Intestine and Intestine-liver Transplantation: Update

Windows on Medical Technology™

Policy Statement

Windows on Medical Technology™ are short-form evidence reports of drugs, devices and procedures. These reports are designed to provide a rapid and accurate overview of a specific application for a specific medical technology. Many of the technologies evaluated are emerging. The information contained in each report derives primarily from the currently available published, peer-reviewed scientific literature and studies chosen for inclusion are generally limited to English-language publications. However, if there is a relative paucity of published data on a topic, data from meeting abstracts or clinical studies appearing on the Internet and elsewhere may be included. The recommendations and conclusions must be interpreted cautiously and judiciously. The data on which they are based are often insufficient to permit unequivocal resolution of the scientific and clinical issues most relevant to patient care. ECRI implies no warranty and assumes no liability for the information, conclusions, and recommendations contained in *Windows on Medical Technology* reports.

The conclusions and recommendations of this *Windows on Medical Technology* report and the studies on which it is based are highly perishable and reflect the state of the technology at the time at which this report was compiled. This report was produced by a multidisciplinary staff of life and physical scientists and health professionals. *Windows on Medical Technology* reports are carefully reviewed by other professionals within ECRI as well as by qualified extramural reviewers in pertinent fields before being issued as final reports. Neither ECRI nor its employees accept gifts, grants, or contributions from or consult for medical device or pharmaceutical manufacturers. This report reflects the views of ECRI and not necessarily those of outside reviewers.

The Health Technology Assessment Information Service (HTAIS) provides *Windows on Medical Technology* reports, comprehensive technology assessments, and information support to help governments, hospitals, health systems, managed-care organizations, health insurers, health professionals, and the public meet the challenge of evaluating healthcare technology objectively and rationally. HTAIS disseminates healthcare technology information derived from its assessments to consumers and patients to help inform their decision making about healthcare options.

HTAIS is a service of ECRI, a nonprofit health services research agency and a Collaborating Center for Healthcare Technology Assessment of the World Health Organization. ECRI has been designated an Evidence-Based Practice Center by the U.S. Agency for Health Care Policy and Research. ECRI's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships.

Scope of this Report

Windows on Medical Technology reports are designed to provide a rapid and accurate overview of a specific application of a particular medical technology. Many, but not all, of the technologies evaluated in these reports are emerging. The clinical studies chosen for inclusion are generally limited to English-language publications in peer-reviewed journals. However, when there is a relative paucity of published data on a topic, data from abstracts of presentations at meetings or clinical studies appearing on the Internet and elsewhere may also be included.

This report provides the reader with an overview of intestinal transplantation for the treatment of short- gut syndrome. A comprehensive evaluation of other technologies for this condition, such as home/total parenteral nutrition (H/TPN), is beyond the scope of this report. H/TPN is discussed briefly as it relates to the patient indications of intestinal transplantation and options after a failed transplant.

ECRI previously issued a technology assessment on this topic in 1996, "Bowel and Bowel-Liver Transplantation." This report updates that assessment.

Overview

Adults having fewer than three meters of functioning intestine (of the usual nine) may have nutritional difficulties,(1) and survival on oral intake normally requires at least 0.7 meters of intestine distal to the duodenum.(2) The minimum length of intestine needed in infants is between 15 and 40 cm, depending on whether the ileocecal valve is present and on other factors.(3-5) An insufficient length of intestine can lead to short-bowel or short-gut syndrome (SGS), which can eventually result in the need for intestinal transplantation. SGS has a variety of causes. In infants and children, the most common cause is necrotizing enterocolitis, followed by intestinal atresia, volvulus, gastroschisis and aganglionosis. In adults, Crohn's disease is the most common cause, followed by mesenteric thrombosis, radiation enteritis, volvulus, trauma and polyposis.(6) In the early 1980s, surgical treatments for obesity produced many model cases of SGS in Europe.(2,4,7)

Dysmotility syndrome is the second leading indication for intestinal transplantation,(8) often caused by pseudo-obstruction or generalized Hirschsprung's disease. In dysmotility syndrome, the intestine is physically intact, but non-functional in whole or part. The resulting inability to absorb sufficient nutrients results in symptoms that are essentially the same as SGS, and therapy for these patients is the same as for those with SGS.(6)

Patients with SGS or dysmotility syndrome who cannot absorb sufficient nutrition are kept alive by intravenous feeding, termed total parenteral nutrition (TPN) or, if administered in the home setting, home parenteral nutrition (HPN). Parenteral nutrition is the precursor therapy to intestinal transplantation for some patients. That is, when H/TPN fails, the only option

remaining is transplantation. However, if transplantation is performed and fails, H/TPN can be reinitiated in some patients.

Other Technologies

Intestinal failure is similar to kidney failure, in that there is a life-supporting alternative to transplantation. In the case of intestinal failure, the alternative is H/TPN. Because the nutrient solution used in H/TPN is concentrated and quite thick, it can be administered through peripheral veins for only a short period of time, typically several weeks. Longer-term feeding requires catheter access to a central vein, often the vena cava. TPN was first developed in the 1960s, and HPN became widely available beginning in the mid-1970s.(9,10)

Incidence

The incidence of SGS is reflected by the incidence of H/TPN use. In the United States there is no central registry for all H/TPN patients (though a registry exists that has many patients(11)). It has been estimated that Medicare patients received H/TPN at a rate of 238 cases per million population per year between 1989 and 1992, and that in the general population the yearly incidence was about 120 cases per million. According to the most recent data available on H/TPN, a total of 40,000 patients were using H/TPN in 1992, at a total cost of $780 million that year. In the United States the number of H/TPN patients has been expanding rapidly with growth particularly marked among patients younger than 10 years of age and those older than 65 years of age.(11-13) In Europe, the prevalence of H/TPN use is lower: the highest prevalence is in Denmark, at 13.9 cases per million population.(14) Overall, in Europe the incidence of new patients on H/TPN is about 1 to 2 cases per million population, with about half remaining on H/TPN for over one year.(9,15)

Since SGS can arise from many medical conditions, it is useful to look at the incidence of H/TPN among the population with the underlying conditions that cause SGS. Data from third-party Medicare payers and from the North American Home Parenteral and Enteral Nutrition (HPEN) registry show that cancer, Crohn's disease and ischemic bowel disease are the leading indications for H/TPN, accounting for about 57% of patients. However, 80% of cancer patients, 90% of AIDS patients and 50% of cystic fibrosis patients are on H/TPN for less than one year, due largely to the high mortality from the underlying disease in these groups. These three indications combined account for about 47% of H/TPN patients. (Such short-term patients are not typically offered H/TPN in Europe.) Examination of the indications for H/TPN that can lead to intestinal transplantation shows a different picture. Crohn's disease, ischemic bowel disease, motility disorders, radiation enteritis, adhesive obstructions or congenital bowel defects account for the underlying disease in about 38% of H/TPN patients. The percentage of patients who remain on H/TPN longer than a year is also higher, ranging from 44% to 49% for patients with ischemic bowel disease, motility disorders, congenital bowel defects and radiation enteritis; and dropping to 34% for patients with adhesive obstructions and to 25% for those with Crohn's disease.(11-13)

H/TPN Morbidity and Mortality

Overall, among long-term H/TPN patients, the survival rate is about 70% to 80% at three years and 60% at five years. The rate of H/TPN mortality reflects the underlying disease. The one-year survival of H/TPN patients with Crohn's disease, ischemic bowel disease, motility disorders, radiation enteritis, adhesive obstructions or congenital bowel defects is 83% to 96%. About 7% to 9% of deaths overall are attributable to H/TPN itself.(10,15,16) Catheter-associated sepsis is the leading cause of H/TPN-associated mortality in adult patients.(16)

Infants and children do not fare as well with H/TPN as do adults. A mortality rate of 50% in the first five years has been reported for all children on H/TPN.(17) Infants with congenital bowel disorders suffer a mortality rate of 10% per year in the first two years of H/TPN, with a decline in deaths after that. H/TPN-induced liver disease occurs in 40% to 60% of infants requiring long-term feeding.(10) The cause of liver disease is unknown, but it is related to sepsis.(18) Adults are less prone to develop liver disease during H/TPN, but there is anecdotal evidence that rates are increasing.(19)

Over the course of 22 years of H/TPN at the Mayo clinic (Rochester, Minnesota), nearly half (45%) of all the (largely adult) H/TPN patients who were followed up required no hospitalization; however, 48% of patients had at least six hospitalizations, generally for infection.(16) Children have average rates of central venous catheter infection of about 4 to 5 infections per 1,000 catheter days, which is higher than the rate for adults. The rate of exit-site infections is lower—about 0.1 to 0.6 infections per 1,000 catheter days. Children younger than two years of age had higher infection rates than older children. The incidence of new infection is independent of previous infection—the risk of infection is simply dependent upon the length of time the patient has been on H/TPN.(20) The incidence of catheter-related sepsis has been increasing over the past 10 years.(21) Treatment of catheter-related sepsis sometimes requires removing the catheter for 5 to 14 days while administering antibiotics. The catheter is replaced 5 to 7 days after the fever has subsided. Thus, a severe incident of catheter sepsis can cost the H/TPN patient about two weeks of normal functioning. Infections of the subcutaneous tunnel, however, do not require removal of the catheter.(22)

Another common H/TPN morbidity is thrombosis. Thrombosis can be life threatening, but even when it is not, over the longer term it can result in the termination of H/TPN. Clotting progressively cuts off different routes of venous access to the vena cava. Ultimately, the vena cava can itself become too occluded to use for proper feeding. Superior vena cava occlusion is a particular problem in infants, occurring at a rate of 5% to 13% and resulting in pleural effusions or pulmonary emboli as well as cardiac infarction. Infants are at higher risk because their veins are smaller relative to the catheters and because they have less blood volume to dilute the infusate.(23) Vena cava occlusion in adults can result in the catheter being inserted into the atrium itself or into the azygous vein. A thoracotomy is required to gain access in either case. An alternative may be hepatic vein cannulation.(24) When clotting is discovered, therapy with streptokinase, urokinase or warfarin may be initiated, or heparin may be added to the H/TPN solution. Thrombosis appears to be a more prevalent problem than sepsis, and thus it is not

easy to distinguish in advance those patients who will run out of H/TPN access sites from those who will not.

Intestinal Transplantation

Underlying Theory

The purpose of intestinal transplantation is to provide the patient with a sufficient amount of intestine to allow normal feeding and independence from H/TPN. Transplantation of the intestine has proven to be more difficult than transplantation of the kidney, heart, liver, or lungs, because of the body's propensity for rejecting the intestine, and the difficulty in monitoring rejection. Thus, management of rejection has been key to the development of this technology.

The first lasting successes in intestinal transplantation in humans came in the mid-to-late 1980s, using cyclosporine A as an immunosuppressant. By October 1991, 35 bowel transplantations had been attempted worldwide, mostly in tandem with the liver. Cyclosporine A, while making liver and kidney transplantations common place, has not been as successful in preventing rejection of the transplanted intestine.(25,26) Believing that "the results using conventional immunosuppression have been unsatisfactory," the University of Pittsburgh (the leading U.S. intestinal transplant center,) began using a new and more powerful immunosuppressant, tacrolimus (Prograf®, FK-506), in 1990.(26) By some measures this drug is 10 to 100 times more powerful than cyclosporine A.(27) Tacrolimus has since been adopted by most other centers performing intestinal transplantation.(28)

The University of Pittsburgh began aggressively pursuing bowel transplantation after adopting tacrolimus.(26,29) Initial data up to June 1993 on the first patients receiving intestine and intestine-liver transplants there (May 1990 to 1993) indicated that the one-year survival of intestinal transplant patients was comparable to that of patients receiving the intestine and liver together (91% for intestine, 76% for intestine-liver).(30) Later evaluations of patients at Pittsburgh were not as optimistic, however, and the center essentially ceased performing intestinal transplants for about a year in 1993–1994 while the program was re-evaluated. Transplantation was resumed, at a slower rate, in 1995.(8)

Though lessened, rejection is not eliminated by tacrolimus, and some centers, notably Pittsburgh and the University of Miami (FL), have been attempting to tolerize (enable patients to develop a tolerance to) the recipient's immune system. They do this by including an adjunct transplantation of the organ donor's bone marrow cells, or (more recently) donor hematopoietic stem cells with the intestinal transplant. The theory is that inclusion of donor immune system cells that take up residence in the recipient's body (a process called chimerization) will result in greater tolerance for donor antigens and thus, less graft rejection. Inclusion of donor marrow or stem cells has been routine at these centers since 1995.(31,32) Both recipient and donor consent are required for this process.

