Intestinal Transplantation Outcomes

Gabriel E. Gondolesi, MAAC, FACS, and Héctor M. Almau, MD

Multiorgan Transplant Institute; Nutritional Support, Rehabilitation and Intestinal Transplant Unit; University Hospital-Favaloro Foundation, Buenos Aires, Argentina

OUTLINE

ABSTRACT

Intestinal transplantation has evolved from being considered an experimental procedure into a clinically accepted therapy for patients with intestinal failure and parenteral nutrition life-threatening complications. Early referral, advances in immunosuppression therapy, standardization of surgical techniques, prophylactic therapy of infections, early diagnosis of rejection, and better posttransplant patient management are some of the changes that have allowed more patients to receive transplants, thus recovering intestinal sufficiency, and at the same time allowing the procedure to spread worldwide. Over the last 2 decades, transplant centers have focused on improving short-term patient survival, which has consequently increased by >20%. It is now clear that even though isolated intestinal-transplant recipients have lower mortality risk on the waiting list, they are at higher risk for long-term graft loss. Mortality is higher on the waiting list and early posttransplant in recipients whose intestinal transplants are associated with liver grafts; however, they have better long-term patient and graft survival. Nevertheless, 3-year actuarial patient survival has not changed over the same period of time, and therefore this is our challenge for the next decade. ***Mt Sinai J Med 79:246–255, 2012.*** © *2012 Mount Sinai School of Medicine*

Key Words: intestine, nutrition, outcomes, quality of life, rejection, survival referral, transplantation, waiting list.

Address Correspondence to:

Gabriel E. Gondolesi
University Hospital-Favaloro Foundation
Buenos Aires, Argentina
Email: ggondolesi@ffavaloro.org

INTRODUCTION

Intestinal transplantation has evolved from being considered an experimental procedure into a clinically accepted therapy for patients with intestinal failure and parenteral nutrition (PN) life-threatening complications.[1]

From the original experiences of intestinal transplants in animals performed by Alexis Carrel in 1901 to the first attempts in humans done by 2 pioneers in the transplantation field, Ralph Deterling (1964; unpublished case) and Richard Lillehei (1967),[2] outcomes have had a common pattern: failure secondary to rejection and sepsis.

Therefore, clinical practice of intestinal transplantation was on hold until the last quarter of the last century. During those years, the appearance of new immunosuppressive agents (cyclosporine and tacrolimus) and a better understanding of posttransplant management allowed the first successful intestinal transplant series at the University of Pittsburgh, reported by Thomas Starzl.[3]

Further success of intestinal transplantation was then recognized by the US Health Care Financing Administration in October 2000, providing coverage only in centers with >10 transplants performed and 65% first-year patient survival. Four centers were the first to qualify: the University of Pittsburgh, the University of Miami, the Nebraska Medical Center, and the Mount Sinai Hospital.[4]

These programs have introduced the relevant concept of managing intestinal-failure patients with

Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI:10.1002/msj.21301

a multidisciplinary approach. Survival benefits of this approach started by optimizing the time frame for referral of patients to intestinal-failure and transplant programs, aiming to reduce mortality on the waiting list. Some other contributions were the standardization of surgical procedures, advances in immunosuppressive therapies, early diagnosis of rejection, and prophylactic therapy of infections.[5,6] These changes have not only allowed more patients to receive transplants, recovering intestinal sufficiency, but they have also allowed the procedure to spread worldwide.

The present review summarizes the evolution and current short-term and long-term outcomes after intestinal transplantation and presents results from single programs worldwide as well as the results reported by the International Intestinal Transplant Registry (IITR), United Network for Organ Sharing (UNOS), and Scientific Registry of Transplant Recipients databases.[7–9]

EARLY REFERRAL

Early recognition of PN failure and referral to specialized centers have proved to reduce mortality on the waiting list.[10] Early transplant (defined by <12 months' duration of PN prior to transplant) was associated with better survival in recipients of isolated grafts.[11] The impact of the time for referral can also be seen when outcomes are analyzed comparing different eras within the same program. As most of the early recipients were referred late, initial results were worse compared with current results. All the complications that can be associated with the long-term use of parenteral support can compromise quality of life (QoL) and survival; however, today, in most cases late referral means, for the pediatric and adult populations, the existence of intestinal failure–associated liver disease.[10–12]

General practitioners, pediatricians, and surgeons should understand the different classic clinical manifestations of progressive liver disease between short-gut patients and patients with normal bowel length. Though they rarely have ascites or esophageal varices, they are more prone to developing hypersplenism or to bleeding at the ostomy site. Jaundice might appear later in the evolution of liver fibrosis to cirrhosis. The degree of hyperbilirubinemia at the time of referral is associated with mortality within pediatric intestinal-failure programs.[10,12] Some patients die before being listed for transplant, waiting for an organ, whereas some others die in the early posttransplant period.[12] A recent publication by Kaufman *et al.* identifies total serum bilirubin as the most powerful predictor of liver failure in PN-associated liver disease and recommends transplant referral when total bilirubin reaches a level of 6 mg/dL in patients aged 3–6 months; the probability of evolving liver failure in this setting is ≥36%.[10] The death risk would reach 50% when referred with an initial conjugated bilirubin >7.2 mg/dL[12] (Figure 1). Therefore, practitioners need to start the referral process as soon as the patients start having a gradual and consistent increase in bilirubin levels. With an early recognition of a candidate, the specialized team is allowed to optimize PN support, to have a better organ selection, and to favor the need for isolated grafts rather than multiorgan ones. Aiming to differentiate those candidates who would perform well after transplant from those who would fail, authors developed a numerical preoperative score for all types of intestinal transplants that is able to predict postoperative survival. It was called the Cambridge-Miami Score (CaMi). This score includes risk factors such as loss of venous accesses and impairment of other organs or systems not corrected by transplantation. It showed that patients scoring >3 did worse than those with

