Special Feature

Intestine Transplantation in the United States, 1999–2008

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relevant data appear in the figures and tables included
here. All of the tables may be found online at:
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Improving short-term results with intestine transplantation have allowed more patients to benefit with nearly 700 patients alive in the United States with a functioning allograft at the end of 2007. This success has led to an increase in demand. Time to transplant and waiting list mortality have significantly improved over the decade, but mortality remains high, especially for infants and adults with concomitant liver failure. The approximately 200 intestines recovered annually from deceased donors represent less than 3% of donors who have at least one organ recovered. Consent practice varies widely by OPTN region. Opportunities for improving intestine recovery and utilization include improving consent rates and standardizing donor selection criteria. One-year patient and intestine graft survival is 89% and 79% for intestine-only recipients and 72% and 69% for liver-intestine recipients, respectively. By 10 years, patient and intestine survival falls to 46% and 29% for intestine-only recipients, and 42% and 39% for liver-intestine, respectively.

Immunosuppression practice employs peri-operative antibody induction therapy in 60% of cases; acute rejection is reported in 30%–40% of recipients at one year. Data on long-term nutritional outcomes and morbidities are limited, while the cause and therapy for late graft loss from chronic rejection are areas of ongoing investigation.

Key words: Intestine transplantation and donation, outcomes, waiting list mortality

Introduction

As experience has increased with intestine transplantation, areas for improvement have become more apparent and include the need to reduce waiting list mortality, as well as optimize long-term outcomes. While the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) Annual Report has heretofore reviewed the status of both liver and intestine transplants in the same manuscript, the present article specifically evaluates intestine transplantation as a discrete field, defining issues for both isolated intestine transplantation as well as intestine transplantation performed with other organs. This article analyzes the trends in intestine donation and transplantation over the last decade using data from the 2009 OPTN/SRTR Annual Report; it also provides additional analysis on donor characteristics and long-term outcomes conducted specifically for this manuscript. The areas of focus in this article mirror the primary areas where improvement can occur within this growing transplant field, with a hope to foster better understanding of both the donor and recipient populations, analysis of waiting list outcomes, changes in allocation policy, analysis of pertinent immunosuppression practices and a review of the short- and long-term outcomes after intestine transplantation.

Nomenclature

Intestinal transplantation remains a challenging effort for patients and clinicians. Central to moving the field forward is the ability to compare similar operations across centers so progress can be achieved. A critical limitation

in this regard is the lack of a consistent system of nomenclature for the various types of transplant procedures. Commonly used terms include isolated small bowel, multivisceral, liver-small bowel and combined liver-small bowel-pancreas transplantation. Often, these abdominal transplants are combined with evisceration of portions of the entire foregut including the spleen. All these variables can have an impact on patient outcomes. As a consequence, consistent nomenclature is essential so similar transplant procedures can be compared, critical analyses performed and efforts initiated to improve outcomes.

In 2007, experts from major intestine transplant programs around the world met at the International Small Bowel Transplant Symposium with the intent of creating a consistent and accurate nomenclature. The consensus reached at this meeting was that the term multivisceral transplantation meant different things to different programs and as a consequence, the term should be abandoned. A more descriptive system was proposed. In particular, it was strongly urged that the type of intestine transplant performed be broadly based on two categories: with or without simultaneous liver transplant. The first category would represent the typical combined liver, small bowel and pancreas transplant. This is the most commonly performed form of intestinal transplant when it is combined with a liver. Modifiers to this operation would then reflect whether the transplant was performed with or without evisceration of the recipient foregut. This would provide greater consistency in identifying the various types of transplants and, in particular, allow appropriate comparisons to be performed. The term isolated small bowel transplantation is accurate in its description, so no changes were proposed to it. Intestine transplants may also include the stomach and the colon, which are not organs that are allocated alone in the United States. In this article, we do not report data on the inclusion of the stomach and colon. For selected analyses, we do separately report on isolated intestine transplants and on intestine transplants that included the liver (and possibly pancreas and/or kidney).

Candidate and Recipient Demographics

Candidates on the waiting list for intestine transplantation have increased from 101 (71 active and 30 inactive) at the end of 1999 to 212 in 2008 (146 active and 66 inactive) [Table 10.1a,b]. The number of inactive registrations may reflect a clinical period of observation to assess potential for intestinal adaptation. Similarly, new registrations have increased from 149 in 1999 to 267 in 2008, with over 50% of the active patients being 5 years of age or younger [Table 10.2]. Although there is some variation from year to year, the racial/ethnic composition of the intestine transplant list at the end of 2008 was 65% white, 18% African American, 16% Hispanic, 1% Asian and 0.5% other or multiple races [Table 10.1a,b]. This is similar to the U.S. population in 2008, although there are fewer Asians on

the intestine waiting list than in the U.S. general population (1). The racial composition of the active (64% white) and inactive candidates (63% white) is similar. Over the decade, male candidates made up approximately 60% of the active waiting list, ranging from 53% in 2000 to 65% in 1999. The blood types of active candidates on the intestine waiting list are also in approximate proportion to those observed in the general population (for 2008: A = 31%, AB = 5%, B = 14% and O = 50%). U.S. residents accounted for over 94% of the listed candidates from 1999 through 2008 (range 94.1%–99.5%).

In the United States, there is no separate waiting list for candidates that are waiting for an intestine and additional organs, such as a liver. To identify these individuals, we matched the candidates on the intestine waiting list to the liver, pancreas and kidney waiting lists at the center where they were listed for an intestine (the thoracic organ lists were also checked and no intestine candidate was simultaneously listed for heart or lung between 1999 and 2008). If the candidate was ever on the list for another organ while they were listed for intestine, we classified them as waiting for either an intestine and liver (and possibly pancreas or kidney) or an intestine without a liver but with other organs. If the candidate never appeared on the waiting list for another organ at their center, he or she was considered to be waiting for an isolated intestine graft (also referred to here as intestine alone or intestine only). If an intestine candidate was listed at more than one transplant center, each registration was considered separately as listing behavior could be different at each center.

Over the decade, the proportions of patients waiting for either an intestine alone or an intestine with organs other than the liver has grown from 27% and 1% in 1999 to 40% and 7% in 2008, respectively. The fraction waiting for an intestine with a liver has decreased from 72% in 1999 to 54% in 2008. There has been a gradual increase in the proportion of candidates listed for isolated intestine transplant, possibly due to earlier listing (prior to the need for liver transplantation), reflecting the recognition that isolated intestine transplant may be effective if liver disease is present but has not progressed too far for recovery to occur (Figure 1A and B). The initial listing status for isolated intestine was Status 2 for most candidates but varied over time from 74% in 1999 to a low of 42% in 2002 and was 62% in 2008. In contrast, candidates listed for both liver and intestine were usually listed at Status 1, from a low of 55% in 1999 to a high of 80% in 2003 and 73% in 2008. Note that not all of these candidates were listed for liver when they were added to the intestine list; many were added to the liver list at some time after intestine listing. The number and proportion of children being listed for intestine without liver appears to be increasing in all age groups except for the <1 year group. Since children constitute the majority of intestine candidates, the aggregate trends do not reflect that, in contrast, in the smaller adult population, the proportion of candidates listed for intestine

Source: SRTR analysis, data as of May 2009. IN candidates never listed for additional organs.