Recent data indicate that immune system chimerization occurs more often following marrow grafting than without marrow grafting (the graft itself is also a source of donor immune system cells), that the procedure is safe when done once (its safety for multiple attempts is not known), and that there may be some benefit of reduction in the amount of immunosuppression needed (but this is not statistically significant).(33) At the London (Ontario, Canada) Health Sciences Center immune system modulation is attempted using donor whole blood.(34)

Basic Procedure

Depending upon the patient's circumstances, one of three different types of intestinal transplantation may be given. In intestine-alone transplantation, the donor's small intestine (ileum and jejunum) are grafted in the place of the recipient's small intestine, with the appendix and gall bladder often removed to prevent future complications. About 40% of all intestinal transplantation is of this type. In intestine-liver transplantation, the small intestine and liver are transplanted *en bloc,* and about 48% of all intestinal transplantation is of this type. Multivisceral transplantation is similar to intestine-liver transplantation, but with additional organs (e.g. stomach, pancreas) included.(32,35) This form of transplantation accounts for about 11% of the total.(28) The definition of multivisceral transplantation varies from center to center. At Pittsburgh, a multivisceral transplant is defined as one that includes the liver, pancreas, stomach, small intestine and duodenum. Transplantation of these organs without the liver is defined as a modified multivisceral graft. A cluster transplant includes the liver, a duodenum, and the pancreas, but these are no longer done at Pittsburgh. Current data obtained from Pittsburgh reflect these definitions.

There are many variations in the arteriovenous connections and in the intestinal anastomoses. Patients have often had several rounds of previous intestinal surgery, and techniques are flexible. Often the graft is exteriorized at the level of an enterostomy, to provide easy access for endoscopy and biopsy, as well as to allow for graft decompression. The colon may be transplanted in conjunction with any of the above modalities, but many centers avoid this due to the higher risk of infection. Other centers transplant the colon to help improve water balance and nutritional status. Donors are cadaveric, but there have been scattered reports of living-related donors for infant and small child recipients. Given the scarcity of donors, the uncertainty of anatomical variability, and the urgency for transplantation, there may be a substantial size mismatch between donor and recipient, that may necessitate inventive means of abdominal closure to accommodate the organ.(36-38)

Patients who are not given tacrolimus for immunosuppression are given cyclosporine (Neoral®), and patients on either drug are usually given adjunctive immunosuppression as well, which may include corticosteroids, OKT3, cyclophosphamide, azothioprine or mycophenolate mofetil (MM) singly or in combination. Often these agents are given episodically to counter acute rejection or to prevent recurrent episodes.(32)

Reported Patient Indications and Contraindications

With the exception of Crohn's disease, the causes of SGS are generally either inborn or catastrophic, and necessitate the onset of H/TPN administration before the patient can be placed on the waiting list for transplantation. Thus H/TPN is virtually an obligatory precursor to intestinal transplantation, and it is the H/TPN-dependent population that constitutes the pool from which intestine transplant candidates are drawn. Whatever the initial cause of intestinal failure, the proximal indication for transplantation is nearly invariably the inability to thrive on or maintain H/TPN, often due to cholestasis (cessation or slowing of bile flow) and the development of liver disease, as well as to loss of venous access from recurrent infections and central vein thrombosis.

In some cases, transplantation is indicated because of an underlying disease process that is life threatening, such as diffuse juvenile polyposis or microvillus inclusion disease. Contraindications include AIDS, uncontrolled infection, unresectable cancer (desmoid tumors, however, may be an indication), cardiac disease, congenital heart disease, and severe chronic lung disease. There is no lower age limit for transplantation, although finding size-matched donors for pediatric patients can be difficult.

As a rule, patients undergoing intestinal transplantation are younger than 60 years old, and thus there has been little need to use advanced age as a contraindication.(39,40) Patients are matched by blood general type (ABO) to donors, but may be human leukocyte-antigen (HLA) incompatible.

Intestine-alone transplantation is indicated for those patients whose other visceral organs are intact except for the intestine. Candidates for combination intestine/liver transplantation have irreversible intestinal failure, H/TPN dependency, and end-stage liver failure, or concomitant thrombosis of the portomesenteric system (in which case the normally functioning intestine is removed). At one center, liver failure is defined as bilirubin levels >100 micromol/L (6 mg/dL), moderate splenomegaly, an INR > 1.2 (a measure of coagulation), moderate varices (grade I-II), and no ascites.(17) Patients without end-stage liver disease but with extensive fibrosis or cirrhosis are listed for intestine/liver transplantation.(39)

Patients may be considered for multivisceral transplantation when organs in addition to the intestine and liver need replacement. Multivisceral transplantation is indicated for patients who have failure of more than two organs, including the intestine—e.g., as a result of arterial/venous thrombosis. Patients with infections or malignancies that can be totally resected during transplant may also be given consideration for multivisceral transplantation.

About 59% of intestinal transplant recipients are children.(28) Criteria for pediatric transplantation of intestine alone include a failure to thrive on H/TPN while maintaining liver function. At one center this translates to a bilirubin level <100 micromol/L (6 mg/dL), spleen size within the normal limit for the age, and absence of coagulopathy, ascites, or varices.(17)

These patients may have some degree of liver damage, but it must be reversible. Typically the patients have frequent central line sepsis and are faced with loss of central venous access.(8,41)

There is anecdotal evidence that in the United States, pediatric patients are referred (i.e., put on a waiting list) for transplantation later than is optimal. At the University of Pittsburgh, a retrospective study of children referred for evaluation found that the mean survival after evaluation was 9.2 months, while the mean time on the wait list before intestinal transplantation was 10.1 months. One-year survival after referral (of patients not given transplantation) was 49%. Examination of the (univariate) determinants of mortality revealed that the worst survival rate was among patients with bilirubin levels >51 micromol/L (3 mg/dL), platelet counts < 100,000/mL, prothrombin times of >15 seconds, or partial thromboplastin times of > 40 seconds. Patients younger than one year fared worse than older patients (the mean age of the studied group was 3.4 years). Patients whose cause of intestinal failure was due to non-anatomic causes (e.g. pseudo-obstruction, Hirschsprung's disease or microvillus inclusion disease) died later than those whose SGS resulted from surgical resections (e.g. necrotizing enterocolitis, intestinal atresia or volvulus). In general, children with intrauterine intestinal catastrophes or ischemic intestinal injury shortly after birth have the worst prognoses.(3)

Multivariate analysis found the two independent significant predictors of poor outcome are hyperbilirubinemia and the severity of histopathologic liver damage. The presence of cirrhosis predicts one-year survival of 30%. Given that 70% of these pediatric patients require intestine/liver transplantation, there is prima facie evidence that children are receiving transplantation too late to save their livers, or in many cases too late to survive long enough to receive a transplant. Many patients are referred with advanced jaundice, and the survival of children with bilirubin levels >200 micromol/L (12 mg/dL) is fewer than six months. Patients evaluated for potential intestine/liver transplant had a worse prognosis (one-year survival 32%) than did those needing an intestine alone (one-year survival 82%).(3)

Compared to liver, kidney or heart transplantation, intestinal transplantation is needed for relatively few patients. Data from the North American HPEN Registry have been used to estimate the number of H/TPN patients who form the pool of potential intestine transplant patients. Although this registry does not cover all patients in the United States, it has been supplemented with data from the U.S. Health Care Financing Administration for these estimates. Based on the most recent data available, there are about 3,400 patients with indications commonly leading to transplantation (Crohn's disease, ischemic intestine, motility disorder, congenital intestine disease, radiation enteritis) who have been on H/TPN for over 1 year and are under 65 years of age. There are about 800 patients who have been on H/TPN for over 3 years and are 55 years of age or younger.(42) These figures provide a rough estimate of the total number of patients who could at any time be eligible for transplantation in the United States—but most will not be.

In the United Kingdom, an estimated 20 to 40 candidates for transplantation per year arise from the H/TPN pool out of the 250 children who are on H/TPN.(17,43,44) In France, one

survey found that 24 pediatric patients out of the 224 children who are H/TPN recipients are considered potential transplant candidates.(45) In Italy, it is estimated between 4 and 14 patients per year could be intestinal transplantation candidates.(46-48) Denmark has approximately 80 patients on H/TPN, a quarter of whom could require transplantation.(14) Surveys in Japan of H/TPN patients have found that at present 21 to 34 patients could be intestinal transplantation candidates.(49,50)

In view of the frequency of H/TPN failure in the pediatric population, it has been suggested in the United Kingdom that all children on H/TPN should be listed as candidates for transplantation.(17) However, in the United States, children who are well adapted to H/TPN are not considered for transplantation.(3)

Evidence Base

Identification of Clinical Studies

The following databases have been searched for relevant information:
Bioethicsline (through March 19, 1999)
The Cochrane Database of Systemic Reviews (through 1999 Issue 1)
The Cochrane Registry of Clinical Trials (through 1999 Issue 1)
The Cochrane Review Methodology Database (through 1999 Issue 1)
Current Contents (through March 1999)
The Database of Reviews of Effectiveness (Cochrane Library) (through 1999 Issue 1)
DIRLINE (through February 10, 1999)
ECRI Library Holdings (through March 1999)
Food and Drug Administration (through March 1999)
Health Devices Alerts (1977 through March 1999)
Health Services Research Projects (HSRProj) (through March 12, 1998)
Healthcare Financing Administration (HCFA) (through February, 1999)
Healthcare Standards (through March 1999)
HealthSTAR (Health Services, Technology, Administration, and Research) (1990 through February 10, 1999)
International Health Technology Assessment (IHTA) (through March 1999)
Medline (1990 through February 8, 1998)
National Guidelines Clearinghouse (NGC) (through March 1999)
TARGET (through March 1999)

The search strategies employed a number of freetext keywords as well as controlled vocabulary terms including (but not limited to): short bowel syndrome; short gut; small bowel; small intestine; malabsorption syndrome; intestin*, bowel*; transplant*; and transplantation.

In addition to searching Current Contents-Clinical Medicine on a weekly basis, over 1,600 journals and supplements maintained in ECRI's collections were routinely reviewed. Other

mechanisms were used to retrieve additional relevant information, including review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature includes trade journal articles, reports and studies produced by federal and local government agencies, private organizations, educational facilities, corporations, etc., that do not appear in the peer-reviewed literature.)

ECRI also sought unpublished data on patients from the U.S. centers performing intestinal transplantation. Two centers (Pittsburgh and Miami) agreed to provide unpublished individual patient data. The University of Nebraska, which had previously provided data for ECRI's technology assessment, declined to participate.

Study Selection

Studies were selected for examination if they contained data on the outcomes of interest (see below), were published since ECRI's last technology assessment (i.e., since July 1996) and did not contain data that was updated in a subsequent publication. All data are from case series, data from about 200 patients were evaluated.