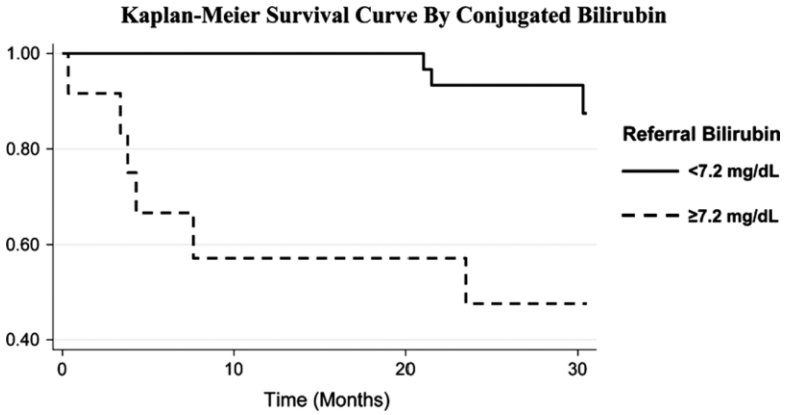

Fig 1. Patient survival related to conjugated bilirubin value ($P = 0.0001$). Reprinted with permission from Javid *et al.*[12]

DOI:10.1002/MSJ

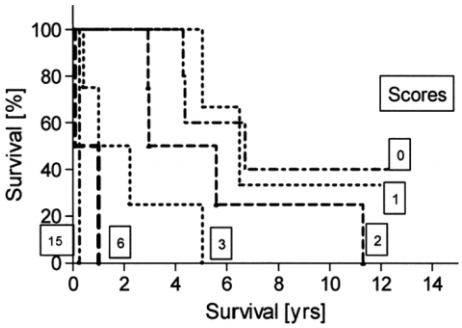

Fig 2. KM survival curve with different CaMi scores and compared using log-rank test. **Abbreviations:** CaMi, Cambridge-Miami Score; KM, Kaplan-Meier. Reprinted with permission from Middleton *et al.*[13]

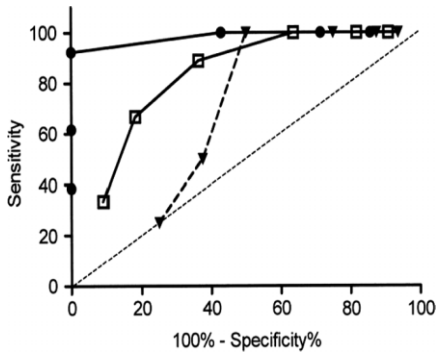

Fig 3. ROC curves constructed for the CaMi score predictions of death at 3 (●), 5 (□), and 10 (▼) years. **Abbreviations:** CaMi, Cambridge-Miami Score; ROC, receiver operating characteristic. Reprinted with permission from Middleton *et al.*[13]

a numeric score ≤2. Receiver operating characteristic–C statistic (95% confidence interval) for predicting death at 3, 5, and 10 years were 0.98 (0.94-1.02), 0.82 (0.63-1.01), and 0.67 (0.43-0.91), respectively (Figure 2, Figure 3).[13] Although this new medical tool has shown encouraging results, it still requires validation in a larger cohort of transplant recipients.

A recent analysis of timing for transplant in children with intestinal failure using a Markov model showed that early listing adds life-years and quality-of-life-years[14]; however, early listing mandates early referral.

MORTALITY ON THE WAITING LIST

Before the year 2000, it was reported that the 3-year patient survival of those candidates who were listed but did not receive a transplant was as low as 20%, which is an extremely low result compared with the 55% survival rate for candidates receiving a transplant in the same time period, proving the benefits of transplantation. Patients with PN-associated liver disease would essentially have a 5-year survival of 0%, whereas the first-year survival for combined liver–intestinal transplant candidates at the time of this publication was 63%, showing, once again, the benefit of transplantation despite undergoing a complex surgical procedure such as combined liver and intestinal transplant.[15]

Allocation policies for candidates awaiting intestine-only transplant have not changed and have been spread worldwide as urgent, nonurgent/elective, or inactive. In contrast, the allocation for composite liver and intestine transplant (with other possible organs) suffered from several changes in order to reduce mortality on the waiting list and has been adapted worldwide to each country's donation rate.

From 1993 to 2001, the overall and standardized-by-age mortality on the waiting list was higher for liver-intestine candidates in comparison with liver-only recipients (323.75 versus 121.06 annual deaths per 1000 patient-years waiting for transplant).[16] In 2002, the grounds for liver allocation were modified with the introduction of the Model for End-Stage Liver Disease (MELD) score for adults and the Pediatric End-Stage Liver Disease (PELD) score for children.[17] Shortly after establishing this policy, it became clear that the proposed score did not benefit liver-intestine candidates compared with liver-only candidates.[9] In November 2002, a change in policy was proposed to give additional MELD/PELD points to candidates simultaneously listed for both liver and intestine, equivalent to an additional waiting-list mortality of 10%.[18] In 2006, with further data collection, a greater mortality discrepancy was still seen between both groups of candidates. For this reason, it was decided to add 23 points to all MELD/PELD scores as a score increase.[19]

In the Argentinean allocation system, the criteria for listing has also evolved. In 2006, all pediatric intestinal transplant candidates waiting for combined grafts were assigned the highest historical PELD score and listed as priority only below the emergencies for liver transplant. Three years later, we reported a waiting-list mortality for isolated candidates of 9%, but a 33% mortality rate (all children) for patients waiting for both a liver and intestine. Therefore, and after a careful analysis of the first results provided after the UNOS change in policy, a modification to our policy was proposed and accepted in order to give candidates for liver-intestine aged <18 years 26 additional points to their real PELD/MELD score, and 23 extra points to their real MELD score for those aged >18 years.[20] The impact of the last modification has not been evaluated yet.