Source: SRTR analysis, data as of May 2009. Includes IN candidates ever listed for liver while waiting.
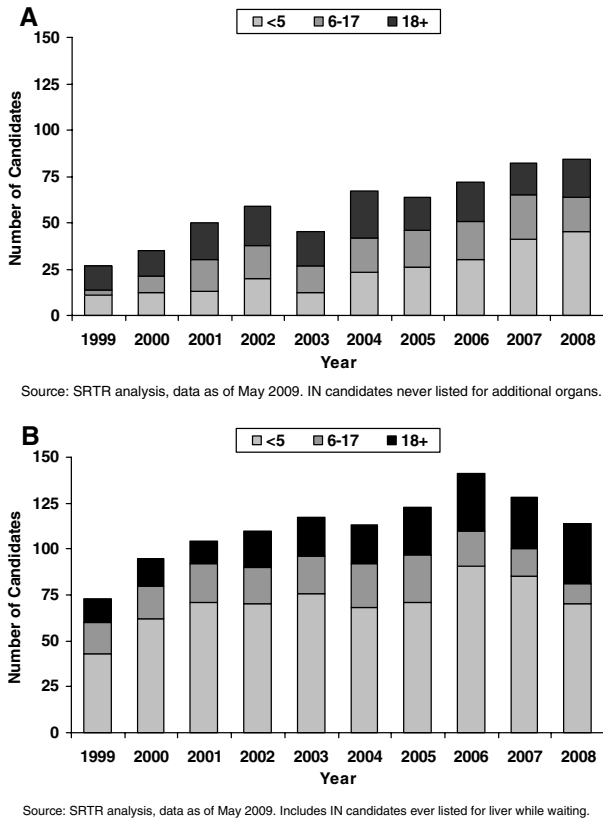
Figure 1: (A). Number of candidates on the intestine waiting list at year-end by age, 1999–2008: intestine only. (B) Number of candidates on the intestine waiting list at year-end by age, 1999–2008: also listed for liver.

with liver is increasing. Approximately 10% of the patients active on the intestine list at the end of 2007 were waiting for a second or third graft, compared to 6% of those active on the waiting list at the end of 2008 [Table 10.1a].

Transplant recipients
Experience with intestine transplantation has increased and changed over the past decade but remains concentrated at a few large centers. In 1999, there were three programs that performed more than 10 intestine transplants and eight programs that performed fewer than 10 transplants. Also in 1999, 81% of intestine transplants performed in the United States were in four OPTN regions (2, 3, 8 and 9). In 2008, four regions still accounted for nearly 82% of intestine transplants, but they were regions 2, 3, 8 and 10. In 2008, intestine transplants were equally divided between pediatric (less than 18 years) and adult recipients and between males and females [Table 10.4]. Two-thirds of the transplant recipients were white, 17% African American and 11% Hispanic. The payment source was private insurance for 37%, Medicaid for 41%, Medicare for 11% and other sources for 11%. Five percent of recipients were nonresident aliens. Short gut syndrome accounted for 73%

of cases in 2008, functional bowel problems for 15% of cases and other causes represented 12% of cases.

Over time, there has been a trend in the community toward either avoiding intestine transplantation in critically ill, unstable patients or listing candidates earlier in the disease process prior to hospitalization. This appears to be reflected in the data. In 1999, almost a third of the recipients were in intensive care at the time of transplantation whereas in 2008, 70% were not hospitalized, 18% were hospitalized and only 12% were in intensive care [Table 10.4]. Interestingly, the calculated laboratory Model for End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) score profiles of patients receiving livers with the intestine graft have not changed substantially over time. Looking at the liver waiting list status (match MELD and PELD) of those patients who also received a liver graft with the intestine graft in 2008 shows that 17% had a liver status of 1B at the time of transplant. Of the remaining patients, almost 80% of the adults had match MELD scores greater than 20 and almost 80% of children had match PELD scores greater than 30. The hospitalization status of the recipient at the time of transplantation remains a strong prognostic factor for patient survival, with an unadjusted 1-year survival rate of 83% for recipients not waiting in the hospital, 73% for recipients waiting in the hospital and only 50% for recipients waiting in the intensive care unit [Table 10.14].

Waiting List Outcomes

Table 1 lists the outcomes at 1 and 3 years after listing for intestine transplant. Of note, only 9% of patients died in 2007 within 1 year of listing compared to nearly 20% in each of the preceding 3 years. For the first time, there appears to be an improvement in the percentage of patients who have died within 1 year of listing. Determining whether this is a permanent improvement and the factors leading to this improvement will require ongoing analysis. In 2007, 18% of listed patients received an isolated intestine transplant and 41% received a multiorgan transplant within 12 months of listing. Only 3% were removed for improved condition. Time to transplant (TT) for the entire intestine waiting list has fallen from a median of 313 days in 1999 to 142 days in 2008 [Table 10.2]. Despite this decline, the longest waiting times are consistently in the youngest children. There does not appear to be any difference in waiting time based on sex or ethnicity.

Median time to transplant is shorter for intestine only candidates but TT appears to be decreasing for all candidates whether they are listed for a liver or not (Figure 2). There is large variation in TT based on age and geography. For isolated intestine transplantation, the longest median TT is for the pediatric patients (under 18 years) at close to 1 year (356 days) in 2008, while adults aged 18 years and older had a median TT of 27 days in 2008, clearly reflecting the availability of appropriately size-matched donors. This

Table 1: Outcomes at 1 and 3 years after listing for candidates on the intestine transplant waiting list (both isolated intestine and multiorgan), 1999–2007

	Year of listing								
	1999	2000	2001	2002	2003	2004	2005	2006	2007
Total listings during calendar year (N)	132	155	210	195	195	244	275	312	278
Status 1 year after listing (%)									
Still on waiting list	22.7	22.6	21.4	16.4	16.9	17.6	18.9	21.2	23.0
Status 1	10.6	12.9	11.4	9.2	10.8	9.8	9.8	11.5	9.7
Not status 1	6.8	5.2	5.7	4.1	3.1	2.9	3.3	4.2	6.5
Inactive	5.3	4.5	4.3	3.1	3.1	4.9	5.8	5.4	6.8
Received transplant	48.5	51.6	51.0	50.3	52.3	56.6	54.2	53.5	59.7
Intestine alone transplant	16.7	20.0	21.9	19.5	21.5	21.3	17.5	17.0	18.3
Multiple organ	31.8	31.6	29.0	30.8	30.8	35.2	36.7	36.5	41.4
Died within one year of listing	22.7	18.1	20.5	24.1	22.1	18.4	17.8	17.0	8.6
Condition worsened/medically unsuitable	3.0	0.6	1.4	1.5	1.5	1.6	5.8	4.5	5.0
No record of subsequent death	1.5	0.0	1.0	1.0	0.5	0.0	2.2	1.9	1.1
Died after removal as too sick	1.5	0.6	0.5	0.5	1.0	1.6	3.6	2.6	4.0
Condition improved	0.0	2.6	1.9	2.6	3.1	3.3	2.2	1.6	2.5
Removed for other reasons	3.0	4.5	3.8	5.1	4.1	2.5	1.1	2.2	1.1
Status 3 years after listing (%)									
Still on waiting list	10.6	9.7	4.8	4.6	4.6	7.0	9.1	+	+
Status 1	3.0	2.6	0.0	1.0	1.5	2.5	1.8	+	+
Not status 1	3.0	3.9	1.0	1.0	1.0	0.8	4.0	+	+
Inactive	4.5	3.2	3.8	2.6	2.1	3.7	3.3	+	+
Received transplant	56.8	56.1	60.0	54.9	57.4	63.1	58.2	+	+
Intestine alone transplant	18.2	21.9	24.8	20.5	23.1	23.8	18.2	+	+
Multiple organ	38.6	34.2	35.2	34.4	34.4	39.3	40.0	+	+
Died within one year of listing	25.8	22.6	25.7	26.2	25.6	18.9	19.6	+	+
Condition worsened/medically unsuitable	3.0	1.3	1.4	2.6	1.5	1.6	6.2	+	+
No record of subsequent death	1.5	0.0	1.0	2.1	0.5	0.0	2.5	+	+
Died after removal as too sick	1.5	1.3	0.5	0.5	1.0	1.6	3.6	+	+
Condition improved	0.0	5.8	3.3	3.6	4.1	4.9	4.0	+	+
Removed for other reasons	3.8	4.5	4.8	8.2	6.7	4.5	2.9	+	+