Key Outcomes

Survival

Two kinds of survival are of interest in transplantation: patient survival and graft survival. Patient survival following transplantation is presented as actuarial survival (Kaplan-Meier curves). Actuarial survival statistically estimates the odds of surviving at continuous times, based on the total experience of the patient group. Patient survival is not, however, synonymous with graft survival. A transplant can fail and the patient can survive. Patients can receive a second transplant or they may return to H/TPN (although an inability to maintain parenteral nutrition is the chief indication for transplantation, it is in some cases possible to resume H/TPN in the event of graft failure). Thus, graft survival more precisely reflects the success of the transplantation itself, rather than patient survival.

Morbidity

Post-transplantation morbidity is a measure of graft failure and may be a precursor of mortality. It is an indirect measure of transplantation success and patient quality-of-life (QOL) and well being. Although data on patient and graft survival are systematically gathered and published by transplant centers, data on morbidity are not. It is very difficult to ascertain how many patients are affected and how often. In general, publications address specific morbidities, such as rejection or infection, but do not address the total impact of posttransplantation morbidity on patients.

Quality of Life

Transplantation is intended as a life-saving measure, but the QOL that ensues is also important. Independence from H/TPN is a key measure of QOL, and data on this outcome are

available. In addition to feeding status, there are some data from the University of Pittsburgh on other aspects of patient well being and parental coping.

Table 1. Reported Outcomes

Reported Patient Outcomes	Definition
Patient survival	Post-transplantation survival of the patient (years)
Graft survival	Survival of transplanted tissue (years)
Morbidity	Percentage of patients incurring various complications
Feeding status	Percent of patients free from H/TPN.
Quality of life	
Quality of Life Inventory (QOLI)	Self-administered survey normalized to the transplantation population. 25 domains of 5 questions each answered on a 9-point Likert scale, with lower scores denoting better quality.
Short-form (SF) 36	A 36 item-self-report questionnaire on quality of life.
Brief Symptom Inventory (BSI)	A 53-item questionnaire that provides an index of global distress (Global Severity Index, GSI) and mental health.
Parenting Stress Index (PSI)	A 120-item questionnaire measuring stress of parenting. Total score can be broken down into separate child and parent domain scores.

Findings

Results

Patient and Graft Survival

Data on patient and graft survival are available in three forms: from journal publications summarizing the experience at different centers, as registry data, and as individual patient data from centers. Data are available from the International Intestinal Transplant Registry covering the period from 1994 to1997.(28) These data are not gathered continuously, but rather are updated every two years, with the next update due in the fall of 1999. Individual patient data are reported in a few publications with relatively small series of patients. In addition, two major centers (University of Miami and University of Pittsburgh) have provided ECRI with unpublished individual patient data on graft and patient survival.(51,52) These data, pooled with published individual patient data, cover 195 patients—approximately 50% of the estimated current worldwide patient experience—and form the basis for the patient and graft survival analyses presented in Figures 1 through 5. Although these data are not as comprehensive as the registry data, they are more current, and may be a preview of the next iteration of registry data, which ECRI will obtain when available.

Published Center Data

The University of Pittsburgh has the largest series (about 40% of the world total(53)) of intestinal transplant patients, and data from these patients have been reported in detail. Abu-Elmagd et al.(31) report the overall actuarial patient survival was 72% at 1 year after transplantation and 48% at 5 years, with the highest death rate occurring in the first month. No significant difference in patient survival based on graft type (i.e., intestine alone, intestine-liver or multivisceral) or bone marrow augmentation was seen, but patients between 2 and 18 years old apparently fared better (68% survival at 5 years) than those younger or older, although the difference was not statistically significant.

Changes were initiated in the management strategy of patients at this center after a one-year moratorium on intestinal transplantation in 1994. These changes included more careful patient selection criteria, not transplanting cytomegalovirus-infected grafts into patients who were not virus carriers, the addition of adjunctive donor bone marrow transplantation, exclusion of the colon from the grafted tissue, and sensitive polymerase chain reaction monitoring of Epstein-Barr virus levels (which can be an early indication of posttransplant lymphoproliferative disorder [PTLD]).

With the resumption of transplantation, the Pittsburgh series can be divided into two eras, before and after the moratorium. Abu-Elmagd et al.(8) report that actuarial patient survival was significantly better ($p<0.04$) for patients receiving transplants in the era from 1994 through 1998 than in the previous years (see Table 2). Patient survival was also better for children than

for adults, and graft loss higher for intestine-alone than for intestine/liver transplants (numerical data not given).

Pittsburgh has published survival data for children (<18 years old) and adults separately (Table 2). A comparison of 55 children given transplants to 127 children with SGS who were not given transplants found an appreciable difference in survival (one year: 72% versus 30%; two years: 62% versus 22%, respectively).(54) The finding of 30% patient survival at one year is similar to that reported by Beath et al. in the United Kingdom for 37 patients referred for transplantation (including three patients who were given intestine-liver transplantation).(55) Patients >10 years old had the best patient survival (89%, number of patients not stated), followed by those ages 2 to 5 years (56%). The survival for children of other ages averaged between 43% and 44%. Patients given intestinal transplantation alone had significantly better patient survival than those given intestine/liver or multivisceral transplantation. The United Network for Organ Sharing (UNOS) status at transplantation did not matter in terms of patient survival after transplantation, but inclusion of the colon in the allograft did reduce graft survival, although the effect did not reach statistical significance.(54) Inclusion of the colon did have a statistically significant deleterious effect on patient survival in adult patients, however. In these 31 patients, there were no statistically significant differences in the effect of transplantation type on graft or patient survival, but at 4 years patient survival for those receiving intestine-alone transplantation was about half that of other modalities (intestine alone: 27%; intestine/liver: 45%; multivisceral: 50%). Graft loss due to rejection and cytomegalovirus (CMV) infection was only seen in intestine-alone transplantations.(56)

Of patients at Pittsburgh given intestine-alone transplants, 13 of 35 (37%) had their grafts removed at a median time of 245 days, usually because of rejection.(31) Three patients received second transplants; two died within six months and one was surviving at 32 months post-transplantation. Of the remaining patients, two were surviving on H/TPN at 28 and 40 months after graft removal. Intestine/liver transplantation patients fared better—4 of 48 (8%) patients had grafts removed; two patients received second intestine/liver transplants (one patient was surviving at 90 days), one received a multivisceral transplant, and one received a replacement liver (neither of these two patients survived).(31,57)

Published reports from centers other than Pittsburgh are fewer, and summarized in Table 2.

Table 2. Patient and Graft Survival

Author, Year Center	No. Patients Given Transplants	Patient Survival (Actuarial)		Graft Survival (Actuarial)		Comments
		Time	% Survival	Time	% Survival	
Abu-Elmagd et al. 1999(8) Pittsburgh	109 patients 115 grafts	1 year	72%	1 year	64%	
		5 years	48%	5 years	40%	
	52 grafts			1 year	66%	All transplants post–1994, data taken from figure
				4 years	66%	
	63 grafts			1 year	57%	Pre-1994 transplants, data taken from figure
				4 years	34%	
Abu-Elmagd et al. 1998(31) Pittsburgh	98 patients 104 grafts	1 year	72%	1 year	64%	Two-year data taken from figure
		2 years	61%	2 years	52%	
		3+ years	48%	3+ years	40%	
Reyes et al. 1998(54) Pittsburgh	55 patients 58 grafts	1 year	72%	1 year	66%	All pediatric patients; two-year data taken from figure.
		2 years	62%	2 years	57%	
		3 to 5 years	55%	3 to 5 years	48%	
Furukawa et al. 1996(56) Pittsburgh	31 patients 33 grafts	1 year	73%	1 year	60%	
		2 years	59%	2 years	44%	
		4 years	39%	4 years	29%	
Farmer et al. 1998(35) UCLA	6 patients 8 grafts	1 year	64%	1 year	71%	
		2 years	64%	2 years	48%	
		5 years	64%	5 years	48%	

Nery et al. 1998(38) Miami	35 patients 37 grafts	3 months median; range 1 to 36 months	69% actual survival	3 months median; range 1 to 36 months	59% actual survival	Note actual survival
Tzakis 1999(51) Miami	61 patients 68 grafts	1 year 2 years 3 years 4 years	49% 41% 31% 21%	1 year 2 years 3 years 4 years	45% 35% 30% 20%	Unpublished individual patient data
Atkison et al. 1998(41) London, Ontario	10 patients 10 grafts	1 year 4 years	77% 77%	1 year 4 years	68% 685	From published individual patient data
Atkison et al. 1998(41) London, Ontario	10 patients 10 grafts	6 months to 5 years range	80% actual survival	6 months to 5 years range	70% actual graft survival	Note actual survival

Registry Data

Data from the International Intestinal Transplant Registry, as of 1997, are available on the World Wide Web.(28) This registry reports on 260 patients (273 transplants) from 33 centers worldwide.

Different centers have different patient mixes, as well as different types of experience with intestinal transplantation. Some centers (e.g., Western Ontario) specialize in children and perform largely intestine/liver transplantations. Other centers have a wider mix of ages and transplantation modalities. Thus, simple comparisons of the rates of survival at different centers are potentially misleading, and complex statistical comparisons that account for the different patient mixes are beyond the scope of this report. One generality that applies, however, is that patients at centers that have performed more than 10 intestinal transplantation procedures report significantly better survival rates than other centers.

The Pittsburgh center's observation of improved survival since 1994 is not echoed in the overall 1997 results of the International Intestinal Transplant Registry from all centers, which reports virtually identical graft survival from 1991–1993 as from 1994–1997 (about 60% at one year, and 48% at two years). No significant difference is reported in the survival of patients given either intestine-alone, intestine/liver or multivisceral transplantation.

Analyses of Individual Patient Data

Patient Survival

To better gauge the robustness of the data published by individual centers and to provide more current data than those found in the registry, ECRI obtained individual patient data on a significant portion (about 50%) of the world's intestinal transplantation patients. Analyses of these data are presented below.

Overall patient survival is shown in Figure 1, containing data from both published and unpublished sources (see Findings, above) (n=195). Actuarial survival is estimated at 66% at one year, 56% at two years, and 45% at three years. No significant difference in patient survival is seen between those transplanted before or after 1994 (data not shown). Though incomplete, these data suggest the better results reported by the University of Pittsburgh (see above) may not be widely replicated.

When patient survival is analyzed by type of transplantation (Figure 2), a statistically significant difference ($p < 0.05$, log-rank test) is found between multivisceral transplantation and intestine-alone transplantation, in favor of intestine-alone transplantation. This observation differs from that found in the registry, or that seen when the Pittsburgh and Miami centers are considered individually (data not shown). There is no statistically significant difference between the survival curves of intestine-alone and intestine/liver transplantation ($p = 0.11$) or between multivisceral and intestine-liver transplantation ($p = 0.13$). However, there is a greater increase in the early mortality of intestine/liver patients, which is likely a reflection

of their more seriously compromised health at time of transplantation (see Reported Patient Indications and Contraindications, above).

No significant difference in patient survival was seen when the results of transplantation were examined by patient age (Figure 3: Patients 18 years and younger are classified as children).

Two centers, the University of Pittsburgh and the University of Miami, have been pursuing the adjunctive transplantation of hematopoietic and immune system cells. As previously noted, the data from the Univiversity of Pittsburgh do not show that this practice confers any advantage on patient survival, and the same holds true for results from Miami. However, both centers report that patients receiving bone marrow have improved survival, though the improvement has not reached statistical significance (data not shown).