DOI:10.1002/MSJ

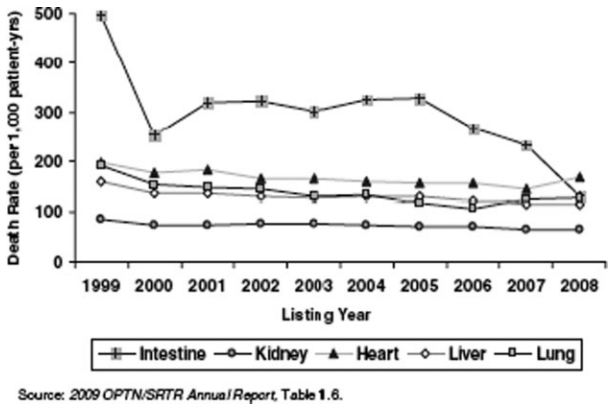

Fig 4. Mortality on waiting list, rates per 1000 patients, comparison between different organs. **Abbreviations:** OPTN, Organ Procurement and Transplantation Network; SRTR, Scientific Registry of Transplant Recipients. Reprinted with permission from Mazariegos *et al.*[19]

As a result of these policies in the United States, in 2010 waiting-list mortality for isolated intestinal transplant was reported for the first time as only 9%, compared with 20% in each of the preceding years. The same analysis showed that by 2008 the number of annual deaths per 1000 patient-years among those waiting for an intestinal transplant was comparable to that of other solid organs, falling below that of heart and heart-lung transplant candidates (Figure 4). The same report has also shown that time to transplant (TTT) has also significantly improved, falling from 313 days in 1999 to 142 days in 2008 for an isolated bowel graft. The best TTT was experienced in the group of candidates aged >18 years waiting for isolated intestinal grafts, with a median time of 27 days, clearly favored by a major availability of appropriate-size matching donors. The majority of deaths observed on the waiting list remained for patients waiting for combined or multivisceral (MTV) grafts, particularly in children aged <5 years.[19]

The falling death rate reflects improved pretransplant medical care and allocation policies; however, it does not show the impact of an increased rate of cadaveric donors.

In 1997, aiming to abolish the need for waiting and to optimize timing for transplant in sensitized patients or in HLA-identical cases or twins, Gruessner *et al.*[21] described the technique for living-related donor intestinal transplant. This technique has not spread as it was initially thought; its major experience is concentrated in a single program in the United States.[22] This group later described the technique for combined liver and intestinal transplant from a living donor, aiming to reduce the mortality for pediatric patients with PN-associated liver disease.[23]

REJECTION, INFECTIONS, AND THEIR IMPACT ON OUTCOMES

Refractory acute cellular rejection and infections remain the leading causes of graft loss and recipient death or need for retransplant. Despite improvement in early patient and graft survival, and regardless of the immunosuppressive regimen chosen by the programs, induction therapy failed to reduce long-term hazard of graft loss.[11]

Reports from single centers, as well as the latest report from the IITR (2011), showed that isolated intestinal transplants and modified MTV transplants (liver-sparing grafts) suffered from higher long-term rejection risk of graft loss.[7] Similar findings were observed when the prevalence of chronic rejection was assessed. Liver-containing grafts experienced a significantly better chronic rejection–free survival (Figure 4). Conversely, MTV recipients experienced a significantly higher risk of life-threatening infections. No new immunosuppressive or specific protocols for intestinal transplant have appeared or have been designed. Diagnosis still remains limited to endoscopy and biopsy, which carries its own morbidity. Reliable noninvasive markers proved to be clinically useful in detecting rejection in the early stage.

Acute humoral rejection is an uncommon event (0.02%), and it is expected to occur mainly in isolated intestinal grafts transplanted into patients with a strongly positive T-cell or B-cell lymphocytotoxic crossmatch. In order to reduce humoral rejection, we published a pretransplant desensitization protocol allowing patients with high panel-reactive antibodies to receive transplant with significant antibody reduction and therefore negative crossmatch.[24] Based on the poor outcomes reported by large centers, others have established the policy of not proceeding with a transplant in case of having a positive prospective crossmatch.[25] To overcome this problem, we have established at our center a serum bank for all listed candidates in order to perform prospective crossmatch at the time of procurement. If the crossmatch is positive, the transplant would be cancelled and the organ could be timely assigned to other recipient or discarded.

The need for retransplant is higher after isolated intestinal transplant compared with liver-containing grafts (34% versus 5%–8%, respectively). Analyzing outcomes after graft loss due to rejection, <50% of the isolated recipients that require enterectomy and are listed for retransplant would be able to receive a new organ, whereas most of the combined or MTV patients waiting for retransplant would obtain

DOI:10.1002/MSJ

organs.[11] Patients undergoing retransplant with liver-containing grafts will also have better long-term survival than those undergoing retransplant with isolated intestinal grafts.

Acute and chronic rejection remain the major causes of graft loss and need for retransplant; this should be an area of future research focus and development in order to improve long-term results.