Source: SRTR analysis, data as of May 2009.
+ Insufficient follow-up available to present statistics for this year.

pattern was similar, but not so marked, for candidates requiring liver as well as intestine transplants. For <1 year old infants, the median TT in 2008 was 324 days, falling to 229 days for adults over 18 years old. TT is appropriately
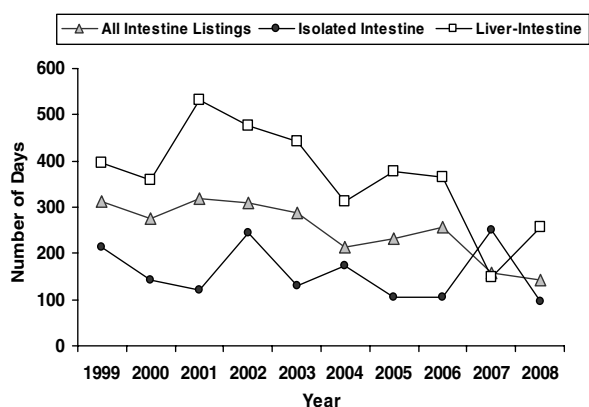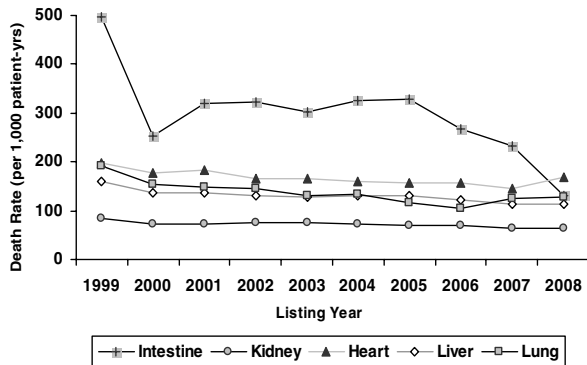

Source: *2009 OPTN/SRTR Annual Report*, Table 10.2 and SRTR Analysis.

Figure 2: Median time to transplant (TT) for new intestine waiting list registrations, 1999–2008.

shorter for isolated intestine candidates listed initially at Status 1 versus Status 2 (41 vs. 109 days in 2008). For liver-intestine candidates, the pattern is different, with those initially listed as Status 2 on the intestine list (about 25% of 2008 new liver-intestine listings) having a shorter median TT (127 days) than those listed as Status 1 (267 days). In 2008, nearly one-third of Status 1 new liver-intestine listings were for candidates aged 18 years and older compared to one-quarter of the Status 2 candidates; pediatric liver candidates are given priority over adults for pediatric liver donors.

The geographical differences observed are challenging to explain, but are likely associated with the location of the larger intestine transplant programs and possibly related to differences in the age mix at different centers. In 2008, there were seven programs that performed more than 10 intestine transplants and 10 centers that performed six or fewer transplants. Region 2, which contains three of the larger programs, had 37% of all new intestine listings in 2008 and a relatively long median TT at 260 days in 2007. Region 5, with one large center and two smaller centers, had the longest median TT at 314 days in 2007.

Source: *2009 OPTN/SRTR Annual Report,* Table 1.6.

Figure 3: Unadjusted death rates per 1000 patient years at risk for patients on the waiting list by organ, 1999–2008.

Region 2 had 52% of the U.S. candidates waiting for isolated intestine transplants in 2008. Median time to transplant for intestine only candidates was 176 days in 2008 in Region 2, down from 264 days in 2007. The remaining intestine only listings were spread across seven regions, with too few candidates per region to calculate meaningful statistics. Median TT for those waiting for both a liver and intestine mirrors that for all intestine candidates.

For the years prior to 2008, annual death rates on the intestine transplant list per 1000 patient-years at risk were greater than for any other organ transplant candidate population (Figure 3). However, the survival of candidates waiting for intestine transplants also showed the greatest improvement among solid organ waiting lists over the last 10 years, falling from 496 deaths per 1000 patient-years at risk in 1999 to 130 deaths per 1000 patient-years at risk in 2008. In fact, in 2008 the death rate fell below that of heart and heart-lung candidates for the first time and was the same as that of lung transplant candidates. The majority of these deaths were among the patients awaiting transplantation with intestine and an additional organ(s), usually liver (2,3). Out of the 28 deaths on the intestine waiting list in 2008, 23 were among candidates waiting for both an intestine and a liver, three were waiting for an intestine and another organ but not the liver, while two were waiting for isolated intestine transplants. The waiting list death rates for candidates listed for isolated intestine transplantation fell from 271 deaths per 1000 patient-years at risk in 1999 to 24 in 2008. Likewise, for combined liver-intestine listings, death rates fell from 576 in 1999 to 194 by 2008. Death rates were highest in the youngest children (aged 5 years or younger) but lowest for the pediatric candidates between 6 and 17 years old. The fall in death rates does not appear to reflect a change in age at listing or other demographic characteristics of the candidates over the decade, as these factors have remained relatively constant. There has been a similar fall in waiting list death rates in all regions with active intestine transplant programs. Despite the aforementioned differences in time to transplant be-

tween regions, the annual death rates do not appear to vary greatly. As previously noted, the median TT has fallen and this may have contributed to the improvements in waiting list mortality rates. Additionally, there has been a substantial emphasis in many intestine transplant programs on intestinal care and rehabilitation for their patients (4,5) and the falling death rates may reflect improved pretransplant medical care.

Additional organs listed over time
Intestinal transplant candidates are dependent on parenteral nutrition (PN) for survival and the primary indication for intestinal transplantation is failure of PN therapy due to the development of life-threatening PN-associated complications, most commonly PN associated liver disease. Consequently, most intestinal transplant candidates are also listed for additional organs, most commonly liver and/or pancreas. The decision to proceed with a liver listing is usually prompted by a clinical determination that irreversible liver damage has occurred and that survival is only possible by including a liver graft at transplant. Conversely, while an additional pancreas listing is sometimes needed for irreversible pancreas disease, more often it is done to facilitate a multiorgan transplant that is technically easier when the intimate anatomical relationships of the liver, pancreas and intestine are preserved. In the interest of optimal organ utilization, it is important to review and monitor the use of additional organs in intestinal transplant candidates.

For this analysis of the timing of the listing of intestine candidates with additional organs, we limited our sample to candidates listing for their first intestine transplant and included listings through 2007 to allow for observation of listing behavior for 1 year following the intestine listing (n = 1882 registrations for 1741 individuals). Most of the 124 people with more than one registration were listed simultaneously at two centers (n = 95), while 13 listed at three centers, and two listed at four centers. Fourteen candidates were listed consecutively rather than concurrently. Each candidate's intestine waiting list experience was consolidated into one record per person. In cases where candidates listed for intestine concurrently at two different centers, the listing for the center that eventually performed the transplant was chosen for those that were transplanted, and the center with the earliest listing date was chosen for those who died while waiting. The 14 candidates listed consecutively had been removed from the intestine list for reasons like condition improved, condition declined and removed in error and were re-listed at the same program within 15 days. These listings were collapsed into one continuous listing. The final sample tracked 1741 candidates, matched to the waiting lists for other organs at their center to determine listing dates relative to the intestine listing.