Graft Survival

Overall graft survival is shown in Figure 4. This curve is similar to that for patient survival. When examined by transplantation modality (see Figure 5), graft survival after either intestine/liver or intestine-alone transplantation was significantly better than that following multivisceral transplantation. There was no difference between those two former measures in graft survival. Graft survival mirrors the corresponding data on patient mortality (Figures 1 and 2). These observations point out that patient survival is closely tied to graft survival, although in some cases patients can survive graft rejection or removal. As with patient survival, no significant differences were found in graft survival as a function of patient age or of bone marrow transplantation (data not shown).

Figure 1. Patient Survival after Intestinal Transplantation (All Modalities) at Four Centers (n = 198)

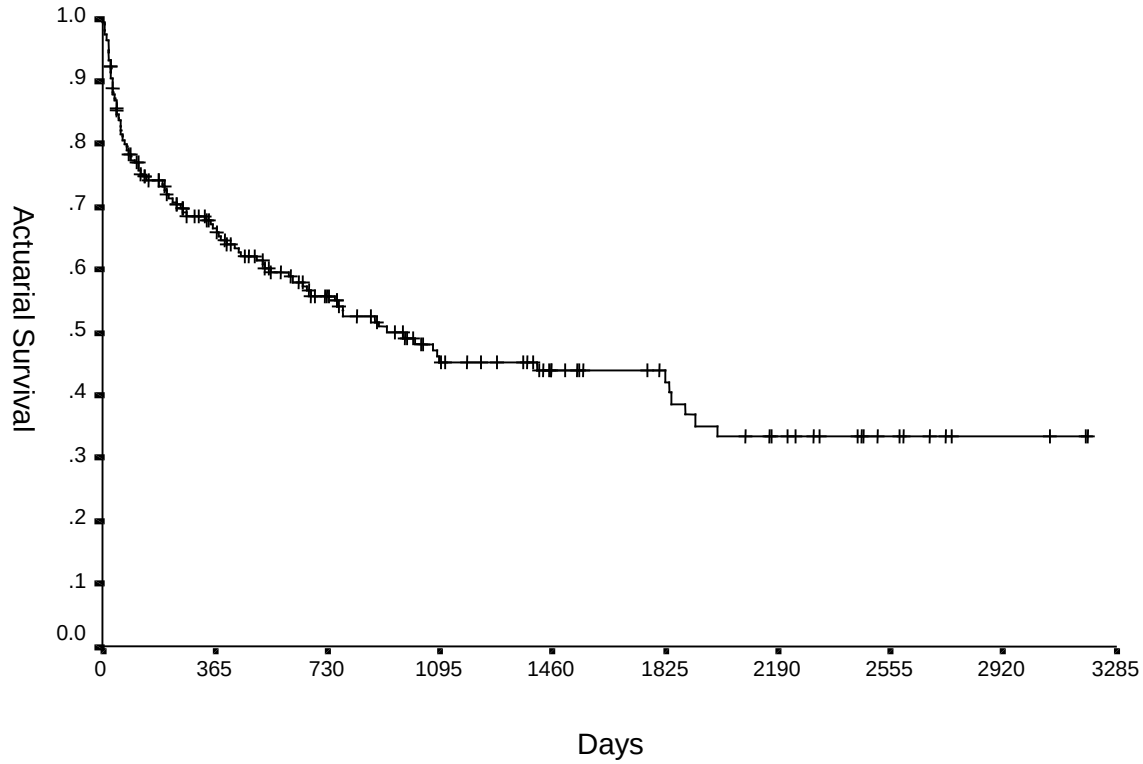
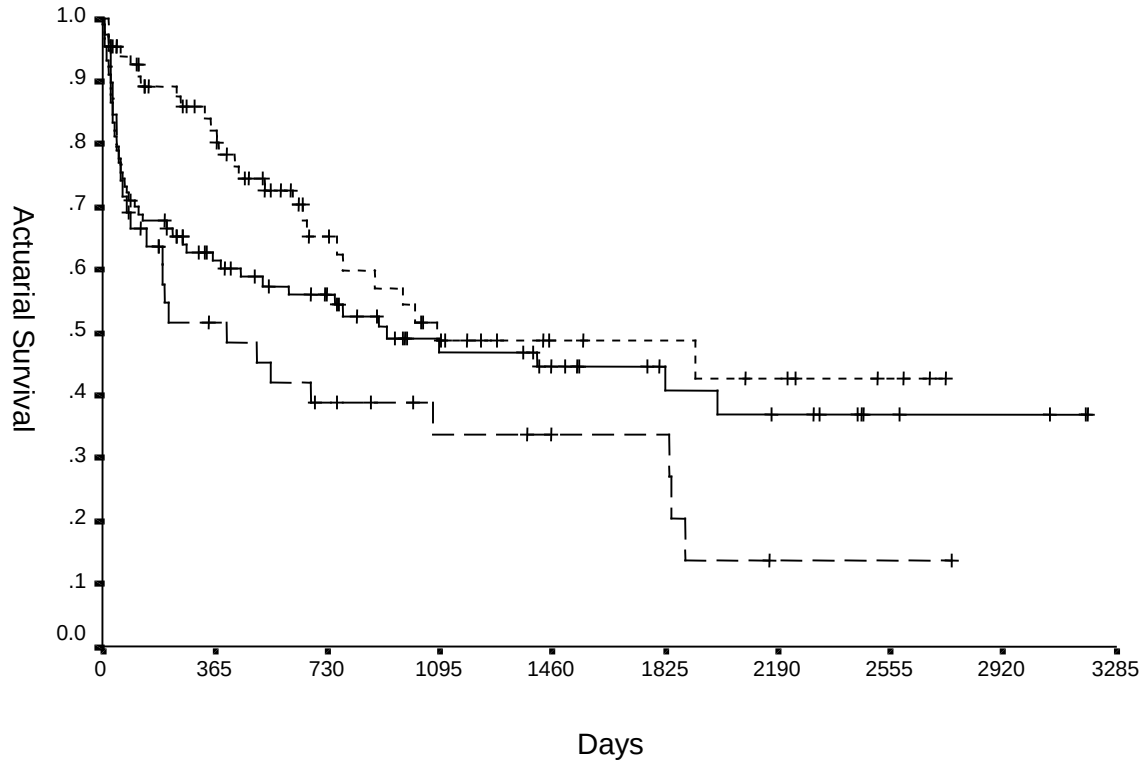
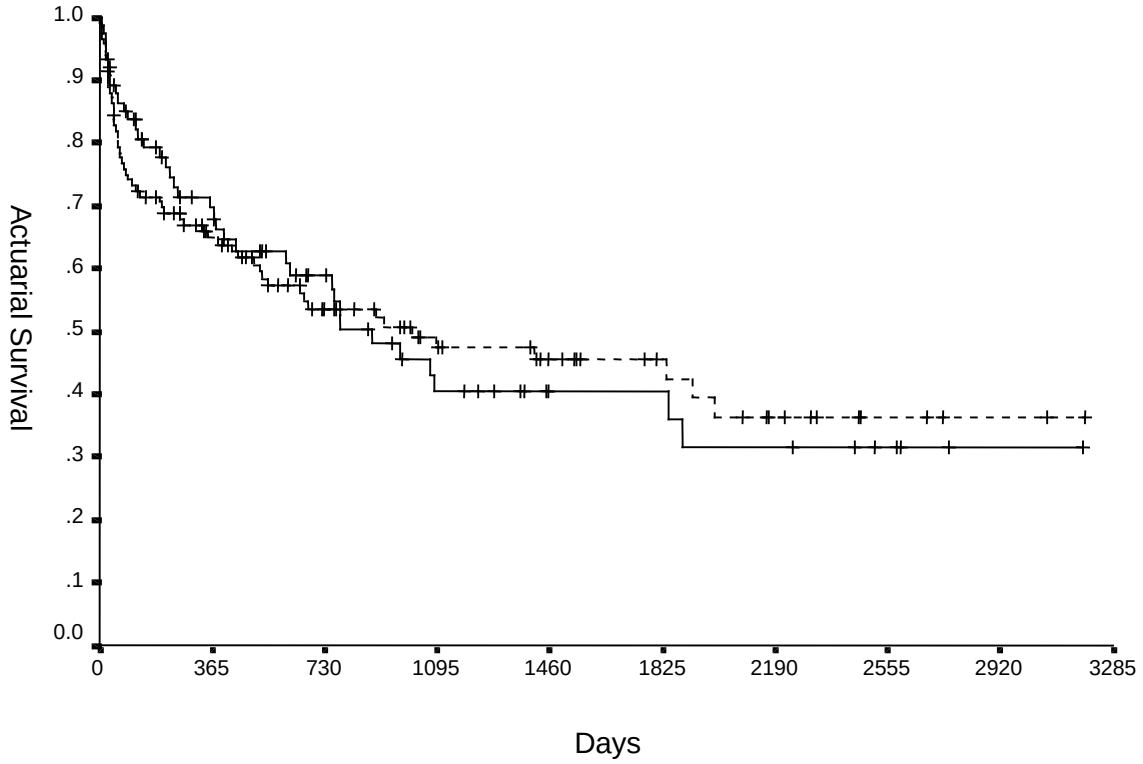


Figure 2. Patient Survival by Transplant Type



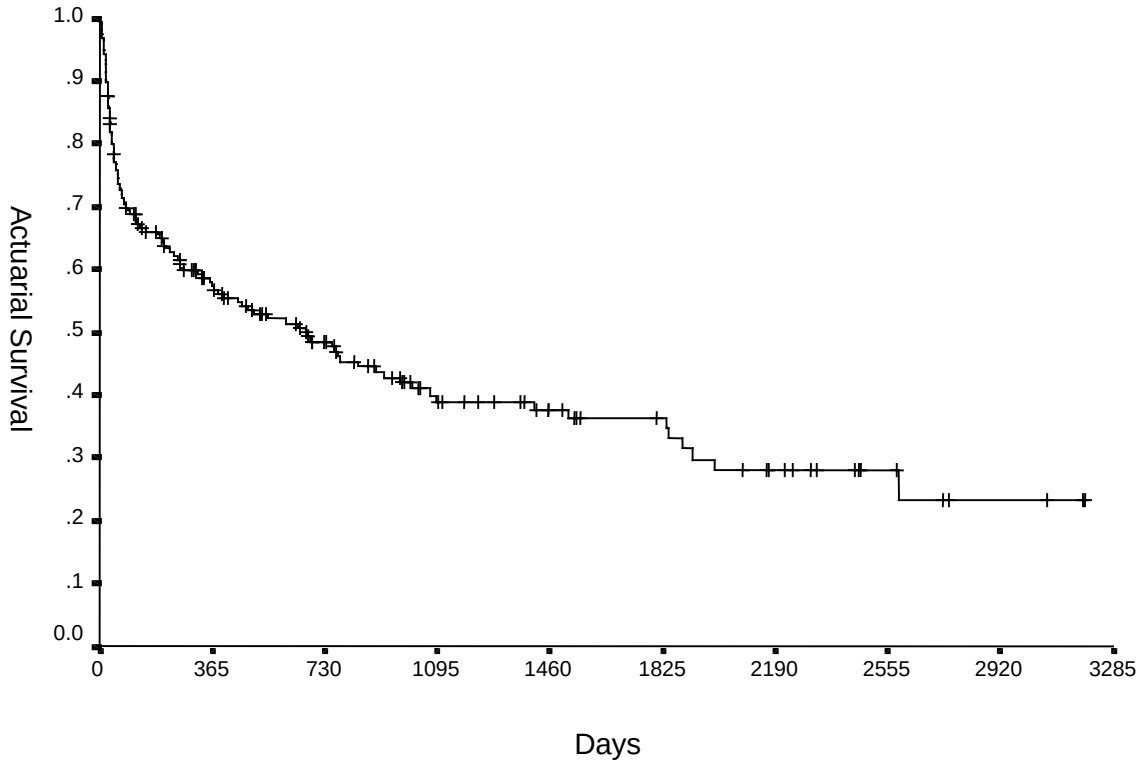
Small dashed line: Intestine-alone (n= 69).
Solid line: Intestine/liver (n = 90).
Large dashed line: Multivisceral (n=39).