NUTRITIONAL OUTCOMES AND QUALITY OF LIFE AFTER TRANSPLANT

Maintenance of posttransplant intestinal autonomy and adequate weight gain and growth are the major aims after intestinal transplant. The need for lifelong immunosuppression, the occurrence of posttransplant infections, the impact of chronic medication on renal function, and the appearance of rejection episodes usually impact the steady improvement of nutritional aspects and QoL after transplant, requiring further hospitalizations.

It has been reported that 90% of the patients who survived >6 months achieved full nutritional autonomy.[26] Lacaille *et al*, the group from Paris, France, has published a complete assessment of long-term nutritional outcome after intestinal transplant in children with a 7-year average follow-up; 31 patients were reported to be free of PN at the end of the second year posttransplant and 84% of them remained free at the end of the follow-up, out of a total of 69 small-bowel transplants performed since 1994.[27] The study showed normal protein and carbohydrate absorption. Interestingly, balance studies demonstrated significant steatorrhea consistent with fat malabsorption. The transplanted intestine absorbs 86% of energy and 76% of lipids. In terms of growth, this comprehensive study showed that linear growth velocity was normal in 25 of 31 patients and delayed in the rest.

Five years after starting our program in Argentina, we reported long-term nutritional outcomes compared with the pretransplant nutritional status finding that our pediatric and adult recipients were able to maintain or improve the nutritional condition observed at evaluation, being their nutritional parameters off PN. (Children: pretransplant z–body mass index [BMI]: -0.57 ± 1.08, posttransplant z-BMI: -0.45 ± 0.87; pretransplant z-Height/Age [z-H/A]: -2.43 ± 1.77, posttransplant z-H/A: -2.53 ± 1.31. Adults: pretransplant BMI: 21.1 ± 4.6, current BMI: 21.7 ± 4.9.)[28]

Other long-term outcomes of interest are QoL and psychosocial adaptation. The initial studies on QoL after intestinal transplant done by Sudan *et al*. and Rovera *et al*.[26,29] showed that intestinal-transplant recipients had a modest improvement in QoL after transplant compared with those remaining on PN; moreover, parents rated QoL of their children as slightly worse than that of normal schoolchildren.

The last published report of the IITR in 2005 showed that when applying a modified Karnofsky performance score to all recipients who survived >6 months after transplant (n = 406), 80% of them declared to be able to perform most of their daily activities, scoring between 90% and 100%.[30]

Recent studies[31,32] performed in long-term adult survivors of intestinal transplant showed significant improvements compared with living on PN; and when the Coping Orientation to Problems Experienced questionnaire was applied, it proved that these groups of transplant recipients had high levels of problem-focused strategies, probably as an adaptive response to circumstances.

In 2009, the University of Bologna evaluated QoL in 27 adult recipients and reported lower scores for psychosocial well-being compared with nontransplant controls, with anxiety disorder as the most common psychiatric diagnosis. The University of California Los Angeles program confirms a lower score using the parent form of the Child Health Questionnaire. In addition, utilizing the children's form they found statistically poorer physical health and social and school function, which was attributed to the existence of devices like gastrostomy tubes, ostomy appliances or lines, and the need for frequent interventions. Recently, abstracts and publications reported fertility and achievement of successful pregnancies and birth of healthy children from recipients of intestinal grafts,[33] probably a major expression of posttransplant recovery of QoL.

OUTCOMES REPORTED BY INDIVIDUAL CENTERS

Single-center data and outcome reports, although limited by the number of patients, have allowed a deeper analysis of uniform care protocols, despite suffering modifications over time. This is the reason why several large-volume centers have reported outcomes based on eras, that, in general, include groups of patients managed with different immunosuppressive regimens (Figure 5).

Most single-center outcome analysis[11,27,34,35] reported pretransplant variables that impact on posttransplant outcome. Most of them have found that long-term PN, graft type (isolated versus multiorgan),

DOI:10.1002/MSJ

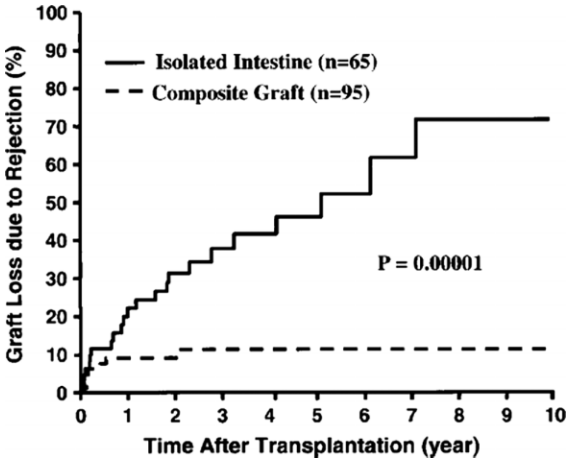

Fig 5. Cumulative risk of graft loss from rejection in the intestine only and composite visceral grafts that contained liver. Reprinted with permission from Abu-Elmagd *et al*.[37]

age (<1 year), pretransplant location (hospital versus home), retransplant, and chronic intestinal pseudo-obstruction were associated with worse outcome.

After the first decade performing intestinal transplant under tacrolimus, the program at the University of Pittsburgh reported their long-term results back in 2001,[36] having 75% first-year, 54% 5-year, and 42% 10-year actuarial survival, with most of the deaths occurring within the first 3 postoperative months. They showed a significant improvement when survivals were analyzed comparing two 5-year periods (Figure 6). They also showed reduction in hospital length of stay and shorter PN discontinuation (from 42 days after transplant to 20 days). The same report states that cumulative risk of long-term graft loss due to chronic rejection was significantly ($P = 0.00001$) greater for isolated grafts compared with liver-containing grafts (Figure 5), thus confirming liver inclusion as protective for long-term rejection graft loss.