Between 1999 and 2007, 38% of candidates who were listed for their first intestine transplants were initially listed
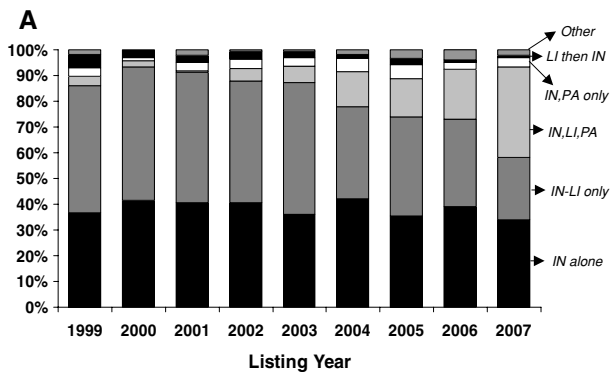
Source: SRTR Analysis, data as of May 2009.   IN=Intestine, LI=Liver, PA=Pancreas.
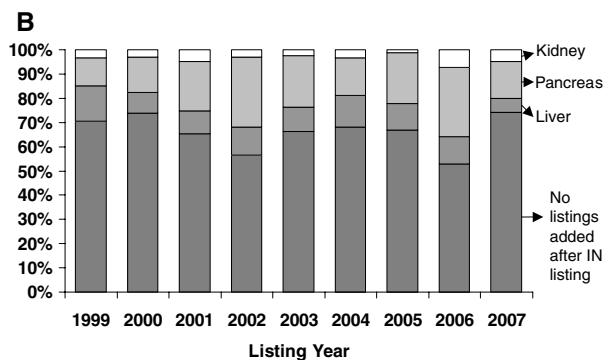
Source: SRTR Analysis, data as of May 2009. IN=Intestine, LI=Liver, PA=Pancreas, KI=Kidney. No intestine candidates were ever listed for Heart or Lung transplants during this time period.

Figure 4: (A) Initial listing of candidates for intestine and other organs on the same day, 1999–2008. (B) Additional listing of candidates for intestine transplant after intestine listing date, 1999–2008.

for intestine only, 4% were initially listed for intestine-pancreas on the same day, 40% were initially listed for intestine-liver on the same day and 13% were initially listed for intestine-liver-pancreas. An additional 2% of intestine candidates had been listed first for a liver transplant before subsequently being listed for intestine also. While most pediatric candidates were initially listed for intestine-liver transplants (53%), most adult candidates were initially listed for intestine only (51%). The percentages of initial listings for intestine only and intestine with liver have remained relatively stable over the past 10 years (Figure 4A).

While Figure 4A displays the additional organs for which intestine candidates were listed prior to or at the same time as the intestine listing, intestine candidates are often listed for additional organs after being added to the intestine waiting list. For the years 1999 to 2007 combined, 34% of all intestine candidates (waiting for their first transplant) were listed for at least one additional organ after their initial intestine listing (Figure 4B). Overall, the most common additional organ that intestine candidates were subsequently listed for was the pancreas (20%), followed

by the liver (10%), and the kidney (4%). With adults (18 years and older), 58% of candidates that were initially listed for both intestine and liver were subsequently listed for an additional organ, most commonly pancreas. With pediatric patients, 32% of candidates initially listed for intestine only and 36% initially listed for intestine-pancreas were subsequently listed for livers also. Furthermore, 27% of pediatric patients initially listed for both intestine and liver were subsequently listed for pancreas. Of note in 2007, the percentage of patients that had no additional listings did increase to over 70% for the first time in several years, as more candidates were listed for liver, intestine and pancreas on the same day. Over the span of 1999 to 2007 as a whole, two-thirds of intestine candidates waiting for their first transplant were either initially or eventually listed for a liver, which was fairly constant across the years, with a high of 73% in 1999 and a low of 63% in 2001. Thirty-eight percent of intestine candidates were either initially or eventually listed for a pancreas, though this fraction has increased over time, likely due to OPTN attention ensuring that patients getting a pancreas with their intestine (to facilitate procurement and implantation of the combined graft by avoiding unnecessary dissection) are listed on the pancreas waiting list. The fraction also listed for pancreas at any time while on the intestine list was 18% in 1999 and 2000, and rose to 55% by 2007. About 5% of intestine candidates (first transplant) were eventually listed for a kidney during this time period, ranging from 3% to 5% for most years, although 2006 had 9% and 2007 had 6%.

Evolution of intestine allocation policy

Allocation policy for candidates awaiting intestine only transplantation has not been changed in the past 10 years; candidates receive offers for intestines according to their status on the waiting list. A patient can be listed as urgent (Status 1), nonurgent (Status 2), or inactive (Status 7). The criteria for listing in either of the active status categories are rather broad, and it is not known how consistently they are applied.

In contrast to the allocation of intestine only grafts, several changes in policy have been made in recent years regarding allocation of a composite liver and intestine allograft. Candidates requiring a simultaneous liver and intestine (and possibly other abdominal organ) transplant are listed on both the intestine waiting list as Status 1 and on the liver list. Prior to February 2002, the liver candidates were prioritized according to criteria derived from Child–Pugh–Turcott scores, into Status 1, 2 (and 2b), or 3. The procuring Organ Procurement Organization (OPO), at its own discretion, could offer the liver from a potential liver and intestine donor to the candidate matched according to the liver waiting list (which likely would have been a liver only candidate) or the intestine list could be run, in which case the composite graft would have been allocated to the next appropriate patient on the intestine waiting list. There are little data regarding practices and the determinants of

which waiting list was run for any given donor, though proximity to an intestinal transplant program is believed to frequently have been one factor. There was dissatisfaction on all sides of this issue. Livers that might have been allocated to a very sick local liver candidate could instead be exported for a distant liver bowel candidate, while there were data demonstrating that liver-intestine candidates were at a substantial competitive disadvantage compared to the liver only candidates, as manifested by significantly higher waiting list mortality rates.

In February 2002, the fundamental basis of liver allocation changed to one based on 90 day waiting list mortality risk with the introduction of the MELD score for adults and the PELD for children (6,7). These scores were applied both to patients listed for liver only, as well as combined liver and intestine transplant candidates despite the fact that the latter patients had been excluded from the analyses that were used to validate these measures. While there was no change in the priority of allocating a composite organ from the intestine list, it did seem likely that these changes in liver allocation had further focused the allocation of such grafts to the liver list, and thereby bypassing the liver-intestine candidates. It also rapidly became clear that the liver-intestine candidates, despite having very high pretransplant mortality, were not scoring as highly on MELD or PELD and therefore not having access to available donors. The OPTN Liver and Intestine committee asked the SRTR to confirm and quantify the increased waiting list mortality risk for candidates awaiting both liver and intestine transplant in relation to liver only candidates, as well as to determine if MELD and PELD could still be expected to predict changes in mortality risk for the liver-intestine transplant candidates.

The first analysis presented to the OPTN Liver and Intestine Committee in November 2002 demonstrated that the overall death rate while on the liver transplant waiting list was eight times higher for candidates awaiting combined liver and intestine allografts compared to those waiting for a liver alone. On the basis of a left-truncated Cox model (censored at the earliest of transplantation, removal from waiting list, or at 90 days), it was determined that each one point PELD increase equated to an 11% average increase in mortality on the waiting list for both liver only and combined liver and intestine candidates, but at any given PELD score the liver and intestine candidates had a 3.6 times greater risk of mortality at 90 days. This analysis resulted in a change in OPTN policy to give additional MELD or PELD points to candidates simultaneously listed on the liver and intestine waiting lists, equating to an additional waiting list mortality of 10% (8).