Figure 3. Patient Survival by Age



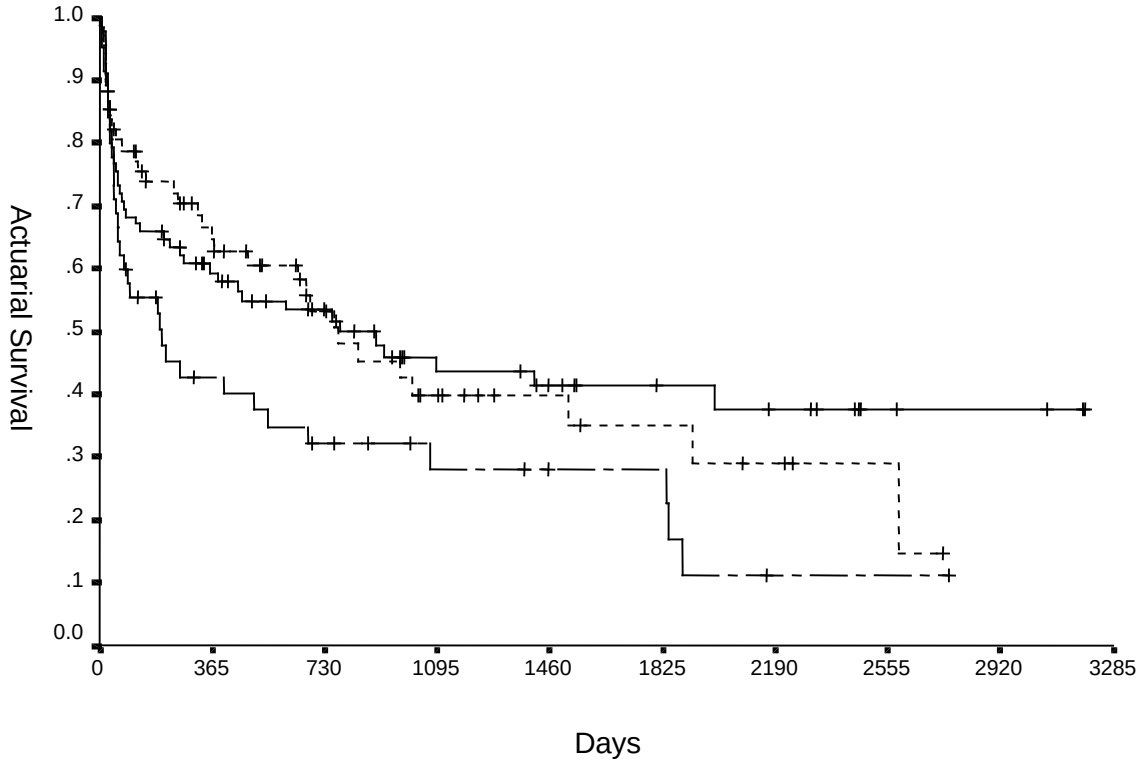
Dashed line: Children (age <18 years, n = 117)
Solid line: Adults (n = 75)

Figure 4. Graft Survival



All patients, including those receiving retransplantations (n=195 grafts).

Figure 5. Graft Survival by Type of Transplantation



Small dashed line: Intestine-alone (with or without colon) (n = 68)
Solid line: Intestine/liver (n = 82)
Large dashed line: Multivisceral (n = 45)

Morbidity

There is a basic level of morbidity associated with immune suppression that all transplantation patients face. Both tacrolimus and cyclosporine are nephrotoxic,(58-61) and both have been associated with the development of insulin-dependent diabetes, as has steroid administration.(62) As a rule, the levels of immunosuppression are gradually decreased over the course of the first year post-transplantation, in accordance with the decreasing risk of rejection.(31,41) The incidence of immunosuppressant drug side effects decreases as well. Other side effects of tacrolimus (seen in at least 15% of patients) include cardiomyopathy, tremor, headache, paresthesia, diarrhea and abdominal pain (both symptoms of rejection as well), fever, and hypertension.(63)

Rejection

Rejection has been a major impediment to intestinal transplantation. Although rejection is lessened by tacrolimus, it is by no means eliminated. Rejection does not occur in all patients, but occurs in a large majority and tends to recur in patients who have experienced it once. Episodes of acute rejection are seen in 79% of intestine-alone recipients, 71% of intestine/liver recipients, and 56% of multivisceral transplant recipients. Patients average 1.2 to 1.7 rejection episodes. Chronic rejection, seen several months after transplantation, is observed more often in patients receiving an intestine-alone transplant (13% of patients) than in those receiving an intestine/liver transplant (3%).(28)

Treatment of rejection depends upon its detection, and this is very difficult in intestinal transplantation patients. There is no blood test for rejection or compromise of intestinal activity, and so assessment relies heavily on endoscopy and biopsy to locate and verify rejection.(64) Rejection of the graft is seldom all-or-none; rather it is often spotty or punctate, although it can be disseminated throughout the graft. As a result, numerous biopsies must be done, and each carries with it a risk of bowel perforation and infection.(34) In a series of 98 patients reported on by the University of Pittsburgh, 4,472 intestinal biopsies were performed (46 biopsies/patient), along with 258 liver biopsies.(31)

Rejection occurs largely within the first months following transplantation; the cumulative risk curve is asymptotic at one year. Although liver rejection can occur independently of intestine rejection, usually it is the intestine that has the most severe rejection, particularly when only the intestine has been transplanted.(31,65,66)

Co-transplantation of the liver with intestine appears to have a protective effect against rejection, particularly during the first year. At Pittsburgh, Abu-Elmagd et al. found an incidence of rejection of 92% among intestine-alone grafts in the first 30 days, compared to 66% in composite (i.e., intestine/liver or multivisceral) grafts ($p = 0.04$). Graft loss from rejection at 30 or more months posttransplant in composite grafts is half that of intestine-alone grafts.(31) Similar results have been observed at Western Ontario.(67)[#239506]

Episodes of rejection are treated by increasing the immune suppression, using steroids, OKT3, MM, cyclosporine, higher dosages of tacrolimus or other drugs. A fine balance must be struck: too much immunosuppression can lead to compromising the recipient's ability to defend against lethal infections and to the development of PTLD. Thus, aggressive attempts to fend off rejection can lead to death by infection. PTLD occurs because Epstein-Barr virus–transformed B cells are not eliminated by the immunosuppressed host. On the other hand, the rejection resulting from too little immunosuppression can lead to the compromise of the intestine's bacterial barriers, with sepsis being one result.(32,41,68)

Daclizumab, a newly developed humanized anti-IL-2 receptor monoclonal antibody used as an induction therapy with tacrolimus, has shown promising results in the first 18 weeks post-transplantation, reducing the incidence of rejection from 100% to 43% in that period.(69) It can also be expected that trials with antibodies to CD 154 (the ligand for CD 40, a key receptor in mediating rejection) will also be commencing at various centers.

Infection

Infection can arise from either too much or too little immunosuppression, and is a continuing danger following transplantation.(35) The published data on the incidence of infection are difficult to interpret and probably incomplete, but the data in Table 3 suggest that the incidence of infection is significant. Previous data from Pittsburgh showed that 97% of adult patients had at least one complication of infection, with a median of five instances per patient. Bacterial, viral and fungal (usually candida esophagitis) were seen in 93%, 69%, and 59% of patients, respectively. Multiple infections were seen in three-fourths of recipients. The most frequent incidence of infection by transplant type in descending order was seen in multivisceral recipients, intestine-liver recipients, and intestine-alone. The origin of infection was often line sepsis (in 43% of episodes), followed by translocation across the intestine (in 19%).(70) Similarly, the published experience at Nebraska shows that complications from infection are common (particularly intestinal abscesses, sepsis, and intestinal perforations), and are the cause of major postoperative problems, and all the mortality.(40) In the absence of more recent data, these reports are presumably still indicative of the current situation. Sepsis is the main cause of death in intestinal transplant patients, accounting for 47% of these patients' deaths.(28)

Cytomegalovirus (CMV) is often carried by both donors and recipients. While the virus is usually harmless, its infections can be lethal in immunosuppressed recipients, and it is a major cause of morbidity and mortality. Earlier data from Pittsburgh suggested that the incidence of infections could be lessened by transplanting only CMV-free grafts into CMV-free hosts,(56) which is now the policy at that center. However, since many hosts and grafts are infected before transplantation, CMV infection remains a problem for many patients.(31) Children have a lower incidence of CMV than adults, possibly due to linkage with major histocompatibility complex markers (D-R-). Generally, CMV infection in children can be managed with gancyclovir, without the need for decreasing administration of immunosuppressive agents.(71) In adults, CMV infection was reported in 45% of recipients, and CMV in adults is more resistant to treatment.(56)

Like CMV, Epstein-Barr virus (EBV) is carried by many recipients and donors prior to transplantation. In immunosuppressed recipients, EBV viremia can be a precursor to the malignant transformation of B-cells, which can no longer be eliminated by the immune suppressed recipient and thus can develop into PTLD. PTLD occurs more often in child recipients.(54,72) At Pittsburgh, patients are screened for EBV viremia with DNA-based tests, and positive findings result in decreasing the immune suppression (when feasible). In this way the body's own defenses can eliminate EBV-infected B cells, and forestall PTLD. Initial evidence suggests that keeping EBV levels low prevents PTLD.(73)

Table 3: Post-transplantation Morbidity

Study, date, center	No of patients	Time of maximum follow up	Rejection*	Bacterial/fungal infection/sepsis	Viral infection	PTLD	CMV	Mechanical/ surgical	Comments
Atkison et al. 1998(41) London Ont	10	5 years	30% 10% severe	20%	20%	10%	—		Tacrolimus-induced cardiac hypertrophy: 40%; renal toxicity:60%
Lacaille et al. 1998(74) Paris	6	39 months	66%	33%	33%	33%			All intestine-liver recipients
Goulet et al. 1998(75) Paris	13	37 months	23% liver 38% intestine	38%	38%	23%	15%	54%	
Farmer et al. 1998(8) UCLA	6	5 years	4 incidents (2 pts)	6 incidents		0	1 incident	9 incidents	
Abu-Elmagd et al. 1998(31) Pittsburgh	98	7 years	93% (97/104) of allografts; 8 grafts lost	18 graft losses or fatalities		20%	36%	8 fatalities	GVHD: 5%, 1 case fatal.
Karatzas et al. 1997(32) Miami	19	2 years	89%	21%	16%		21%		

* Expressed as percentage of patients unless otherwise stated
* PTLD = Post-transplant lymphoproliferative disorder
* CMV = Cytomegalovirus

Quality of Life

The available quality-of-life (QOL) data come from series at Pittsburgh. DiMartini et al.(76) administered the Quality of Life Inventory (QOLI) survey to 9 adult transplant recipients (of Pittsburgh's 12 adult survivors with functioning grafts), comparing their QOL before H/TPN to that during H/TPN, and the QOL after transplantation to both that before and during H/TPN. Respondents who had received small intestine, intestine/liver, or multivisceral transplantation rated life on H/TPN as worse than life before H/TPN on 21 of 25 domains (e.g., pain, stress, coping, finances, sex, energy, etc.). The difference in ratings was statistically significant. Three domains were unchanged and one (alcohol use) significantly improved. Life after transplantation (at an average of 22 months) was rated as statistically significantly improved compared to that while on H/TPN in 16 of 25 domains, with the remaining 9 unchanged. Comparison of life after transplantation to life before H/TPN was, as might be expected, less favorable. Three domains were rated better, seven were rated worse, and 15 were rated the same (i.e., no statistically significant difference).