The Pittsburgh program has the largest experience at a single center, having performed approximately 25% of all transplants done worldwide. In 2009, they reported their long-term outcomes after achieving 500 consecutive procedures performed in 453 recipients.[11] Their current actuarial survival compared with previous reports showed a 10% increase at 1 year (from 75% in 2001 to 85% in 2009) and a 7% increase at 5 years (from 54% to 61%), but no change was seen at 10-year survival (steady at 42%). Another interesting feature of their results is the fact that of 34 recipients surviving for >10 years, 23 (68%) have multiorgan grafts. Refractory rejection and infections are still the leading causes of graft loss.[37]

In 2009, the Miami group reported their experience with >300 intestinal and MTV transplants. They concluded that good patient and graft survival rates are now achievable. Rejection remains the most difficult to prevent and manage complication, whereas their preferred immunosuppressant regimen includes induction with antilymphocyte agents, followed by maintenance with tacrolimus.[38] The current status of long-term adult survivors was presented by this group at the XII International Small Bowel Transplant Symposium (ISBTS 2011), with 36 patients who survived >5 years; 53% were multiorgan transplants including liver; and 91.6% resumed normal activities. In the group of patients receiving an isolated intestinal graft who survived 5 years, 71% of them could be followed up for 10 years.[39]

The University of California Los Angeles has recently published a significant improvement in short-term outcome for transplants performed after the year 2000 (80% 1-year patient survival). This change has been reasonably attributed to cumulative

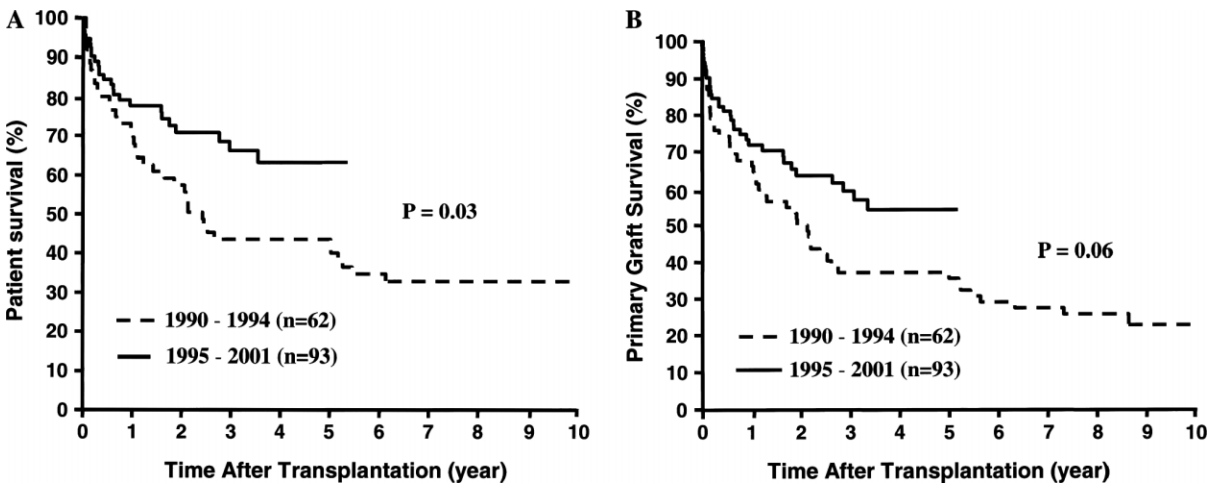

Fig 6. Patient and graft survival rates in 2 different eras. Reprinted with permission from Abu-Elmagd *et al*.[37]

DOI:10.1002/MSJ

experience, refinements in surgical techniques, and advances in immunotherapy. Authors have also reported an additional improvement at 5-year survival, achieving 65% patient survival and 64% graft survival.[40] Their univariate analysis revealed that pretransplant renal dysfunction adversely impacted patient survival. Females had a reduced risk of graft loss due to rejection (as was also noted by the Pittsburgh group).[17] From their multivariate analysis, the 3 factors found to independently predict long-term survival were the presence of donor-specific antibodies, liver-inclusive graft, and recipient splenectomy. The outcome improved with the absence of donor-specific antibodies or inclusion of the liver. Both factors had the potential for improvement and manipulation before transplant.[36]

Matsumoto *et al.* presented the long-term experience of the Washington program at ISBTS 2011.[41] They performed 134 intestinal transplants in 131 recipients; 9 were retransplants; with 68 adults. The overall 1- and 3-year patient/graft survival were 81.4%/80.5% and 67.9%/67.2%, respectively. The 1-year survival for isolated, combined, or MTV transplant was 84.5%, 88.6%, and 60.1%, respectively, with 3-year patient survival of 64.1%, 79.6%, and 56.2%, respectively. The program reported excellent results in terms of first-year rejection-free survival, with 63.3% and 81.3% for adult and pediatric populations, respectively. Opportunistic infections and acute cellular rejections remain as clinical issues for management in this group.