These analyses were repeated with a greater amount of accumulated data in 2006 and a greater discrepancy was noted in waiting list mortality risks between these two groups of candidates. Again, there was no evidence of an interaction between the PELD or MELD scores for liver-

intestine and liver alone candidates in the pediatric age range (0–17 years), indicating that the difference in waiting list mortality for the two groups stayed the same for all MELD or PELD scores; in this analysis the mean difference in mortality risk equated to a difference of 23 PELD points. For adults, however, there was a large difference in mortality risk for those with relatively low MELD scores (the liver-intestine candidates having a significantly higher 3 month mortality risk). However, as the MELD scores increased, the waiting list mortality risk for both liver-intestine and liver only candidates approached similar levels. For this reason, it was decided to add the additional 23 points to all pediatric PELD or MELD scores automatically and to continue to add the 10% equivalent risk to adults, which results in fewer additional points being added as the MELD score increases.

The OPTN Board of Directors approved this change in December 2006, along with two other changes meant to further refine the allocation process. The first was to clarify whether a combined liver and intestine allograft could be allocated to a candidate on the basis of their position on the intestine list or whether the liver list had to be used. It was decided that, provided there were no Status 1A or 1B candidates in the donor OPTN region to whom the liver could be offered, the composite liver and intestine allograft could be offered for a liver-intestine candidate either regionally or nationally. The second change approved was to offer composite liver-intestine allografts from donors less than 11 years specifically to the candidates listed for both organs, both regionally and nationally, ahead of candidates listed regionally for liver only, with the exception of Status 1 liver alone candidates listed locally or regionally. This change was made to better serve the pediatric waiting list.

In the same time frame, the tightening of criteria for a child to be listed as Status 1B that was introduced with the review of all Status 1 listings made it more difficult for children with chronic liver disease to have their listing priority elevated to this status. One of the criteria made more stringent was the transfusion requirement following gastrointestinal (GI) bleeding. It became clear that patients with GI bleeding awaiting combined liver and intestine transplantation could spend weeks with continuous blood loss but never achieve the required 30 cc/kg/24 h required to be upgraded to Status 1B. In May 2007 the transfusion requirement was reduced back to 10 cc/kg in a 24 h period for those candidates listed simultaneously for liver and intestine.

The most recent change to allocation affecting intestine and liver candidates is presently being programmed into UNET and came about as a result of a directive given to the OPTN Pediatric committee to reduce waiting list deaths. It was recognized that livers from donors younger than 11 years of age rarely if ever were used in adults and consequently these organs could be allocated on a wider geographical basis to children without adversely affecting

Table 2: Intestine consent, recovery and transplant by OPTN region, 1999–2008

	U.S. total	OPTN region										
		1	2	3	4	5	6	7	8	9	10	11
Total deceased donors of at least 1 organ (N)	69 374	2431	8832	11 257	6396	9581	2561	6237	4548	3833	6433	7265
Disposition of intestine (%)												
Consent for IN not requested	18.1	22.0	21.4	18.1	13.7	5.2	10.6	19.1	18.2	28.3	14.1	33.7
Consent for IN not obtained	8.9	12.8	10.0	8.5	8.4	10.2	5.3	5.4	3.5	12.2	11.1	9.6
IN not recovered	69.2	63.4	65.0	67.9	75.9	82.6	82.9	67.0	73.3	56.8	71.4	53.4
IN recovered but not for transplant	1.7	0.0	1.7	2.5	0.2	0.6	0.2	7.0	2.7	0.3	0.9	0.6
IN recovered for transplant, discarded	0.2	0	0.2	0.1	0.2	0.1	0.1	0.3	0.1	0.3	0.3	0.2
IN transplanted	1.9	1.8	1.7	3.0	1.5	1.2	0.8	1.2	2.2	2.2	2.2	2.6
Disposition of intestine (N)												
Consent for IN not requested	12 571	536	1890	2038	878	499	271	1192	828	1084	907	2448
Consent for IN not obtained	6176	310	883	952	540	981	137	336	159	467	717	694
IN not recovered	47 981	1541	5740	7639	4855	7916	2123	4181	3334	2179	4591	3882
IN recovered but not for transplant	1174	1	151	278	11	60	6	434	124	10	57	42
IN recovered for transplant, discarded	125	0	18	15	14	10	3	18	5	10	20	12
IN transplanted	1347	43	150	335	98	115	21	76	98	83	141	187

Source: SRTR analysis, data as of May 2009. IN = intestine.

the adult waiting list. One part of the changes will be to allocate the young pediatric donor livers to Status 1A pediatric recipients regionally and then nationally before offering to the combined liver-intestine candidates. This is expected to reduce the national allocation of composite liver-intestine allografts by a small but, as of yet, unquantifiable proportion.

As allocation policy continues to be refined, there is growing interest in considering the potential to evaluate transplant benefit as a part of allocation strategy (9). Simply stated, transplant benefit seeks to determine the benefit received with a transplant compared to the benefit received without transplantation. Indeed, such consideration of 'benefit' is a foundation of all clinical decision-making. With respect to survival benefit, this can be determined by comparing survival with a transplant to survival without a transplant. Accordingly, to calculate transplant benefit, one needs statistical models to predict survival both on the waiting list as well as posttransplant. While this is possible for many patients considered for liver transplantation, there are several populations where this approach is less sound, including liver-intestine candidates. One reason is that the relatively small number of liver-intestine candidates limits the statistical power of the survival models. Additionally, all models use current data to predict future outcomes. Given the significant improvement in results over recent years in intestine transplantation, it would be desirable to have the parameters used in the model be in a relatively steady state. Any future changes in liver allocation, whether benefit based or not, need to be developed with consideration of the impact on this unique population.

Donor Utilization

As with all deceased organ donors over the past 10 years, the number of deceased intestine donors has plateaued or slightly decreased in the past 3 years. In 2008, there were 197 intestine donors compared to a peak of 206 in 2007 [Table 1.1]. As detailed previously, the limited number of intestine donors, coupled with an increase in overall waiting list registrations, has kept the waiting list mortality for a patient awaiting an intestine transplant high.

From 1999 to 2008, between 1.2% and 2.4% of deceased donors of at least one organ were utilized for intestine donation annually. Of the 69 374 deceased donors between 1999 and 2008, consent for the intestine was not requested for 18% and in another 9% of cases, consent was not granted (Table 2). Failure to request consent for intestine transplant varied across OPTN regions during this time frame from 5% to 34%. Reasons most commonly stated for not requesting intestine consent were: donor age (67%), donor was DCD (donation after cardiac death; 11%) and donor quality (8%). Primary reasons listed for the intestine not being recovered after consent was obtained include poor organ function (25%), no recipient located (21%), donor medical history (10%) and organ refused by all national programs (9%). Not recovering the intestine because the organ was refused by all national programs has been increasing over the past 10 years from 1% in 1999 to 16% in 2008.

Efforts to increase the donor pool and improve intestine waiting list mortality potentially include consideration of

living intestine donation, DCD donors, extension of acceptable donor criteria, improved utilization of existing donors, and optimized donor allocation. Intestine transplants from living donors have not substantially impacted the intestine waiting list. After a peak of 13 intestine living donors between 2004 and 2005, there were only 5 reported between 2006 and 2007, and none in 2008 [Table 1.1]. Similarly, DCD intestine donation is not expected to significantly impact intestine availability in the near future, due to the sensitivity of the intestine to ischemia.

