formal tube feedings and eventually a regular diet. Again, it is gratifying that about two thirds to 75% of these patients have achieved nutritional autonomy.