In 2006, six years after starting the program, the group of the University of Bologna published their results. They performed 28 isolated and 9 MTV transplants in adults; 25 of 37 patients were alive with a mean follow-up of 892 days. Three-year patient survival was 70% for isolated transplants versus 41% for MTV ones ($P = 0.01$); 88% of the grafts provided intestinal autonomy to their recipients.[42]

Lacaille *et al.* updated us at ISBTS 2011 with their 17-year program experience at Hôpital Necker–Enfants Malades in Paris. Over this period, 89 children received 96 transplants, with 54 isolated, 39 combined, and 3 MTV. The 10-year overall patient survival was 52% for patients (same for combined or isolated) and 33% for grafts. However, survival was 46% for liver-containing grafts and only 9% for isolated intestinal transplants. Their mortality rate was 35%. Ten children died after isolated transplants and 21 after combined procedures. Their experience had high early mortality for combined recipients but better long-term graft survival compared with isolated grafts.[43]

In Sweden from 1998 to 2010, 20 intestinal transplants were performed (15 adults). They reported an improvement in survival when comparing 2 eras (57% 2-year patient survival for the period 1998–2002 versus 85% for the period 2003–2010).[44]

Gupte *et al.* presented the results of their program in Birmingham, UK. From 1993 to 2011, they performed 78 transplants in 72 recipients; 53 were liver inclusive grafts. Thirty patients died (24 after combined transplant), 16 of them 6 months after transplant, the majority due to chronic rejection. Their program also showed improvements in long-term results by eras.[45]

Our group at University Hospital–Favaloro Foundation, Argentina, has recently reported the largest pediatric intestinal transplant experience in South America, with 15 transplants performed (12 isolated, 2 combined, and 1 MTV) with a mean follow-up of 28 months. The median length of stay was 42 days; 10 recipients were free of PN at 2.27 months. The 3-year patient and graft survival was 73% and 73% respectively; being 83% and 83% respectively for isolated cases. Mortality on the waiting list was 10% for isolated and 33% for combined candidates from March 2006 to March 2010.[46] Our overall long-term results were presented last year at ISBTS 2011 as well. We performed 30 intestinal transplants in 29 recipients; 23 were isolated, 2 were combined, and 5 were MTV. Nineteen of the recipients were children. The mean time on the waiting list was 137 days (SD: 2–646 days), being 179.4 days for children and 56.4 days for adults ($P < 0.006$). The overall 3- and 5-year patient survival were 67% and 60%, respectively, with 81% and 71% for isolated transplants, respectively.[28]

Living donor intestinal transplant has been performed in a reduced number of patients in a few centers worldwide. The gap between the number of candidates and the availability of potential donors does not exist, at least in Western countries. Therefore, it is difficult to justify the indication of a living donor surgery. However, pediatric intestinal candidates, and mainly those with associated liver disease, still have a high mortality risk when compared with adult candidates. In 2010, Tzvetanov *et al.* reported that their center performed 26 of the 43 cases performed worldwide. Lower ischemia time and the possibility of scheduling the procedure are the 2 major advantages.[47] The short- and long-term survivals were comparable to those reported for cadaveric cases. Authors also described the technique for combined living donor intestinal/liver transplant (CLDILT), having performed 5 cases. The 1- and 2-year survival were 100% for the liver grafts and 80% for the intestinal grafts.[47,48]

The current experience of intestinal transplant in Japan was reported by Ueno *et al.* From 1996 to 2011,

DOI:10.1002/MSJ

17 intestinal transplants were performed; out of 11 from living donors, 1 received a CLDILT and a second one received an isolated living donor intestine after a living donor liver graft. The reported overall survival at 5 years was 69% for patient and 60% for graft. The lack of national health coverage and the limited number of cadaveric donors were the 2 major reasons for starting the living donor experience in Japan. Proving acceptable results, authors are now aiming to obtain coverage and to expand indications.[49]

OUTCOMES REPORTED BY MULTICENTER REGISTRIES

The relative infrequency of intestinal transplant in a reduced number of centers is a major limiting factor to analyze results and outcomes. To overcome this limitation, the IITR was established[7]; it is updated every 2 years. The registry has the advantage of analyzing a larger number of patients, but it is limited by its multicenter nature and the limited number of variables collected to obtain adequate compliance from all centers.

Early patient and graft survival after intestinal transplant have improved over the last 10 years unlike any other transplant. In 1998, the first-year graft and patient survival were 52% and 69%, respectively; in 2007, the survivals reported were 75% and 79%, respectively. A gain of 23% for graft and 10% for patient survival was achieved.

The last published report from 2009 presents a total of 2188 intestinal transplants performed in 73 registered centers worldwide.[7] This analysis showed that outcomes were affected by graft type (liver-inclusive grafts), pretransplant location (home), transplant era, and center volume. In September 2011, during the closing session of ISBTS 2011, David Grant presented the latest report of the registry.[50] Currently, the world has 79 centers registered; only 35 are actively performing intestinal transplants. Overall, 2611 transplants have been done: 44% isolated, 32% combined liver-intestine, and 24% MTV. Graft survivals have improved when analyzing the period 2006–2011 (60% at 3 years). Once again, independent prognostic factors for the multivariate analysis are age <1 year (negative), to be transplanted at the top 40%-volume programs (positive), and patients located at home at the time of transplant (positive). For liver-containing grafts, if recipients survive the first year, they would have a better long-term survival (unpublished data). It was also mentioned that there is trend toward having less incidence of PN-associated liver disease among the pediatric population over the last 2 years, probably as result of early referral to intestinal-failure programs and a timely improvement in management.