While the intestine waiting list has grown over time, only 212 patients were waiting for intestine transplant at the end of 2008 [Table 10.1a,b]. Increasing use of existing donors would be hypothesized to significantly increase intestine availability, further reducing waiting list mortality and time to transplant. In an effort to understand intestine recovery practice and identify areas for potential improvement, an analysis of the OPTN data during the past 10 years was evaluated for potentially underutilized donors, using the following criteria for potential intestine donation: donors 50 years of age or less, who had other organs utilized (for donors age 0–2 years, any organ used; for donors age 2–50 years, liver transplanted); terminal AST and ALT <500; last serum sodium prior to procurement < 170 meq/L; serum creatinine less than 1.0 mg/dL for age < 1 year or less than 2.0 mg/dL for age > 1 year; confirmed negative virus serology (human immunodeficiency virus [HIV], human T-lymphotropic virus [HTLV], hepatitis B core antibodies [HBcAb], hepatitis B surface antigen [HBsAg] and hepatitis C antibodies [HCV]); two inotropes or less at time of recovery; if a cardiac arrest occurred after declaration of brain death and the resuscitation time was less than 15 min (cardiac arrest <15 min); and donation after brain death.

Table 3 shows the impact of these criteria, implemented as exclusions for not meeting the criterion (for example, the donor age < 50 years is shown as excluding all donors older than 50 years), starting with all donors and ending with the potential intestine donors. In 2008, approximately 35% of the nearly 8000 deceased donors of at least one organ met the designated criteria as potential intestine donors. Proportionally, the greatest number of donors were excluded based on age >50 years, not having the liver transplanted for donors older than 2 years, evidence of renal insufficiency and cardiac arrest >15 min.

The actual disposition of the intestine in the potential intestine donors is listed in Table 4. Of note, the rates of 'consent for intestine not requested' have fallen in this selected population from 12% in 1999 to 4% in 2008 and rates of 'consent for intestine not obtained' have also fallen. However, the rates for intestine not recovered have risen to 86% in 2008 from 71% in 1999. Less than 6% (n = 158) of donors meeting the criteria, listed previously, for potential intestine donors were transplanted in 2008.

To validate the selection criteria used, the potential intestine donor criteria were applied to actual donors whose intestine was transplanted during the study period (1999 to 2008). As shown in Table 5, 85% of actual donors utilized in 2008 met the selection criteria used to search for potentially underutilized intestine donors. Twenty-seven actual intestine donors (15%) failed to meet at least one criterion used to define potential intestine donors, most commonly the serum creatinine criterion (n = 8), cardiac arrest >15 min (n = 9) or more than two inotropes at cross clamp (n = 4). These data suggest that intestine donor selection criteria used for this analysis are similar to those used in current clinical practice, and that intestine donor utilization may be significantly increased by improvement in obtaining consent, awareness of appropriate age and medical criteria, as well as standardization of practice across OPTN regions.

Patient and Graft Survival, Early versus Late

Early patient and graft survival after intestinal transplantation have markedly improved over the past 10 years. In 1998, the 1-year adjusted graft and patient survival was 52% and 69%, respectively, while in 2007, these same survivals increased to 75% and 79%, respectively, a gain of more than 20 percentage points for graft survival [Tables 1.11a and 1.12a]. These outcomes are now nearly on par with other solid organ transplants such as pancreas, lung and liver. While we cannot determine the reasons behind this improvement, a multifactorial etiology is presumed. Important contributing factors include advances in immunosuppression, increased experience and advances in the detection and treatment of rejection.

Intestinal transplant recipients have received a variety of immunosuppressive regimens. Similar to other organ transplants, there can be a broad range of drug combinations used with the cornerstone for maintenance immunosuppression being tacrolimus (Prograf, Astellas, Tokyo, Japan). A review of the literature suggests that two broad classes of immunomodulatory agents have gained increasing acceptance and have been associated with marked improvements in 1-year survival. Antilymphocyte antibody therapies in the form of rabbit antithymocyte globulin (rATG, Thymoglobulin, Genzyme Corp., Cambridge, MA) and alemtuzumab (Campath-1H, Genzyme Corp., Cambridge, MA) have both been reported in single center publications to be associated with improved short-term survival and decreased rejection rates and severity (10–12). Likewise, induction with interleukin-2 receptor antagonists (daclizumab [Zenapax, Roche Group, Nutley, NJ]) or basiliximab [Simulect, Novartis, Basel, Switzerland]) has been associated with similar improvements in survival and reduction in acute rejection episodes and their severity (13,14).

OPTN data show that at the time of discharge in 2008, 99% of intestinal transplant recipients received tacrolimus

Table 3: Assessment of potential intestine donors among donors of at least 1 organ, 1999–2008

	Total	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total deceased donors of at least 1 organ (N)	69 373	5824	5986	6080	6190	6457	7152	7594	8019	8087	7984
Potential intestine donors (N)	27 144	1800	2613	2634	2819	2770	2923	2947	2963	2919	2756
Exclusion criteria implemented in the order listed below (N)											
Age>50 years	22 229	1714	1780	1792	1818	2047	2329	2607	2680	2718	2744
Age<2 and no organs transplanted	36	2	7	2	2	5	5	5	2	3	3
Age≥ 2 and liver not transplanted	8353	804	842	818	752	659	764	818	874	999	1023
Terminal SGOT/AST > 500 u/L	706	48	46	42	56	64	80	80	89	96	105
Terminal SGPT/ALT > 500 u/L	267	14	16	18	18	24	24	30	39	41	43
Last serum sodium > 170 mEq/L	159	0	0	0	0	1	16	40	42	32	28
Serum creatinine>1 mg/dL, under age 1	135	10	6	9	14	16	17	13	8	23	19
Serum creatinine>2 mg/dL, age 1–50	3637	257	240	286	258	356	348	378	483	505	526
HIV or HTLV not confirmed negative	146	27	11	7	21	15	7	16	26	10	6
HBV core antibody not negative	1431	146	166	172	125	145	130	136	150	123	138
HBV surface antigen not negative	123	9	8	24	12	9	18	12	14	8	9
HCV antibody not negative	694	54	48	46	59	61	89	76	96	85	80
More than 2 inotropes at cross clamp	828	14	64	68	78	87	120	98	105	107	87
Did not meet cardiac arrest <15 min	2832	913	115	120	110	136	172	182	257	410	417
Donation after cardiac death	653	12	24	42	48	62	110	156	191	8	0
Potential intestine donors (%)	39.1	30.9	43.7	43.3	45.5	42.9	40.9	38.8	36.9	36.1	34.5
Exclusion criteria implemented in the order listed below (%)											
Age>50 years	32.0	29.4	29.7	29.5	29.4	31.7	32.6	34.3	33.4	33.6	34.4
Age<2 and no organs transplanted	0.1	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0
Age≥ 2 and liver not transplanted	12.0	13.8	14.1	13.5	12.1	10.2	10.7	10.8	10.9	12.4	12.8
Terminal SGOT/AST > 500 u/L	1.0	0.8	0.8	0.7	0.9	1.0	1.1	1.1	1.1	1.2	1.3
Terminal SGPT/ALT > 500 u/L	0.4	0.2	0.3	0.3	0.3	0.4	0.3	0.4	0.5	0.5	0.5
Last serum sodium > 170 mEq/L	0.2	0.0	0.0	0.0	0.0	0.0	0.2	0.5	0.5	0.4	0.4
Serum creatinine>1 mg/dL, under age 1	0.2	0.2	0.1	0.1	0.2	0.2	0.2	0.2	0.1	0.3	0.2
Serum creatinine>2 mg/dL, age 1–50	5.2	4.4	4.0	4.7	4.2	5.5	4.9	5.0	6.0	6.2	6.6
HIV or HTLV not confirmed negative	0.2	0.5	0.2	0.1	0.3	0.2	0.1	0.2	0.3	0.1	0.1
HBV core antibody not negative	2.1	2.5	2.8	2.8	2.0	2.2	1.8	1.8	1.9	1.5	1.7
HBV surface antigen not negative	0.2	0.2	0.1	0.4	0.2	0.1	0.3	0.2	0.2	0.1	0.1
HCV antibody not negative	1.0	0.9	0.8	0.8	1.0	0.9	1.2	1.0	1.2	1.1	1.0
More than two inotropes at cross clamp	1.2	0.2	1.1	1.1	1.3	1.3	1.7	1.3	1.3	1.3	1.1
Did not meet cardiac arrest <15 min	4.1	15.7	1.9	2.0	1.8	2.1	2.4	2.4	3.2	5.1	5.2
Donation after cardiac death	0.9	0.2	0.4	0.7	0.8	1.0	1.5	2.1	2.4	0.1	–

