The Role of Intestinal Transplantation in the Management of Intestinal Failure

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Significantly reduced morbidity and mortality is needed before intestinal transplantation will be applicable in most patients with intestinal failure who are on long-term total parenteral nutrition (TPN). However, transplantation does play a role if TPN fails, with failure defined by Medicare as liver failure, frequent line sepsis, major central vein thrombosis, or recurrent dehydration. Of these complications, the relationship between liver failure and subsequent death in high-risk subgroups of long-term TPN patients has been shown clearly. Patients with less than 100 cm of postduodenal small bowel, an end-jejunostomy, no ileocecal valve or cecum, or persistently elevated liver function levels are at high risk for end-stage liver disease (ESLD). Early referral to experienced centers is suggested in these circumstances. High-risk patients may also take part in clinical trials of promising therapies to increase intestinal adaptation and prevent liver failure. Living donors should be considered for transplant candidates to minimize waiting time and optimize HLA matching. ESLD patients need a liver–intestine transplant. Because their waiting-list mortality is very high, their status on the liver waiting list should be elevated if possible. High incidence of early death from sepsis is reported after intestinal transplant, even at experienced centers. Aggressive measures should be taken if uncontrolled sepsis occurs, including discontinuing immunosuppression and removing the graft. Further research is needed in intestinal immunology and in development of strategies to decrease the need for aggressive immunosuppression in these transplant recipents. The ultimate role of intestinal transplantation will be determined by its capacity to show superiority, both in effectiveness and safety, to long-term TPN.

Introduction

Intestinal transplantation is a therapeutic option for patients with intestinal failure. The exact role that intestinal transplantation will ultimately play in intestinal failure management is not yet clear and will ultimately be determined by its effectiveness compared with other available therapeutic options. Data from both the International Intestinal Transplant Registry [1••] and the United Network for Organ Sharing (UNOS) registry [2••] indicate that the number of intestinal transplants performed per year has increased each year since 1990, with the exception of 1994. The suboptimal results achieved thus far, the inconsistent insurance coverage policies, and the lack of clear guidelines regarding the role of transplantation in the management of patients with intestinal failure, have contributed to uncertainty among managing physicians about when to refer patients for evaluation for this procedure. This article summarizes the key issues for practitioners to consider in determining when to refer such patients for intestinal transplantation.

Indications for Intestinal Transplantation

Whereas debate regarding the appropriate indications for intestinal transplantation continues in the medical community, Medicare has recently decided to cover intestinal transplants in patients who have failed TPN (Medicare Coverage Policy Decisions, Intestinal and Multivisceral Transplantation, CAG-00036, October 4, 2000). The Health Care Finance Administration (HCFA) based this decision on their review of three independent evaluations, including 1) data submitted by an individual requestor; 2) a 1999 technology assessment performed by the Blue Cross Blue Shield Technology Evaluation Center; and 3) a separate technology assessment performed by the Center for Practice and Technology Assessment at the Agency for Health Care Research and Quality (AHRQ). Based on this information, Medicare has determined that intestinal transplantation is indicated only if TPN therapy has failed. They have defined "TPN failure" as the development of at least one of the following: liver failure, major vein thrombosis, frequent line-related sepsis, or recurrent dehydration (Table 1).

Complications associated with TPN failure

Currently, TPN is the accepted therapy for intestinal failure. TPN is life-sustaining for many individuals, but its long-term use can be associated with serious complications in some patients. Reports of TPN-related complications vary

Table 1. Medicare definition of TPN failure

Patients are considered to have failed TPN therapy if one or more of these complications occurs:
Impending or overt liver failure (*ie*, elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastroesophageal varices, coagulopathy, stomal bleeding, or hepatic fibrosis/cirrhosis)
Thrombosis of major central venous channels (*ie*, ≥2 thromboses in subclavian, jugular, or femoral veins)
Frequent central line–related sepsis (*ie*, ≥2 episodes of systemic sepsis secondary to line infection per year, ≥1 episode of line-related fungemia, septic shock, or ARDS)
Frequent severe dehydration

ARDS—adult respiratory distress syndrome;
TPN—total parenteral nutrition.

significantly in the literature, and many reports are based on cohorts of long-term TPN patients, who are not likely to be representative of the entire population.