A second group of 18 patients on H/TPN who were without terminal illness and not experiencing complications were also asked to compare their current QOL to that prior to H/TPN, and rated it worse in 11 of 25 domains, compared to 21/25 domains for the transplant patients. There is some variance reported in the literature in the quality-of-life scores of H/TPN patients, but it not surprising that those with near-fatal complications (the transplant recipients) would rate it worse than those on stable maintenance. That the transplant recipients viewed their lives as being not much worse than before H/TPN raises the question of the severity of their medical conditions before beginning H/TPN. Six had thrombotic disorders or trauma and thus may have had essentially normal lives; while three had Crohn's disease or a desmoid tumor and thus may have had a lower QOL than the others. Thus, there is reason to interpret these data as indicating that the transplant patients felt a good quality of life had been restored, rather than a sickly one.

Using the same QOLI instrument, Rovera et al.(77) surveyed 10 adult transplant recipients at Pittsburgh at an average of 33 months after transplantation. Two of the twelve total adult recipients were excluded; one because her graft had been removed, and one because she required H/TPN. Of the 10 respondents, two had PTLD at the time of the interview, and one was legally blind from diabetic retinopathy. Three patients were questioned within six months of transplantation; two of these were hospitalized for up to 12 months before transplantation. Responses of transplantation patients were compared to those of 10 H/TPN patients who were potentially intestinal transplant candidates, but of which only two had significant complications (and were subsequently given transplantation). There were few differences between groups. Transplantation patients were worse in measures of drug use (due to sleep medications) and medical compliance, and marginally better ($p=0.07$) on optimism. Intestinal transplant patients' scores were similar to those of liver transplant patients.

In each group, four patients had previously taken the questionnaire (an average of 2.7 years earlier for the transplantation patients, and 1.3 years for the H/TPN patients). Statistically

significant improvement was seen in measures of sleep, anxiety and impulsiveness/control (which relates to concerns about bodily symptoms) in the transplantation group, while the H/TPN group had improvement in finances and worsening of mental status (concentration, forgetfulness, interpersonal reactions).

Tarbell et al.(78) compared the effects of H/TPN and transplantation on QOL of 61 parents from 42 families with child intestinal graft recipients, surveyed pretransplantation and two months after transplantation. Parental psychological distress (from the Global Stress Index) was significantly elevated in most families, particularly for fathers, but there were no significant differences pre- and post-transplantation. Also unchanged after transplantation was parenting stress (from the PSI), overall physical health (from the SF-36). Thus, the early period after transplantation is as stressful for parents as is pretransplantation, but no more so.

H/TPN Dependence

Transplantation of a new intestine does not instantly or automatically confer freedom from H/TPN. Infants and children who had developmental abnormalities may never have had solid food, and can require two to 30 weeks of adjustment for the establishment of autonomous feeding; Pittsburgh reports a mean time of 41 days for its children. Adults also require a period of adjustment, though typically not as long. For adults, nasogastric tube enteral feeding for up to a year is an intermediate step toward a normal oral diet, but most transition to normal oral intake within six months.(54,75,79) Allergies to wheat and milk are common after transplantation, but both adults and children maintain a good nutritional status once off H/TPN.(80,81)

The current food intake status of surviving patients is shown in Table 4.

Table 4: Feeding Status

Study, date	Number of patients*	% H/TPN-free	Comments
Abu-Elmagd et al. 1999(33) Pittsburgh	60	95% (57/60)	Abstract; number of H/TPN-free patients inferred from percentage.
Abu-Elmagd et al. 1999(8) Pittsburgh	55	93% (51/55)	2 patients on partial (presumably temporary) H/TPN for treatment of rejection; 2 patients on H/TPN for graft dysmotility.
Reyes et al. 1998(54) Pittsburgh	30	97% (29/30)	All children
Tzakis 1999(51) Miami	30	83% (25/30)	Lower rate of H/TPN independence may be due to a larger fraction of patients having recent transplantations.
Atkison et al. 1998(41) London, Ont	7	100% (7/7)	
Goulet et al. 1998(75) Paris	10	70% (7/10)	3 patients partially H/TPN dependent due to electrolyte losses from the graft
Farmer 1998(35) UCLA	3	66% (2/3)	1 patient partially dependent on H/TPN

*Denominated as patients alive at time of report

Clinical Perspectives

Survival

ECRI's previous assessment of intestine and intestine-liver transplantation(82) stated "Progress in intestinal transplantation can be expected to be incremental. Matching for cytomegalovirus status, prophylaxis for lymphoproliferative disorder, and better assessment of rejection can all be expected to improve mortality."(83) The most recent data from Pittsburgh, the center with the largest patient series, has fulfilled this expectation. After a moratorium on intestinal transplantation at that center, a number of measured changes were instituted, including CMV-status matching, sensitive EBV screening, and the abandonment of colon transplantation. These measures have significantly increased the graft survival compared to that seen prior to these changes.(8) Although Pittsburgh accounts for a large fraction (40%) of worldwide intestinal transplants, it cannot be determined whether this increase in survival is particular to that center or is also found elsewhere, reflecting the widespread adoption of improved transplant management technologies. The one- and five-year patient survival rates (72% and 48% respectively) seen overall at Pittsburgh are comparable to those seen following some other types of organ transplantation, such as lung transplantation (77% and 43% (84)), which is covered by Medicare. Pittsburgh is making a case for Medicare coverage(53); however, it is likely that the Health Care Financing Administration, which administers Medicare, would demand that these survival rates be widely attainable throughout centers in the United States. In this regard, the current data from the International Intestinal Transplant Registry are not supportive, though the current data are out of date and would be expected to lag behind the results obtained at Pittsburgh and other major centers in any case. Similarly, the overall individual patient data analyzed by ECRI do not yet show a statistically significant improvement since 1994, as found at Pittsburgh. As greater concordance on methodology and patient selection evolves among the centers, further incremental progress in patient and graft survival is to be expected. As it is, the success of intestinal transplantation is about the same as the success of heart/lung transplantation(84)

Morbidity and Quality of Life

Intestinal transplantation is meeting with increased success, but "hospital courses and complications are . . . formidable."(35) Rejection, infection and lymphoma are the most serious threats to the graft and patient, and it can be inferred that for at least the first year after transplantation close monitoring is required and hospitalizations are not infrequent, although there are no published data on how frequent. Despite the manifest difficulties, patients rate their QOL after transplantation to be higher than that while on H/TPN before transplantation. Posttransplantation QOL appears lower than that before H/TPN, however, and is roughly comparable to that enjoyed by patients who manage H/TPN without difficulty. Of course for most patients given transplantation, the alternative would be death, and this may (appropriately enough) influence their responses. Also, QOL was not analyzed on an intent-to-treat basis, accounting for the lowered quality of life of deceased patients, and thus the data

may be biased more favorably toward transplantation. Successful intestinal transplantation is very likely to be accompanied by oral feeding, and with it, relief from the adversities encountered by this group of patients on H/TPN.

Service Provider

Intestinal transplantation is provided at selected major tertiary care centers associated with major medical schools. Major centers in North America include medical centers at the University of Pittsburgh, the University of Nebraska, the University of Miami, and the University of Western Ontario (London). In Europe, active centers include the Hopital Necker-Enfants Malades in Paris, and the Birmingham Childrens' Hospital in the United Kingdom.

Transplant Charges

Data on charges of intestinal transplantation are scarce. Reported charges at the University of Pittsburgh between 1994 and 1998 averaged (whether mean or median was not stated) $132,285 for transplantation of the intestine-alone, $214,716 for intestine-liver transplants, and $219,098 for multivisceral procedures. These costs were lower than those of the previous four-year period by 35%, 15% and 23% respectively.(8) Individual charges can on rare occasions be much greater.

Cost Considerations

The costs of intestinal transplantation are not limited to those of the surgery and attendant hospital charges. To those charges must be added the costs of rehospitalization for infection or rejection, and the costs of long-term medication.

Currently, patients on long-term H/TPN are not automatically placed on the waiting list for intestinal transplantation, which is reserved only for the critically ill. Accordingly, comparison of the costs of H/TPN and those of transplantation are not strictly relevant to the present situation. Nonetheless, those who propose that intestinal transplantation be more widely available point out that H/TPN is also quite expensive, costing Medicare an average of $150,000 per patient per year, not including the costs of hospitalization and nursing care.(8)

Regulatory Status

Intestinal transplantation is not regulated by government agencies.

Medicare Status

Intestinal transplantation is not covered by Medicare. The University of Pittsburgh has called upon the CMS to reimburse for this operation, asserting that the 72% one-year survival rate is similar to that of lung transplantation, which is paid for by Medicare.(53)

Phase of Diffusion

Intestinal transplantation is in an early (and relatively slow) phase of diffusion. The International Intestinal Transplant Registry reports that as of February 1997 there were 33 centers throughout the world that performed intestinal transplantation,(28) up from 25 centers in 1996.(85) Most activity is concentrated in North America, where 20 centers are reporting to the registry. As of 1997, a total of 260 patients had received transplants; although the current figure may be near 360.

Conclusions and Recommendations

Since ECRI's last assessment in 1996, intestinal transplantation has made slow but steady progress in measures of patient and graft survival. Patient survival at one year is approximately 70%, at two years is 55% to 60%, and at three to five years is nearly 50%. Results from the University of Pittsburgh, which has the single largest series of patients (30% to 40% of the worldwide total), have significantly improved during the past five years, but it is yet unclear to what degree these gains are generalizable to other centers, which may transplant candidates with different patient characteristics.

Because of the general success of H/TPN and the comparative rarity of intestinal failure, there is not likely to be a large pool of intestinal transplant candidates. Infants, however, are a population at high risk for H/TPN failure, because of liver damage necessitating intestine-liver transplantation. There is evidence that these children are being referred for intestinal transplantation later than is optimal for their survival, and this may account for the higher early mortality of intestinal-liver transplant patients compared to intestine-alone patients.

Treatment of rejection depends upon its monitoring, which is especially difficult with intestinal transplantation, and requires numerous biopsies. Extensive immunosuppression is needed to prevent rejection. Too much immunosuppression can lead to infections or sepsis. Too little immunosuppression can lead to rejection, which breaks down the barrier to the intestinal flora, and can lead to infection and sepsis. Thus, intestinal transplant patients require close monitoring, and rehospitalizations are not infrequent.

The advent of tacrolimus has improved patient and graft viability, and this immunosuppressant has been widely adopted. Efforts continue to reduce the incidence and severity of rejection, which has prevented intestinal transplantation from having the same

degree of success as liver transplantation. The adjunctive transplantation of donor immune system cells, which Pittsburgh and Miami in particular have been pursuing, appears not to have had a major impact on rejection yet, but may turn out to be another incremental improvement.

Nonetheless, QOL attained post-transplantation is higher than that experienced before transplantation, and it is on a par with that reported by patients who manage H/TPN without difficulty. Intestinal transplantation is successful in obviating H/TPN, and >90% of patients who survive resume oral feeding.

Intestinal transplantation remains more difficult than the transplantation of many other organs. The long-term prognosis of intestinal transplantation is still open: follow up data are scarce after 6 years, and the field as a whole is fairly young. Nonetheless, there is solid evidence of improvement in patient and graft survival, and continued incremental progress in intestinal transplantation can be expected.