Source: SRTR analysis, data as of May 2009.

for maintenance immunosuppression *[Table 10.6e]*. During the first posttransplant year, very few patients were removed from this drug, with nearly 97% remaining on it *[Table 10.6g]*. Induction therapy was used in 60% of recipients *[Table 10.6a]*. The most commonly used drug for induction was rATG, with approximately a third of the patients with induction therapy receiving rATG. Interest- ingly, 15% of patients were administered muromonab-CD3 (OKT3, Orthoclone OKT3, Centocor Ortho Biotech, Hor- sham, PA) for induction. Other drugs commonly used for induction included daclizumab and alemtuzumab. Over the past four years, a review of immunosuppression use by discharge regimens demonstrates a wide variety of drug combinations. No specific trends or changes can be noted

Table 4: Final disposition of intestine for potential intestine donors identified by selection criteria, 1999–2008

	Total	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total potential intestine donors (N)	27 144	1800	2613	2634	2819	2770	2923	2947	2963	2919	2756
Disposition of intestine (%)											
Consent for IN not requested	10.3	12.2	14.5	13.5	15.0	12.2	12.4	9.8	6.4	4.3	3.8
Consent for IN not obtained	7.9	12.2	10.8	10.3	8.5	9.0	7.5	6.3	6.5	5.9	3.6
IN not recovered	75.5	71.2	70.5	70.7	70.8	72.5	71.8	76.8	79.6	82.0	86.2
IN recovered but not for transplant	2.0	1.8	1.5	1.9	2.3	2.6	3.6	1.7	2.1	2.0	0.3
IN recovered for transplant, discarded	0.3	0.3	0.1	0.1	0.2	0.2	0.5	0.3	0.3	0.2	0.3
IN transplanted	4.2	2.3	2.6	3.5	3.1	3.5	4.2	5.1	4.9	5.7	5.7
Disposition of Intestine (N)											
Consent for IN not requested	2785	219	378	356	422	339	362	289	191	125	104
Consent for IN not obtained	2133	219	283	271	241	249	218	186	194	172	100
IN not recovered	20 483	1281	1842	1862	1997	2009	2100	2263	2359	2393	2377
IN recovered but not for transplant	544	33	39	51	66	71	104	50	63	59	8
IN recovered for transplant, discarded	72	6	3	3	5	6	15	10	10	5	9
IN transplanted	1127	42	68	91	88	96	124	149	146	165	158

Source: SRTR analysis, data as of May 2009.
Notes: selection criteria are delineated in Table 3.

for the years 2004 to 2008. Some of the more common regimens include alemtuzumab, rATG, or daclizumab, combined with tacrolimus. Interestingly, the use of steroids at the time of discharge for the years 2004 to 2008 combined was seen in 75% of the patients, increasing to 83% at 1 year posttranplant [Table 10.6c,g].

Experience is another contributing factor to the early improved outcomes in these highly complex patients. This factor was first identified through the analyses of the Intestinal Transplant Registry, an international dataset that includes nearly all such transplants performed worldwide to date, where centers performing more than 10 intestinal transplants had better patient survival than those performing less than 10 (15). In the United States today, there are five transplant centers that each have performed 100 or more intestinal transplants and have contributed heavily to these results.

Lastly, rejection has been one of the most formidable obstacles to successful intestinal transplantation. These data demonstrate that rates of rejection treated with antirejection medication between 2005 and 2008 have been steady at 30%-40% [Table 10.6i]. In other published literature, the incidence of rejection after intestinal transplantation has decreased from historic levels of 80% or more to current levels of 20%-40%, mainly related to induction immunotherapy. Perhaps even more important is the observation that the severity of rejection has decreased over time, coincident with the use of induction agents (16).

Table 5: Characteristics of actual intestine donors (intestine was transplanted), 1999–2008

	Total	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total donors with intestine transplanted (N)	1347	71	79	112	106	112	144	170	171	197	185
Meets potential intestine donor criteria (N)	1127	42	68	91	88	96	124	149	146	165	158
Criteria implemented in the order listed below (N)											
Age>50 years	10	0	0	3	3	0	1	1	1	1	0
Age<2 and no organs transplanted	6	0	1	0	1	0	1	1	0	1	1
Age≥ 2 and liver not transplanted	14	2	1	0	3	1	3	1	0	0	3
Terminal SGOT/AST > 500 u/L	9	1	0	1	1	0	0	3	2	0	1
Terminal SGPT/ALT > 500 u/L	5	1	1	0	1	1	0	0	0	0	1
Last serum sodium > 170 mEq/L	8	0	0	0	0	0	0	2	4	2	0
Serum creatinine>1 mg/dL, under age 1	30	1	1	1	4	3	4	4	3	4	5
Serum creatinine>2 mg/dL, age 1–50	19	0	0	4	0	2	0	2	4	4	3
HIV or HTLV not confirmed negative	3	0	0	0	1	0	1	0	0	1	0
HBV core antibody not negative	23	5	5	5	1	2	2	1	1	1	0
HBV surface antigen not negative	2	0	0	1	0	0	1	0	0	0	0
HCV antibody not negative	0	0	0	0	0	0	0	0	0	0	0
More than 2 inotropes at cross clamp	23	0	1	3	0	2	1	1	2	9	4
Did not meet cardiac arrest <15 min	68	19	1	3	3	5	6	5	8	9	9
Donation after cardiac death	0	0	0	0	0	0	0	0	0	0	0
Meets potential intestine donor criteria (%)	83.7	59.2	86.1	81.3	83.0	85.7	86.1	87.6	85.4	83.8	85.4

Source: SRTR analysis, data as of May 2009.
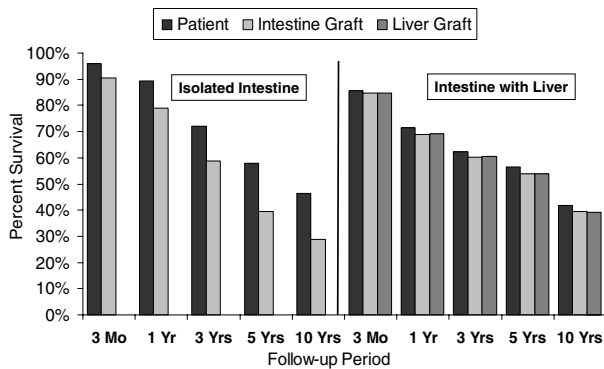
Figure 5: Unadjusted patient and graft survival for isolated intestine and intestine with liver recipients.