Between 1985 and 1992, the Oley Foundation maintained a North American registry of patients on home parenteral nutrition (HPN) or home enteral nutrition (HEN) that included data on complications (North American Home Parenteral and Enteral Nutrition Patient Registry, Annual Report, with outcome profiles, 1985–1992) [3]. These registry data were based on information submitted voluntarily by 223 North American centers and included outcome profiles on 5481 TPN patients with 8-year follow-up. Although these data represent a larger population of North American TPN patients than other published reports, national estimates based on Medicare data suggest that the registry sampled only 5% of US home-TPN patients. The Oley registry did not stratify outcomes based on duration of HPN therapy, although more than 50% of the patients in these diagnostic categories were weaned from TPN within 1 year. Furthermore, the registry data were largely based on information provided by physician-directed programs (78%) that followed several patients (64% from programs with more than six patients). Therefore, these data may not accurately reflect the overall North American experience if most HPN patients are managed by physicians who follow only one or two HPN patients.

The Oley registry recognized only those complications associated with a hospital admission, and therefore its data may not have been all-inclusive. Hospital admissions for HPN-related complications occurred at a rate of 0.70 to 2.23 times/patient-year on TPN, depending on the disease category. Hospitalization for complications was highest with congenital bowel problems and lowest with radiation enteritis. Sepsis made up the majority of these complications (54% to 64%) in all diagnostic categories. The mortality rate in these patients ranged from 5% to 25% per year depending on disease category.

Whereas the Oley registry may still provide some of the best available North American data, an updated and comprehensive registry of long-term TPN patients is sorely needed in North America to give a more accurate determination of outcomes in these patients. Because the North American registry of long-term TPN patients has not existed since 1994, more recent data evaluating outcomes in long-term TPN patients must be extrapolated from reports from individual centers or from registry data from other countries.

Liver failure is one the of the Medicare criteria for TPN failure. Liver abnormalities are a recognized complication in long-term TPN patients. These abnormalities can present in a broad spectrum of pathologic entities including steatosis, cholestasis, steatohepatitis, fibrosis, and cirrhosis [4,5••]. Liver complications appear to be especially prevalent in pediatric patients on long-term TPN [6]. In the last official report from the Oley Foundation registry in 1994, there were no specific data on liver complications [3]. A recent study from Harvard found that 15% of patients receiving TPN for more than 1 year developed end-stage liver disease (ESLD), which was associated with 100% mortality within 2 years of onset [7]. Another recent report, from France [5••], suggests that more than 50% of adult patients on TPN for more than 5 years will develop complicated liver disease (*ie*, grade 2 or 3 fibrosis, or one of the following: bilirubin greater than 3.5 mg/dL for more than 1 month, ascites, portal hypertension, hepatic encephalopathy, portal hypertension, or liver failure with Factor V less than 50%). Because, in France, all HPN patients are treated and monitored by a small number of authorized regional HPN centers, these results may be more representative of an entire population of HPN patients than are data from center-specific studies.

Several factors may influence the development of liver complications. The composition of the TPN solution influences hepatic changes [5••,8], although there is no consensus as to which combination of nutrients is optimal. Certain elements in TPN may be toxic [9], whereas other elements that are lacking in TPN may be protective [10]. The length and anatomic details of the remaining intestine influence the development of liver pathology [5••,11••]. The shorter the remaining small intestine, the more likely liver complications will develop [5••]. A terminal jejunostomy is associated with a higher incidence of TPN dependence and greater mortality than if intestinal continuity is maintained with a jejunal-colic anastomosis. Other factors that may contribute to liver complications in short-gut syndrome patients include altered bile absorption, altered release of gut hormones, bacterial overgrowth, and translocation [4].