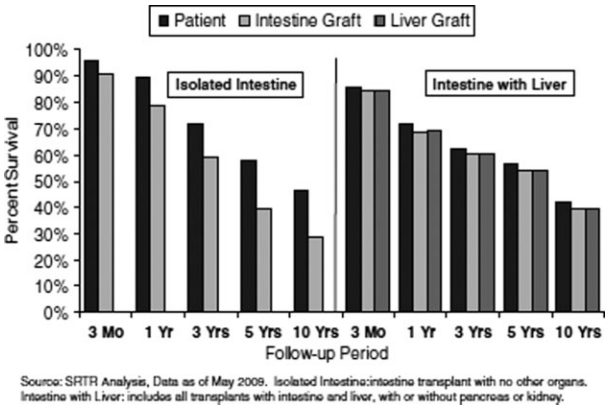

Fig 7. Patient and graft survival for isolated intestine and intestine with liver recipients. **Abbreviations:** SRTR, Scientific Registry of Transplant Recipients. Reprinted with permission from Mazariegos *et al*.[19]

Another source of multicenter data, limited to the United States, is the UNOS/Organ Procurement and Transplant Network database. It shows similar results (Figure 7). The 10-year patient survival for isolated intestine and intestine-associated-to-liver grafts were 46% and 42%, respectively. The graft survivals for the same period were 29% and 39%, respectively. These results are comparable with lung and heart-lung patient survival, or graft survival for pancreas.[19]

Retransplants, based on the analyses written by Mazariegos *et al*,[19] count for 11% of the total number of intestinal transplants performed in the United States. Fifty percent of these recipients were hospitalized at the time of retransplant, and acute or chronic rejection were the main causes of graft loss. Most recipients required a liver-containing graft. Only 72% of the retransplant patients were discharged with functional grafts after the second transplant. Graft failure and sepsis were the leading causes of patient death and rejection the leading cause of graft loss in unsuccessful cases.

SUMMARY

Intestinal transplant outcomes have improved; nevertheless, clinically successful intestinal transplants came relatively late when compared with other solid-organ transplants, mostly as a result of graft immunogenicity. Intestinal-transplant candidates currently have shorter TTT and reduced waiting-list mortality.

It is now clear that isolated intestinal-transplant recipients have a lower mortality risk on the waiting list, but they are at higher risk for long-term graft loss.

DOI:10.1002/MSJ

Recipients of intestine associated with liver grafts have a higher mortality on the waiting list and early posttransplant mortality; however, they have better long-term patient and graft survival.

Single-center reports started to show long-term improvements, but multicenter data still do not reflect that improvement. This could probably be due to the nature of the data provided from centers with different degree of experience.

Over the last 2 decades, transplant centers have focused on improving short-term patient survival, being able to increase it by >20%. After achieving short-term outcomes comparable with those of other solid organs, it is now time to make every possible effort to improve long-term survival. This is our challenge for the next decade.

DISCLOSURES

Potential conflict of interest: Nothing to report.

REFERENCES

1. Gondolesi G, Fauda M. Technical refinements in small bowel transplantation. *Curr Opin Organ Transplant* 2008; 13: 259–265.
2. Lillehei RC, Idezuki Y, Feemster JA, et al. Transplantation of stomach, intestine, and pancreas: experimental and clinical observations. *Surgery* 1967; 62: 721–741.
3. Starzl TE, Rowe MI, Todo S, et al. Transplantation of multiple abdominal viscera. *JAMA* 1989; 261: 1449–1457.
4. Centers for Medicare and Medicaid Services: Decision memo for intestinal and multivisceral transplantation (CAG-00036N). October 4, 2000. http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp. Accessed December 15, 2012.
5. Sudan D, DiBaise J, Torres C, et al. A multidisciplinary approach to the treatment of intestinal failure. *J Gastrointest Surg* 2005; 9: 165–176.
6. Modi BP, Langer M, Ching YA, et al. Improved survival in a multidisciplinary short bowel syndrome program. *J Pediatr Surg* 2008; 43: 20–24.
7. Intestinal Transplant Association. http://www.intestinaltransplant.org. Accessed December 15, 2012.
8. United Network for Organ Sharing. http://www.unos.org. Accessed December 15, 2012.
9. USTransplant, Arbor Research Collaborative for Health. http://www.ustransplant.org. Accessed December 15, 2012.
10. Kaufman SS, Pehlivanova M, Fennelly EM, et al. Predicting liver failure in parenteral nutrition-dependent short bowel syndrome of infancy. *J Pediatr* 2010; 156: 580–585.
11. Abu-Elmagd KM, Costa G, Bond GJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. *Ann Surg* 2009; 250: 567–581.
12. Javid PJ, Malone FR, Bittner R, et al. The optimal timing of referral to an intestinal failure program: the relationship between hyperbilirubinemia and mortality. *J Pediatr Surg* 2011; 46: 1052–1056.
13. Middleton SJ, Nishida S, Tzakis A, et al. Cambridge-Miami score for intestinal transplantation preoperative risk assessment: initial development and validation. *Transplant Proc* 2010; 42: 19–21.
14. Lopushinsky SR, Fowler RA, Kulkarni GS, et al. The optimal timing of intestinal transplantation for children with intestinal failure: a Markov analysis. *Ann Surg* 2007; 246: 1092–1099.
15. Sigurdsson L, Reyes J, Kocoshis SA, et al. Intestinal transplantation in children with chronic intestinal pseudo-obstruction. *Gut* 1999; 45: 570–574.
16. Fryer J, Pellar S, Ormond D, et al. Mortality in candidates waiting for combined liver-intestine transplants exceeds that for other candidates waiting for liver transplants. *Liver Transpl* 2003; 9: 748–753.
17. Freeman RB Jr, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl* 2002; 8: 851–858.
18. Reyes J, Mazariegos GV, Bond GM, et al. Pediatric intestinal transplantation: historical notes, principles and controversies. *Pediatr Transplant* 2002; 6: 193–207.
19. Mazariegos GV, Steffick DE, Horslen S, et al. Intestine transplantation in the United States, 1999–2008. *Am J Transplant* 2010; 10(4 part 2):1020–1034.
20. INCUCAI. Norms and resolutions for intestinal allocation, asigment and distributions. [Normas y procedimientos para distribución, asignación y adjudicación de intestinos para trasplante] 2011. http://www.incucai.gov.ar/docs/resoluciones/resolucion_incucai_098_11.pdf.
21. Gruessner RW, Sharp HL. Living-related intestinal transplantation: first report of a standardized surgical technique. *Transplantation* 1997; 64: 1605–1607.
22. Testa G, Panaro F, Schena S, et al. Living related small bowel transplantation: donor surgical technique. *Ann Surg* 2004; 240: 779–784.
23. Raofi V, Beatty E, Testa G, et al. Combined living-related segmental liver and bowel transplantation for megacystis-microcolon-intestinal hypoperistalsis syndrome. *J Pediatr Surg* 2008; 43: e9–e11.
24. Gondolesi G, Blondeau B, Maurette R, et al. Pretransplant immunomodulation of highly sensitized small bowel transplant candidates with intravenous immune globulin. *Transplantation* 2006; 81: 1743–1746.
25. Bond G, Reyes J, Mazariegos G, et al. The impact of positive T-cell lymphocytotoxic crossmatch on intestinal allograft rejection and survival. *Transplant Proc* 2000; 32: 1197–1198.
26. Sudan D. Quality of life after intestinal transplantation. *Prog Transplant* 2004; 14: 284–288.
27. Lacaille F, Vass N, Sauvat F, et al. Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation. *Gut* 2008; 57: 455–461.
28. Gondolesi G, Solar H, Echevarria C, et al. Long term results after intestinal transplantation from a single South American center. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract 319.
29. Rovera GM, DiMartini A, Schoen RE, et al. Quality of life of patients after intestinal transplantation. *Transplantation* 1998; 66: 1141–1145.