Windows on Medical Technology™

Checkpoints:
Intestinal Transplantation

ü *Technology Description*

The purpose of intestinal transplantation is to prolong the lives of patients whose intestines are of inadequate length or function to absorb nutrients, and who can no longer be fed parenterally (i.e., by home/total parenteral nutrition [H/TPN]). There are three different modalities of intestinal (or small intestine) transplantation. In the first, a major portion or the whole intestine consisting of the ileum and jejunum are transplanted (intestine-alone transplantation). In intestine-liver transplantation, the ileum and jejunum are transplanted with the liver, *en bloc.* Multivisceral transplantation procedures are more variable, but generally include the stomach, duodenum and pancreas along with the small intestine and liver. On occasion the colon is also transplanted, but only when necessary. The mainstay of immunosuppression for intestinal transplantation is tacrolimus (Prograf® or FK506). At some centers donor immune system cells (from bone marrow or peripheral lymphocytes) are adjunctively transplanted along with the intestine. At some centers kidney or pancreas transplantation may accompany intestine-alone or intestine-liver transplantation.

ü *Evidence Base*

The evidence pertaining to intestinal transplantation comes from three sources: journal publication, registry data, and patient data from particular centers. All data are from case series on a total of about 200 patients.

ü *Key Outcomes and Results*

Patient survival following intestinal transplantation varies from center to center, but overall is approximately 70% at one year, 60% at 2 years, and 50% at three years. Graft survival is slightly lower. Over 90% of surviving patients are free of parenteral nutrition. Post-transplantation quality of life is judged by patients to be at least as good as that on H/TPN.

ü *Conclusions*

Intestinal transplantation has made slow but steady progress in measures of patient and graft survival. However, intestinal transplantation remains more difficult than the transplantation of many other organs, and patients need close monitoring for infection and rejection after transplantation. Intestinal transplantation is successful in obviating H/TPN, andnearly all patients can resume oral feeding. The overall quality of life following intestinal transplantation is comparable to and possibly better than that enjoyed by patients who manage H/TPN without serious complications.

ü *Reported Patient Indications and Contraindications*

Candidates for intestinal transplantation can no longer be effectively fed using parenteral nutrition, due to loss of venous access, sepsis, clotting, or liver failure. Candidates may range in age from infants to adults (usually younger than 60 years old). Contraindications include AIDS, uncontrolled infection, unresectable or aggressive cancer (desmoid tumors may be an indication), cardiac disease, congenital heart disease, and severe chronic lung disease. About 59% of all intestinal transplant recipients have been childen.

ü *Care Setting*

Intestinal transplantation is an inpatient procedure.

ü *Service Provider*

Intestinal transplantation is performed at selected university-based hospitals.

ü *Regulatory Status*

Intestinal transplantation is not regulated by federal agencies.

ü *Costs*

At the University of Pittsburgh, the predominant center for intestinal transplantation, costs averaged $132,285 for transplantation of the intestine alone, $214,716 for intestine-liver transplants, and $219,098 for multivisceral procedures.

ü *Medicare Status*

Intestinal transplantation is not covered by Medicare.

ü *Phase of Diffusion*

This technology is in early adoption because it is highly complex and is only performed at a small number of highly sophisticated tertiary care medical centers worldwide.

Selected References

1. Meguid MM, Muscaritoli M. Current uses of total parenteral nutrition. Am Fam Physician 1993 Feb 1;47(2):383-94.

2. Malledant Y, Tanguy M, Saint-Marc C. [The so-called short bowel syndrome in adults]. Ann Fr Anesth Reanim 1987;6(3):195-203. (Fre).

3. Bueno J, Ohwada S, Kocoshis S, Mazariegos GV, Dvorchik I, Sigurdsson L, Di Lorenzo C, Abu-Elmagd K, Reyes J. Factors impacting the survival of children with intestinal failure referred for intestinal transplantation. J Pediatr Surg 1999 Jan;34(1):27-33.

4. Schwartz MZ, Maeda K. Short bowel syndrome in infants and children. Pediatr Clin North Am 1985 Oct;32(5):1265-79.

5. Wesley JR. Efficacy and safety of total parenteral nutrition in pediatric patients. Mayo Clin Proc 1992 Jul;67(7):671-5.

6. Berger DL, Malt RA. Management of the short gut syndrome. Adv Surg 1996;29:43-57.

7. Vanderhoof JA, Langnas AN, Pinch LW, Thompson JS, Kaufman SS. Short bowel syndrome. J Pediatr Gastroenterol Nutr 1992 May;14(4):359-70.

8. Abu-Elmagd K, Reyes J, Fung JJ, Mazariegos G, Bueno J, Janov C, Colangelo J, Rao A, Demetris A, Starzi TE. Evolution of clinical intestinal transplantations: improved outcome and cost effectiveness. Tranplant Proc 1999 Feb-Mar;31(1/2):582-4.

9. Mughal M, Irving M. Home parenteral nutrition in the United Kingdom and Ireland. Lancet 1986 Aug 16;2(8503):383-7.

10. Howard L, Heaphey L, Fleming CR, Lininger L, Steiger E. Four years of North American registry home parenteral nutrition outcome data and their implications for patient management. JPEN J Parenter Enteral Nutr 1991 Jul-Aug;15(4):384-93.

11. 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. In: Proceedings of the 4th International Symposium on Small Bowel Transplantation and Nursing Forum on Small Bowel Transplantation; 1995 Oct 15-17; Pittsburgh (PA); 1995. 12 p. (Gastroenterology 1995 Aug; 109(2)).

12. Howard L, Malone M. Clinical outcome of geriatric patients in the United States receiving home parenteral and enteral nutrition. Am J Clin Nutr 1997 Dec;66(6):1364-70.

13. Howard L, Malone M. Current status of home parenteral nutrition in the United States. Transplant Proc 1996 Oct;28(5):2691-5.

14. Jeppesen PB, Staun M, Mortensen PB. Adult patients receiving home parenteral nutrition in Denmark from 1991 to 1996: who will benefit from intestinal transplantation. Scand J Gastroenterol 1998 Aug;33(8):839-46.

15. Messing B, Lemann M, Landais P, Gouttebel MC, Gerard-Boncompain M, Saudin F, Vangossum A, Beau P, Guedon C, Barnoud D, et al. Prognosis of patients with nonmalignant chronic intestinal failure receiving long-term home parenteral nutrition. Gastroenterology 1995 Apr;108(4):1005-10.

16. 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 Mar;74(3):217-22.

17. Brook G. Quality of life issues: parenteral nutrition to small bowel transplantation--a review. Nutrition 1998 Oct;14(10):813-6.

18. Kelly DA. Liver complications of pediatric parenteral nutrition--epidemiology. Nutrition 1998 Jan;14(1):153-7.

19. The Oley Foundation. Spirit of Oley moves clinicians, consumers at 1998 ASPEN clinical congress [article online]. 1995 [cited 1999 Apr 26]. [5 p]. Available: http://www.wizvax.net/oleyfdn/lifeline/95-059.html.

20. Lange BJ, Weiman M, Feuer EJ, Jakobowski D, Bilodeau J, Stallings VA, Hirschl R, Bell LM, Harper J, Cnaan A. Impact of changes in catheter management on infectious complications among children with central venous catheters. Infect Control Hosp Epidemiol 1997 May;18(5):326-32.

21. Howard L. Septic complications of TPN [article online]. 1995 [cited 1999 Apr 26]. [6 p]. Available: http://www.wizvax.net/oleyfdn/lifeline/95-042.htm.

22. Wesley JR. Home parenteral nutrition: indications, principles, and cost-effectiveness. Comp Ther 1983;9(4):29-36.

23. Swaniker F, Fonkalsrud EW. Superior and inferior vena caval occlusion in infants receiving total parenteral nutrition. Am Surg 1995 Oct;61(10):877-81.

24. de Csepel J, Stanley P, Padua EM, Atkinson JB. Maintaining long-term central venous access by repetitive hepatic vein cannulation. J Pediatr Surg 1994 Jan;29(1):56-7.

25. D'Alessandro AM, Kalayoglu M, Sollinger HW, Pirsch JD, Belzer FO. Liver-intestinal transplantation: report of a case. Transplant Proc 1992 Jun;24(3):1228-9.

26. Todo S, Tzakis A, Reyes J, Abu-Elmagd K, Casavilla A, Fung JJ, Starzl TE. Intestinal transplantation in humans under FK 506. Transplant Proc 1993 Feb;25(1 Pt 2):1198-9.

27. Furukawa H, Reyes J, Abu-Elmagd K, Todo S. Clinical intestinal transplantation [review]. Clin Nutrition 1996 Apr;15(2):45-52.

28. The intestinal transplant registry website [online]. London (Canada): London Health Sciences Centre; [updated 1999 Jun 03]; [cited 1999 Jun 07]. Available: http://www.lhsc.on.ca/itr/.

29. Tzakis A, Todo S, Reyes J, Starzl TE, McAlister V, Grant D. Liver and small bowel transplantation for short gut syndrome in a child. Transplant Sci 1991 Apr;1(1):27-33.

30. Tzakis AG, Todo S, Starzl TE. Intestinal transplantation. Annu Rev Med 1994;45:79-91.

31. Abu-Elmagd K, Reyes J, Todo S, Rao A, Lee R, Irish W, Furukawa H, Bueno J, McMichael J, Fawzy AT, Murase N, Demetris J, Rakela J, Fung JJ, Starzl TE. Clinical intestinal transplantation: new perspectives and immunologic considerations. J Am Coll Surg 1998 May;186(5):512-25; discussion 525-7.

32. Karatzas T, Khan F, Tzakis AG. Clinical intestinal transplantation: experience in Miami. Transplant Proc 1997 May;29(3):1787-9.

33. Abu-Elmagd K, Reyes J, Mazariegos G, Demetris J, Murase N, Rakela J, Rao A, Starzl TE, Fung J. Intestinal transplantation and end stage gastrointestinal disease: improved outcome and cost effectiveness. In: American Society of Transplantation (AST) 18th Annual Scientific Meeting; May 15-19, 1999; Chicago, IL. Thorofare (NJ): American Society of Transplantation (AST); 1999 Apr 30. 1 p.

34. Atkison P, Williams S, Wall W, Grant D. Results of pediatric small bowel transplantation in Canada. Transplant Proc 1998 Sep;30(6):2521-2.

35. Farmer DG, McDiarmid SV, Smith C, Stribling R, Seu P, Ament MA, Vargas J, Yersiz H, Markmann JF, Ghobriel RM, Goss JA, Martin P, Busuttil RW. Experience with combined liver-small intestine transplantation at the University of California, Los Angeles. Transplant Proc 1998 Sep;30(6):2533-4.

36. Pollard SG. Intestinal transplantation: living related. Br Med Bull 1997;53(4):868-78.

37. Fujimoto Y, Uemoto S, Inomata Y, Kurokawa T, Koshiba T, Takatsuki M, Hino H, Tanaka K. Living-related small bowel transplant: management of rejection and infection. Transplant Proc 1998 Feb;30(1):149.

38. Nery JR, Weppler D, DeFaria W, Liu P, Romero R, Tzakis AG. Is the graft too big or too small? Technical variations to overcome size incongruity in visceral organ transplantation. Transplant Proc 1998 Sep;30(6):2640-1.

39. Kocoshis SA, Reyes J, Todo S, Starzl TE. Small intestinal transplantation for irreversible intestinal failure in children. Dig Dis Sci 1997 Oct;42(10):1997-2008.

40. Langnas AN, Shaw BW, Antonson DL, Kaufman SS, Mack DR, Heffron TG, Fox IJ, Vanderhoof JA. Preliminary experience with intestinal transplantation in infants and children. Pediatrics 1996 Apr;97(4):443-8.