TPN patients who develop ESLD have a very high mortality rate, and most die within 2 years [7]. In these circumstances, a combined intestine–liver transplant may be the only option. In patients who will require TPN permanently, transplantation of the liver alone has gen-

erally resulted in recurrence of ESLD and poor outcome (Farmer *et al.*, Fifth International Symposium on Small Intestinal Transplantation, Cambridge, England, July 31, 1997). However, in ESLD patients with a significant amount of residual intestine who are very likely to be weaned from TPN soon after transplant, transplanting the liver alone can be considered [12]. Conversely, transplanting only the intestine in the setting of ESLD is likely to yield poor results, although it is not yet clear at what stage of the progressive hepatic pathological process associated with long-term TPN that an intestine-only transplant is contraindicated. Although there appears to be some consensus that an intestine-only transplant should not be performed if severe fibrosis, cirrhosis, or portal hypertension is present, the risks associated with foregoing liver transplantation if potentially reversible lesions such as cholestasis are present are less clear [13]. Unfortunately, outcome data stratifying intestine-only transplant recipients based on pretransplant liver pathology do not currently exist.

Recurrent or life-threatening central venous catheter–related sepsis is another Medicare criterion for TPN failure. The Oley registry data indicate that, on average, TPN patients were hospitalized for infectious complications approximately once a year [3]. Messing *et al.* [11••] found that intestinal failure patients on permanent TPN have a high mortality rate (>50%, with median follow-up of 64 months) with 31% of deaths attributable to sepsis. In this series the central venous catheter was clearly identified as the source of sepsis in 50% of septic deaths. Other centers have reported that, with experience and proper line care, the rate of catheter-related infections in pediatric patients receiving HPN for gastrointestinal disorders can be as low as 1.13 infections/1000 patient-days [14].

Because many catheter infections result from contamination related to poor sterile technique, recurrent infections may be a warning sign of poor patient compliance. This possibility must be thoroughly evaluated in a transplant candidate because patient noncompliance is a contraindication to transplantation. Recurrent line sepsis is especially hazardous following transplant in the immunosuppressed recipient, where central lines are temporarily maintained until adequate enteral nutrition and hydration are achieved. Unfortunately, it is not always possible to determine whether poor technique and/or compliance are responsible for catheter-related sepsis, and therefore patients should not automatically be labeled as noncompliant. Bacterial translocation of gastrointestinal (GI) organisms may also contribute to catheter sepsis, despite good catheter technique [15]. Furthermore, even in programs where supervised catheter care practices have resulted in low infection rates, some individual patients still experience very high rates of infection [14].

The long-term requirement for central venous catheters (CVC) in intestinal failure patients predisposes to thrombus and/or fibrin formation and ultimately to occlusion of central veins. The Oley registry does not provide data for all central vein occlusions, but they indicate that the superior vena caval (SVC) thrombosis resulted in less than 0.3 hospital admissions/patient-year. Moukarzel *et al.* [14] found that, in long-term pediatric TPN patients, the mean lifespan of a CVC was 22.4 ± 14.7 months (range, 1.5 to 178 months), and 25% of catheter removals were for thrombotic complications. Typically, TPN catheters are first placed in the SVC by accessing the internal jugular, the brachial, or the subclavian veins. If these veins are no longer accessible, the catheters are usually placed in the inferior vena cava (IVC) via the femoral veins. Femoral catheters are less convenient for the patient and are more susceptible to infection [16]. Other life-threatening complications can be associated with the progressive loss of venous access, including superior vena caval syndrome, pulmonary embolus, and septic thrombi [17–19]. When all the usual central veins have been exhausted, alternatives include translumbar or transhepatic access to the IVC, or thoracotomy with direct placement of an intra-atrial catheter [20–22]. Although these aggressive alternative approaches can provide venous access in most patients, they can also be associated with significant complications [17–20], and the need for their use is often indicative of a poor overall prognosis.

Severe recurrent dehydration is another potential complication of short-gut syndrome [23], although it is rarely unmanageable. Patients with short-gut syndrome can lose in excess of 5 L of gastrointestinal fluids (saliva, gastric secretions, and pancreatico-biliary secretions) per day, predisposing them to dehydration and electrolyte disturbances. Massive fluid and electrolyte shifts may contribute to the renal impairment [24] and severe neurologic derangement [25] associated with long-term TPN.