DOI:10.1002/MSJ

30. Grant D, Abu-Elmagd K, Reyes J, et al. 2003 report of the intestine transplant registry: a new era has dawned. *Ann Surg* 2005; 241: 607–613.
31. O'Keefe SJ, Emerling M, Koritsky D, et al. Nutrition and quality of life following small intestinal transplantation. *Am J Gastroenterol* 2007; 102: 1093–1100.
32. Golfieri L, Lauro A, Tossani E, et al. Psychological adaptation and quality of life of adult intestinal transplant recipients: University of Bologna experience. *Transplant Proc* 2010; 42: 42–44.
33. Guerra J, Kozlowski S, Matsumoto C, et al. Male and female fertility after intestinal transplantation. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract 209.
34. Gupte G, Srivasta R, Beath S, et al. Successful pregnancy outcome following triple organ transplantation. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract P37.
35. Kato T, Tzakis AG, Selvaggi G, et al. Intestinal and multivisceral transplantation in children. *Ann Surg* 2006; 243: 756–764.
36. Farmer DG, Venick RS, Colangelo J, et al. Pretransplant predictors of survival after intestinal transplantation: analysis of a single-center experience of more than 100 transplants. *Transplantation* 2010; 90: 1574–1580.
37. Abu-Elmagd K, Reyes J, Bond G, et al. Clinical intestinal transplantation: a decade of experience at a single center. *Ann Surg* 2001; 234: 404–416.
38. Selvaggi G, Nishida S, Levi D, et al. Intestinal and multivisceral transplantation at the University of Miami. *Clin Transpl* 2009: 211–217.
39. Uchida K, Nishida S, Levi D, et al. Current status of long-term survivors after intestinal and multivisceral transplantation in adults. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract 321.
40. Farmer DG, Venick RS, Busuttil RW. Improving outcomes after intestinal transplantation at the University of California, Los Angeles. *Clin Transpl* 2010: 245–252.
41. Matsumoto C, Kaufman S, Fenelly E, et al. Eight years of intestinal transplantation in Washington, DC. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract 323.
42. Lauro A, Zanfi C, Ercolani G, et al. Italian experience in adult clinical intestinal and multivisceral transplantation: 6 years later. *Transplant Proc* 2007; 39: 1987–1991.
43. Lacaille F, Chardot C, Goulet O, et al. Intestinal transplantation 17 years down the road: lessons and future. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract 320.
44. Varkey J, Simren M, Herlenius G. Long term follow-up of patients referred for intestinal or multivisceral transplantation: the Nordic experience. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract 318.
45. Gupte G, Sharif K, Muiesan P, et al. Small bowel transplant programme, 1993–2011: strategies for improvement in medium and long-term survival. Presented at: XII International Small Bowel Transplant Symposium; September 15–18, 2011; Washington, DC. Abstract 322.
46. Trentadue J, Rumbo C, García Hervás MD, et al. Intestinal transplantation in pediatrics: analysis of the first recipient series in Argentina [article in Spanish]. *Arch Argent Pediatr* 2011; 109: 135–141.
47. Tzvetanov IG, Oberholzer J, Benedetti E. Current status of living donor small bowel transplantation. *Curr Opin Organ Transplant* 2010; 15: 346–348.
48. Gangemi A, Tzvetanov IG, Beatty E, et al. Lessons learned in pediatric small bowel and liver transplantation from living-related donors. *Transplantation* 2009; 87: 1027–1030.
49. Ueno T, Wada M, Hoshino K, et al. Current status of intestinal transplantation in Japan. *Transplant Proc* 2011; 43: 2405–2407.
50. Grant D. Current results of intestinal transplantation: the International Intestinal Transplant Registry. *Lancet* 1996; 347: 1801–1803.

DOI:10.1002/MSJ