41. Atkison P, Williams S, Howard J, Wall W, Paradis K, Seidman E, Grant D. Neoral cyclosporine as maintenance immunosuppression in pediatric small bowel transplantation. Transplant Proc 1998 Aug;30(5):1973-4.

42. Howard L. Lecture III-3, Current status of home TPN in the United States. In: 4th International Symposium on Small Bowel

Transplantation and Nursing Forum on Small Bowel Transplantation; 1995 Oct 15-17; Pittsburgh, PA. 1995.

43. Beath SV, Brook GA, Kelly DA, Buckels JA, Mayer AD. Demand for pediatric small bowel transplantation in the United Kingdom. Transplant Proc 1998 Sep;30(6):2531-2.

44. Powell-Tuck J. Management of gut failure: a physician's view. Lancet 1994 Oct 15;344(8929):1061-4.

45. Colomb V, De Potter S, Goulet O, Cuenod B, Salomon R, Jan D, Revillon Y, Ricour C. Potential candidates for small bowel transplantation in pediatric patients on home parenteral nutrition. Transplant Proc 1996 Oct;28(5):2698.

46. Balzola F, De Francesco A, Boggio Bertinet D, Fadda M, Balzola FA. The Italian need for intestinal transplantation. Transplant Proc 1997 May;29(3):1792-4.

47. Dionigi P, Spada M, Alessiani M, Jemos V, Cebrelli T, Viazzo F, Fossati GS, Balzola F. Potential small bowel transplant recipients in Italy. Italian National Register of Home Parenteral Nutrition. Transplant Proc 1994 Jun;26(3):1444-5.

48. Dionigi P, Spada M, Alessiani M, Fadda M, Balzola F, Vaccarisi S, Molina M, Zonta A. Two-year follow-up of potential candidates for small bowel transplantation. Transplant Proc 1996 Oct;28(5):2696-7.

49. Takagi Y, Okada A. Candidates for small bowel transplantation: our experience and a survey of home parenteral nutrition in Japan. Transplant Proc 1994 Jun;26(3):1446.

50. Azuma T, Nakai H, Fukuzawa M, Wasa K, Takagi Y, Okada A. Potential candidates for small bowel transplantation: from our experience and survey of home parenteral nutrition in Japan. Transplant Proc 1998 Sep;30(6):2529-30.

51. Tzakis A. (University of Miami, Jackson Memorial Hospital). Personal communication. 1999 May 5. 2 p.

52. Martin D. (Thomas E. Starzl Transplantation Institute, University of Pittsburgh). Personal communication. 1999 May 6. 1 p.

53. University of Pittsburgh Medical Center (UPMC). UPMC news bureau. Favorable results with intestinal transplants at UPMC basis for appeal for medicare coverage [press release online]. Pittsburgh (PA): UPMC Health System; 1999 Mar 1 [cited 1999 Mar 04]. [3 p]. Available: http://www.upmc.edu/NewsBureau/intestinal.htm.

54. Reyes J, Bueno J, Kocoshis S, Green M, Abu-Elmagd K, Furukawa H, Barksdale EM, Strom S, Fung JJ, Todo S, Irish W, Starzl TE. Current status of intestinal transplantation in children. J Pediatr Surg 1998 Feb;33(2):243-54.

55. Beath SV, Needham SJ, Kelly DA, Booth IW, Raafat F, Buick RG, Buckels JA, Mayer AD. Clinical features and prognosis of children assessed for isolated small bowel or combined small bowel and liver transplantation. J Pediatr Surg 1997 Mar;32(3):459-61.

56. Furukawa H, Abu-Elmagd K, Reyes J, Hutson W, Tabasco-Minguillan J, Lee R, Kusne S, Starzl TE, Todo S. Intestinal transplantation in 31 adults. Transplant Proc 1996 Oct;28(5):2753-4.

57. Jabbour N, Reyes J, Todo S, Bueno J, Mieles L, Kocoshis S, Yunis E, Starzl TE. Intestinal retransplantation. Transplant Proc 1996 Oct;28(5):2773-4.

58. Tauxe WN, Mochizuki T, McCauley J, Starzl TE, Jain A, Charron M. A comparison of the renal effects (ERPF, GFR, and FF) of FK 506 and cyclosporine in patients with liver transplantation. Transplant Proc 1991 Dec;23(6):3146-7.

59. McCauley J, Takaya S, Fung J, Tzakis A, Abu-Elmagd K, Jain A, Todo S, Starzl TE. The question of FK 506 nephrotoxicity after liver transplantation. Transplant Proc 1991 Feb;23(1 Pt 2):1444-7.

60. Porayko MK, Textor SC, Krom RA, Hay JE, Gores GJ, Wahlstrom HE, Sanchez-Urdazpal L, Richards T, Crotty P, Beaver S, et al. Nephrotoxicity of FK 506 and cyclosporine when used as primary immunosuppression in liver transplant recipients. Transplant Proc 1993 Feb;25(1 Pt 1):665-8.

61. Stock PG, Ascher NL, Osorio RW, Tomlanovich S, Lake JR, Nikolai B, Freise C, Roberts JP. Standard sequential immunosuppression with Minnesota antilymphoblast globulin and cyclosporine vs FK 506: a comparison of early nephrotoxicity. Transplant Proc 1993 Feb;25(1 Pt 1):675-6.

62. Paolillo JA, Wagner K, Boyle GJ, Law YM, Miller SA, Pigula FA, Webber SA. Post-transplant diabetes mellitus in pediatric thoracic organ recipients receiving tacrolimus-based immunosuppression. In: American Society of Transplantation (AST) 18th Annual Scientific Meeting; May 15-19, 1999; Chicago, IL. Thorofare (IL): American Society of Transplantation (AST); 1999 Apr 30. 1.

63. Physicians' desk reference. 53rd ed. Montvale (NJ): Medical Economics Company, Inc; 1999. Prograf. p. 1044-8.

64. Sigurdsson L, Reyes J, Putnam PE, del Rosario JF, Di Lorenzo C, Orenstein SR, Todo S, Kocoshis SA. Endoscopies in pediatric small intestinal transplant recipients: five years experience. Am J Gastroenterol 1998 Feb;93(2):207-11.

65. Sigurdsson L, Reyes J, Todo S, Putnam PE, Kocoshis SA. Anatomic variability of rejection in intestinal allografts after pediatric intestinal transplantation. J Pediatr Gastroenterol Nutr 1998 Oct;27(4):403-6.

66. Demetris AJ, Murase N, Lee RG, Randhawa P, Zeevi A, Pham S, Duquesnoy R, Fung JJ, Starzl TE. Chronic rejection. A general overview of histopathology and pathophysiology with emphasis on liver, heart and intestinal allografts. Ann Transplant 1997;2(2):27-44.

67. Atkison PR. (Children's Hospital of Western Ontario). Personal communication. 1999 Jul 29. 2 p.

68. Tzakis AG, Weppler D, Khan MF, Koutouby R, Romero R, Viciana AL, Raskin J, Nery JR, Thompson J. Mycophenolate mofetil as primary and rescue therapy in intestinal transplantation. Transplant Proc 1998 Sep;30(6):2677-9.

69. Abu-Elmagd K, McGhee W, Martin D, Mazariegos G, Fung JJ, Starzl TE, Reyes J. The efficacy of Daclizumab for intestinal transplantation: preliminary report [abstract proposal]. In: The American Society of Transplant Surgeons 25th Annual Scientific Meeting; May 19-21, 1999; 1999 Jan.

70. Kusne S, Abu-Elmagd K, Furukawa H, Irish W, Todo S, Rakela J, Fung J, Starzl TE. Infectious complications after small bowel transplantation (SBTX) in adults. In: 4th International Symposium on Small Bowel Transplantation and Nursing Forum on Small Bowel Transplantation; 1995 Oct 15-17; Pittsburgh, PA. 1995. 1p.

71. Bueno J, Green M, Kocoshis S, Furukawa H, Abu-Elmagd K, Yunis E, Irish W, Todo S, Reyes J, Starzl TE. Cytomegalovirus infection after intestinal transplantation in children. Clin Infect Dis 1997 Nov;25(5):1078-83.

72. Finn L, Reyes J, Bueno J, Yunis E. Epstein-Barr virus infections in children after transplantation of the small intestine. Am J Surg Pathol 1998 Mar;22(3):299-309.

73. Green M, Bueno J, Rowe D, Mazareigos G, Qu L, Reyes J. Predictive negative value (PNV) of persistent low EBV viral loads after intestinal transplantation (ITx) in children [abstract]. In: American Society of Transplantation (AST) 18th Annual Scientific Meeting; May 15-19, 1999; Chicago, IL. Thorofare (NJ): American Society of Transplantation (AST); 1999 Apr 30. 1 p.

74. Lacaille F, Jobert-Giraud A, Colomb V, Cuenod B, Sarnacki S, Michel JL, Jan D, Revillon Y, Ricour C, Goulet O. Preliminary experience with combined liver and small bowel transplantation in children. Transplant Proc 1998 Sep;30(6):2526-7.

75. Goulet O, Michel JL, Jobert A, Damotte D, Colomb V, Cezard JP, Lacaille F, Faure C, Jan D, Jabri B, Sarnacki S, Brousse N, Peuchmaur M, Aigrain Y, Ricour C, Revillon Y. Small bowel transplantation alone or with the liver in children: changes by using FK506. Transplant Proc 1998 Jun;30(4):1569-70.

76. DiMartini A, Rovera GM, Graham TO, Furukawa H, Todo S, Funovits M, Lu S, Abu-Elmagd K. Quality of life after small intestinal transplantation and among home parenteral nutrition patients. JPEN J Parenter Enteral Nutr 1998 Nov-Dec;22(6):357-62.

77. Rovera GM, DiMartini A, Schoen RE, Rakela J, Abu-Elmagd K, Graham TO. Quality of life of patients after intestinal transplantation. Transplantation 1998 Nov 15;66(9):1141-5.

78. Tarbell SE, Kosmach B. Parental psychosocial outcomes in pediatric liver and/or intestinal transplantation: pretransplantation and the early postoperative period. Liver Transpl Surg 1998 Sep;4(5):378-87.

79. Rovera GM, Graham TO, Hutson WR, Furukawa H, Goldbach B, Todo S, Fung JJ, Rakela J, Abu-Elmagd K. Nutritional management of intestinal allograft recipients. Transplant Proc 1998 Sep;30(6):2517-8.

80. Rovera GM, Abu-Elmagd K, Hutson WR, Furukawa H, Goldbach B, Todo S, Rakela J, Fung JJ, Graham TO. Long-term nutritional monitoring after clinical intestinal transplantation. Transplant Proc 1998 Sep;30(6):2515-6.

81. Rovera GM, Strohm S, Bueno J, Kocoshis SA, Abu-Elmagd K, Todu S, Reyes J. Nutritional monitoring of pediatric intestinal transplant recipients. Transplant Proc 1998 Sep;30(6):2519-20.

82. ECRI. Bowel and bowel/liver transplantation [technology assessment report]. Plymouth Meeting (PA): ECRI; 1996 Nov. 92 p.

83. ECRI. Intestinal transplantation for short-bowel syndrome. Plymouth Meeting (PA): ECRI; 1996 Nov. 13 p. (Executive briefings; vol. 2, no. 53).

84. U.S. Scientific Registry of Transplant Recipients, Organ Procurement and Transplantation Network. 1997 OPTN/SR annual report. Richmond (VA): United Network for Organ Sharing (UNOS); 1997. Table 4: graft and patient survival rates at one, three, and five years.

85. Grant D. Current results of intestinal transplantation. The International Intestinal Transplant Registry. Lancet 1996 Jun 29;347(9018):1801-3.