Nontransplant Alternatives for Patients with Intestinal Failure

Not all patients who fail TPN therapy will need intestinal transplantation. Because significant morbidity and mortality can be associated with intestinal transplantation, other reasonable alternatives should also be considered. Alterations in the composition of the TPN solution [5••,8,10], treatment of bacterial overgrowth [4], and aggressive investigation for unidentified sources of sepsis should be considered. Furthermore, clinical trials evaluating promising strategies to prevent the progression of liver failure [10] or enhance intestinal adaptation [26] should be considered. However, because of the high mortality rate in patients waiting for combined intestine–liver transplants, the opportunity for timely performance of an intestine-only transplant before ESLD develops must not be jeopardized. Therefore, to ensure that a balanced strategy is applied, early referral to a center that specializes in intestinal failure management and has a multidisciplinary approach, including intestinal transplantation, is essential.

Table 2. Deaths on the liver transplant waiting list in candidates requiring combined intestine–liver transplants, based on UNOS medical urgency status at time of death

Year	Not reported	Status 1	Status 2A	Status 2B	Status 3	Status 7 (temporarily inactive)	Total
1999	7	4	1	21	5	6	44
1998	1	7	2	20	6	11	47

UNOS—United Network for Organ Sharing.

In some carefully selected patients, surgical procedures other than intestinal transplant can be beneficial to patients with short-gut syndrome [27•]. Surgical procedures to reestablish intestinal continuity can benefit such patients by enhancing conditions for enteral feeding, thereby optimizing nutrient absorption by the residual small intestine. If the colon is in continuity, it enhances absorption of fluid and electrolytes, salvages carbohydrate calories [28], reduces the risk of ESLD, and prolongs survival in short-gut syndrome [11••]. Other surgical procedures attempting to lengthen the intestine [29] or decrease intestinal transit time [27•] have not been shown to be safe or effective enough for routine use, although they may be helpful in individual situations.

Intestinal Transplantation

Waiting-list issues

In an intestinal transplant candidate, it must first be determined which organs need to be transplanted. If the patient requires an intestine only, he or she is placed on the intestine waiting list. If ESLD has developed and a combined intestine–liver transplant is needed, the patient is placed on the liver waiting list, and the intestine is automatically assigned when such a patient is allocated the liver. If transplantation of multiple organs including the liver and the intestine is necessary (multivisceral transplant), the patient is placed on the liver list, and the intestines and other needed organs are automatically assigned when the liver is allocated. Multivisceral transplants that include the intestine and liver are considered in the following circumstances: 1) when a benign pathologic process has involved multiple organs (pseudoobstruction); 2) when both the celiac and superior mesenteric axes have been disrupted or are thrombosed (resection of desmoids or other benign tumors); or 3) when extensive portal venous system thrombosis precludes a lesser procedure.

Intestinal transplant candidates in need of a cadaveric donor are placed on a UNOS waiting list. The UNOS database maintains waiting list data for all solid organs. UNOS data reveal that, although the waiting list for intestinal transplants is still fairly small (116 patients on the last day of 1999), it has continued to grow every year since 1993. Average patient waiting times for intestine transplants range from 285 to 320 days depending on the patient's ABO blood group. For patients on the intestinal transplant waiting list, 78% must wait longer than 3 months, and 44% longer than 1 year, to receive a transplant. Although these waiting times compare favorably with those for other solid organ transplants, the death rate on the waiting list for intestinal transplants is significantly higher than that seen on any other waiting list [2••]. Of the 192 intestinal waiting-list deaths that have occurred since 1993, all but 12 have been in patients who also needed livers. As indicated previously, patients waiting for both a liver and an intestine are allocated organs based on their position on the liver waiting list rather than their position on the intestine waiting list. Priority on the liver waiting list is primarily determined by medical urgency based on standard criteria for determining severity of liver disease (currently Child-Turcotte-Pugh score). Despite their high mortality compared with those patients waiting only for livers, candidates with coexistent short-gut syndrome and/or TPN failure do not currently receive special priority on the liver waiting list.

In 1999, the median waiting time for all liver transplant candidates was inversely correlated with medical urgency, *ie*, only 2 days if status 1 (the sickest, with highest priority), 6 days if status 2A (second highest priority), 296 days if status 2B, and so forth. However, in 1998 and 1999, 85% of intestine–liver waiting-list deaths occurred in patients who were prioritized as status 2B or less (Table 2). Further analysis of UNOS data indicates that intestine–liver candidates have a much higher waiting-list mortality rate than liver transplant candidates of similar status (except status 1) or age (Table 3). The high waiting-list mortality rate for candidates needing both an intestine and a liver also emphasizes the need to consider intestine-only transplants early in patients who are at high risk for progressing to ESLD.

Other issues that can prevent expeditious transplantation in some candidates on the intestinal transplant waiting list include donor–recipient size incompatibility and cytomegalovirus (CMV) status. Most candidates for intestinal transplant have had massive bowel resections, and consequently there is a significant reduction in the capacity of their peritoneal cavity. Therefore, they are not capable of accommodating organs from donors their own size and often require donors who are 50% to 75% smaller, limiting the field of potential donors. This is extremely problematic

Table 3. Comparison of liver transplant waiting-list death rates between liver-only candidates and intestine–liver candidates

Death rates on the liver transplant waiting list (deaths/1000 patient-years waiting) by year							
Year	Liver	Intestine–liver					
1997	145	434					
1998	135	447					
1999	138	326					
1999 Death rates on liver waiting list (deaths/1000 patient-years waiting) by UNOS status at time of death							
Status	1	2A	2B	3	7	Unknown	Overall
Liver	3111	358	175	66	196	0	138
Intestine–liver	654	855	796	176	292	0	326
1999 Death rates on liver waiting list (deaths/1000 patient-years waiting) by age							
Age group (years)	<1	1–5	6–10	11–17	18–34	35–39	Overall
Liver	234	92	48	80	119	113	138
Intestine–liver	573	115	178	234	231	353	326

UNOS—United Network for Organ Sharing.

in infants, emphasized by the fact that, in 1998 and 1999, the majority of the deaths on the intestine–liver waiting list (66%) occurred in candidates aged under 6 years. In some situations, the donor–recipient size issue can be managed by surgically resecting segments of bowel and/or liver from grafts that would otherwise be too big [30•]. Because CMV enteritis is a significant problem following transplant [31], many centers avoid using CMV-positive donors in CMV-negative recipients, which can also exclude potential donors.

Post-transplant issues

Within the first week following transplant, the integrity of the newly established GI tract should be evaluated with a GI contrast study. If no significant problems are detected, enteral feeding should be established immediately. TPN is eliminated in 90% of successful intestinal transplants.

Because the primary cause of death in intestinal transplant recipients is sepsis, suggesting over-immunosuppression, whereas the primary cause of graft loss is rejection, indicating under-immunosuppression, the "therapeutic window" associated with available immunosuppressive agents may be extremely narrow. The vast majority of patients receiving intestinal transplants to date have received immunosuppression with tacrolimus and prednisone [1••,32]. Recently, other agents, including mycophenolate mofetil [33], sirolimus [34], and anti–interleukin-2 (IL-2) receptor antibodies [35] have also been used. There have been no randomized, prospective studies performed to compare immunosuppressive regimes in intestinal transplant patients.

The extremely delicate balance between rejection and sepsis in intestinal transplantation suggests that novel immunosuppressive strategies may be required. To facilitate donor hyporesponsiveness or tolerance to the intestinal graft, the simultaneous administration of bone marrow from the same donor has been attempted [36•]. Although this approach has not had any significant impact on early graft loss or mortality, the long-term effects have not been fully evaluated. Better HLA matching between donors and recipients may reduce the need for immunosuppression [37–39]. Whereas HLA matching improved results in the early kidney transplant experience, with modern immunosuppressive agents the benefit has been obscured except in combinations with no mismatch. However, with intestinal transplants, in which current immunosuppressive agents are not as effective, the benefits of HLA matching may be more significant. Although living donors are especially suitable for HLA matching [37,38], matching may also be feasible with cadaveric donors [39].

Whereas intestinal rejection is difficult to control, it is also difficult to detect. Unlike the liver or the kidney, there is no marker that reliably heralds rejection in the intestine. Clinical signs associated with rejection include fever, diarrhea or increased stomal output, nausea, vomiting, and abdominal pain. Once suspected, the diagnosis must be confirmed with endoscopy and biopsies. Because rejection can be very patchy in distribution, multiple biopsies of abnormal and normal-appearing mucosa should be obtained. Zoom video endoscopy has greatly improved the ability of the endoscopist to identify mucosal abnormalities indicative of rejection [40].

Virus-related illnesses are a major cause of post-transplant morbidity with intestinal transplantation. Pretransplant serologies are required in all intestinal transplant candidates to determine if they have been previously exposed to CMV or Epstein-Barr virus (EBV). Naïve recipients of intestines from CMV-positive donors are at high risk of developing severe CMV infections, especially CMV enteritis [31]. Naïve recipients of EBV-positive organs are at high risk of developing a lymphoproliferative disorder following transplant [41]. Therefore, in intestinal transplant candidates who have not been previously exposed to CMV or EBV, organs from virus-negative donors should be sought. Because the majority of the adult population has been exposed to both of these viruses, this can contribute to longer waiting time. If circumstances dictate that CMV-positive or EBV-positive donors are used, aggressive surveillance of viral activity and/or aggressive use of antiviral

Table 4. Intestinal Transplant Registry data indicating the influence of center experience on graft and patient survival with intestinal transplants

Center experience	Survival	1 Year, %	5 Years, %
>10 Transplants	Graft*	60	40
	Patient†	70	43
<10 Transplants	Graft	40	22
	Patient	43	30

*P=0.002.
†P=0.001.

agents should be considered [42]. If pretransplant serologies indicate that the candidate has been previously exposed to the virus, the patient is still at moderate risk of virus-related complications regardless of the donor status and should receive antiviral prophylaxis.

Current Results with Intestinal Transplantation

There are no randomized trials comparing intestinal transplantation to long-term TPN or other available therapies. Currently, data on the results of intestinal transplants are available from three sources: the International Intestinal Transplant Registry (ITR), the UNOS database, and individual center reports.

Data summarizing the world experience with intestinal transplantation are maintained in the ITR, which is updated every 2 years and available by website [1••]. Because intestinal transplants are high profile and are performed in relatively small numbers at very few academic transplant centers around the world, it is likely that these registry data represent most, if not all, of the intestinal transplants performed worldwide since 1985. At the time of the last ITR update in 1999, 474 intestinal transplants had been performed on 446 patients at 46 different centers in 16 different countries. This total includes intestine-only transplants (216/45%), combined intestine–liver transplants (186/40%), and multivisceral (*eg*, intestine, liver, pancreas, stomach) transplants (72/15%). Most transplants have been performed in patients aged under 16 years (62%).

UNOS has collected both recipient and donor data for intestinal transplants performed since 1990. These data were compiled and published for the first time in the past year and represent the US experience up to September 5, 2000 [2••]. Data submission to the UNOS registry is mandatory for all accredited transplant centers. Based on UNOS data, the number of intestine-only transplants performed in the United States has increased steadily since 1996. In 1999, there were 36 intestine-only, 20 intestine–liver, and 12 multivisceral (intestine included) transplants performed. The primary diagnoses in these recipients were short-gut syndrome in 64%, functional bowel problems in 26%, graft failure (retransplant) in 6%, and other diagnoses in 4%.

Table 5. Intestinal Transplant Registry data indicating influence of multivisceral transplants on graft and patient survival in intestinal transplant recipients

Transplant type	Survival	1 Year, %	5 Years, %
Intestine only	Graft*	60	37
	Patient†	71	45
Intestine–liver	Graft	55	30
	Patient	62	37
Multivisceral	Graft	48	30
	Patient	45	40

*P=0.32.
†P=0.02.

With ITR data, overall patient and graft survival in the most recent cohort of patients (*ie*, after 1995) was 65% and 57% at 1 year and 50% and 40% at 4 years. These results indicate a statistically significant improvement in graft (P=0.02) but not patient (P=0.46) survival from earlier cohorts. In all cohorts, the highest patient mortality occurs in the first 6 months following transplant. A high mortality rate in the early period following transplant was also seen in the UNOS data [2••] and in individual reports from the most experienced centers [36•,43,44]. However in the ITR data, 1-year and 5-year patient (P=0.001) and graft (P=0.002) survival were significantly better at centers that had performed more than 10 transplants. Overall, these data indicate that, as the experience with intestinal transplantation increases, the results continue to improve (Table 4).

With the ITR data, patient (P=0.02), but not graft (P=0.32) survival was significantly better in intestine-only transplants, compared with transplants involving additional organs (Table 5). With the UNOS data, in the most recent cohort evaluated, (1997 to 1998) the 1-year patient and graft survival rates were 79% and 64%, respectively, for intestine-only transplants, and 50% and 49% in intestine–liver recipients, respectively. With long-term analysis, patient and graft survival rates after intestine-only transplants were 62% and 49% at 3 years, and 50% and 38% at 5 years, respectively. Long-term patient and graft survival rates after combined intestine–liver transplants were 43% and 41% at 3 years, and 37% and 36% at 5 years, respectively.

Living donors have been used in a small number of intestinal transplants performed to date. Living donors enhance the opportunity to minimize ischemic time and optimize donor–recipient HLA matching. Furthermore, living donors eliminate the need to wait, which is associated with high mortality in intestinal transplant candidates. The ITR data showed no differences in graft survival between recipients of cadaver and living-donor intestinal grafts. Early evidence suggests that use of HLA-matched living donors may be associated with less rejection and fewer infectious complications [37,38].

With the ITR data, complications following transplant associated with intestinal transplantation included acute rejection, chronic rejection, post-transplant lymphoproliferative disease (PTLD), and cytomegalovirus infection [1••]. Although the differences were not significant at this time, there appears to be a trend toward less rejection but more virus-related complications in multiple-organ transplants. For intestine-only, intestine–liver and multivisceral transplants, acute rejection occurred in 79%, 71%, and 56%, and chronic rejection in 13%, 3%, and 0% respectively, whereas CMV infection occurred in 24%, 18% and 40%, and PTLD in 7%, 11%, and 13%, respectively.

In the ITR data, patient deaths were attributed most frequently to sepsis or multiorgan failure (69%), followed by lymphoma (14%), ischemia/bleeding (13%), and rejection (12%). In surviving patients, 78% had full graft function, 10% had partial function, and 12% had their grafts removed. The most common indication for graft removal was rejection (57%), followed by ischemia/bleeding (23%), sepsis (6%), multiorgan failure (2%), lymphoma (1%), and other causes (10%).

Quality-of-life Issues

Quality of life associated with long-term TPN has been evaluated by different investigators, who have reached different conclusions [45,46•]. There are very few reports in the literature based on quality-of-life comparisons between intestinal failure patients who remain on TPN and those who undergo intestinal transplantation. Retrospective comparisons between small groups of intestinal transplant patients and long-term TPN patients matched for age and duration of illness suggest that quality of life is the same or slightly better with transplantation [47].

Financial Issues

Provision of basic home parenteral nutrition can result in charges of between $300 and $500 a day for a given patient [3], excluding the additional charges associated with home-care services, monitoring, and management of complications. Therefore, if parenteral nutrition is administered 5 days a week, overall HPN charges can exceed $150,000 a year. Although the yearly charges associated with intestinal transplantation have been less clearly defined, most estimates indicate that they can exceed those associated with HPN in the first few years following transplant, but costs are significantly less than HPN in subsequent years.

Conclusions

Although results with intestinal transplantation are steadily improving, its associated morbidity and mortality must be further decreased before it will gain wide acceptance as an alternative therapy for patients with intestinal failure on TPN. On the other hand, an accurate evaluation of the morbidity and mortality associated with long-term TPN patients in North America is sorely needed and will only be achieved through the establishment of a comprehensive registry.

Ultimately, clinical trials may be necessary to determine the best management for patients with intestinal failure. Because intestinal transplants are currently performed only in patients who have failed TPN, these patients are usually sicker than TPN patients who have not failed. A meaningful comparison, therefore, would require randomization of patients who have either failed TPN or who are at some other common starting point. This type of comparison may be warranted in high-risk patient subgroups where the prognosis currently associated with nontransplant therapy is similar to that seen with intestinal transplant. Based on the data provided by Messing *et al*. [11••], patients with short-gut syndrome who have had mesenteric infarctions (57%), or who have been left with less than 50 cm of small bowel (57%) or an end-jejunostomy (44%), have 5-year mortality rates that are comparable with those seen in the most recent cohorts of intestinal transplant recipients (49%) [1••]. This subgroup of patients should be considered for clinical trials comparing intestine-only transplantation to optimal TPN management.

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