Some potentially important evolving advances in the early detection of rejection include monitoring with serum citrulline (16) and stool calprotectin (17).

Unfortunately, while marked advances in short-term survival have been seen, long-term survival still remains low (Figure 5). The 10-year patient survival for isolated intestine and intestine with liver grafts is only 46% and 42%, respectively. Similarly, the intestine graft survival for the same interval is only 29% and 39%, respectively. These outcomes are similar to those seen in lung and heart-lung transplantation (and graft survival for pancreas) but compare unfavorably to kidney, liver and heart transplantation where 10-year patient and graft survivals are typically more than 50%.

The reasons for these results are more difficult to ascertain. Most importantly, these figures are derived from patients transplanted more than 10 years ago and thus in the 1990s and earlier. Most in the field of intestinal transplantation would agree that the era of transplantation is an important determinant of outcome. Therefore, insufficient time has passed to assess long-term outcomes in the current era of transplantation. Of concern in these results is the potential for graft loss due to chronic rejection. In general, chronic rejection is under-diagnosed and reported due to limitations in analysis. There are now more published reports on chronic rejection after intestinal transplantation (18,19) and the definitive incidence remains to be seen.

Late Morbidities After Intestinal Transplantation

Renal function
Short- and long-term renal function after transplantation of extra-renal solid organs has become a topic of concern as transplant recipients live longer. The significance of the

problem was exposed in a study by Ojo and colleagues that examined SRTR data over a 10-year period with a median of 36-months follow-up to determine the incidence of renal failure (20). The risk of chronic renal failure was highest in intestinal transplant recipients at 60 months with an incidence of 21%. Further analysis of intestine transplant recipients receiving their first transplant who had not been on dialysis prior to transplant and did not receive a kidney as part of a multiorgan transplant, between 1999 and 2008, is shown in Table 6. In interpreting these data, one must bear in mind that nearly 60% of the recipients are children and that nonsurvivors are not included. The trend of the overall data is a 50% increase in serum creatinine from discharge to 5-year follow-up.

Two single center studies from the University of Miami examined renal function in pediatric and adult recipients of intestinal transplants (21,22). By 2 years posttransplant, both adults and children experienced a significant decrease in glomerular filtration rate (GFR) which correlated with tacrolimus levels in the first year posttransplant. In perhaps the most detailed report to date, the University of California, Los Angeles examined calculated GFR at multiple time points after intestinal transplant (23) and compared this value to standard, predicted norms. The results indicated that, overall, GFR was 84% of normal after intestinal transplant and that by 5 years posttransplant, this value was 64%. Predictors of renal dysfunction included low pretransplant GFR, ICU-bound prior to transplant and high-dose tacrolimus therapy. An estimated GFR less than 75% of normal was a predictor of poor survival. These studies clearly elucidate the scope and gravity of the problem and that further investigation into preservation of renal function is of paramount importance.

Posttransplant lymphoproliferative disorder
From the earliest reports, posttransplant lymphoproliferative disorder (PTLD) has been a major problem in intestinal transplant recipients, with incidences reported as high as 15%–20% (15,24). Our analysis of patients receiving their first intestine transplant that didn't include a kidney, for the years 1999 to 2008, revealed an unusually low incidence of PTLD after intestinal transplantation, with incidences ranging from 0.6%–1.3%; inaccurate reporting is a likely explanation. In one of the largest single-center series published to date, the University of Miami examined PTLD after 119 pediatric intestinal transplants (25). The overall incidence of PTLD was 11.8% with a median onset 21 months after transplantation. Fifty percent of cases resulted in graft failure or death. The administration of OKT3 was the only risk factor identified. The magnitude of PTLD is significant after intestinal transplantation and warrants further investigation into prevention and treatment.

Nutritional status
There are surprisingly few studies examining nutritional outcomes after intestinal transplantation (26–29). All

Table 6: Serum creatinine at discharge, 6 months, 1, 3 and 5 years following intestine transplant by year of transplant, 1999–2008

	Total	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total deceased donor intestine transplants	1177	57	71	103	91	103	143	150	146	157	156
Discharge*											
Sample size for serum creatinine	1158	57	70	98	88	103	140	149	143	156	154
Mean serum creatinine (mg/dL)	0.65	0.75	0.60	0.66	0.66	0.60	0.62	0.68	0.61	0.71	0.61
Median serum creatinine (mg/dL)	0.50	0.50	0.45	0.60	0.60	0.50	0.50	0.60	0.60	0.60	0.50
Six months posttransplant											
Sample size for mean serum creatinine	762	26	45	72	69	86	109	120	107	128	+
Mean serum creatinine (mg/dL)	0.98	1.31	1.13	1.22	0.94	0.86	0.89	0.98	0.90	0.96	+
Median serum creatinine (mg/dL)	0.70	1.25	1.00	0.85	0.70	0.65	0.80	0.80	0.60	0.60	+
One year posttransplant											
Sample size for mean serum creatinine	720	29	47	64	66	80	107	110	100	117	+
Mean serum creatinine (mg/dL)	0.99	1.04	1.06	1.05	0.95	0.95	0.95	1.07	1.00	0.91	+
Median serum creatinine (mg/dL)	0.70	0.70	0.90	0.80	0.70	0.60	0.70	0.85	0.85	0.60	+
Three years posttransplant											
Sample size for mean serum creatinine	385	21	38	45	49	58	88	86	+	+	+
Mean serum creatinine (mg/dL)	0.94	1.10	1.11	1.00	0.81	0.87	0.97	0.88	+	+	+
Median serum creatinine (mg/dL)	0.70	1.00	0.95	0.60	0.70	0.70	0.80	0.60	+	+	+
Five years posttranplant											
Sample size for mean serum creatinine	172	16	29	39	40	48	+	+	+	+	+
Mean serum creatinine (mg/dL)	0.92	1.09	0.88	1.01	0.88	0.83	+	+	+	+	+
Median serum creatinine (mg/dL)	0.70	0.70	0.80	0.80	0.80	0.50	+	+	+	+	+

Source: SRTR analysis, data as of May 2009.
+ Insufficient follow-up available to present statistics for this year. *Includes recipients that died or had graft failure prior to discharge.
Notes: sample excluded recipients with prior transplants of any organ, those who received a kidney with their intestine transplant and those receiving dialysis treatments prior to transplant.

series report a high rate of enteral nutritional autonomy. Interestingly, while serum nutritional parameters normalized posttransplant, the anthropometric data was mixed. In our analysis of the OPTN/SRTR data, the only available information is the center follow-up report on use of parenteral and enteral feedings. We restricted the population for this analysis to first intestine transplants and excluded recipients who also received kidney grafts or who were on dialysis at transplant. Table 7 shows the percentage of patients reported to require some form of parenteral nutrition at each follow-up interval by year of transplant. At discharge, nearly one-third of patients require PN support. However, by

Table 7: Dependence on parenteral nutrition at discharge, 6 months, 1, 3 and 5 years following intestine transplant by year of transplant, 1999–2008

	Total	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total deceased donor intestine transplants	1177	57	71	103	91	103	1143	150	146	157	156
Discharge											
Total sample size (N)	996	38	54	84	80	91	122	130	124	133	140
Percent using parenteral nutrition (%)	27.6	21.1	20.4	16.7	20.0	26.4	23.8	29.2	31.5	33.8	36.4
Six months posttransplant											
Total sample size (N)	775	27	46	74	72	86	113	122	108	127	+
Percent using parenteral nutrition (%)	13.8	29.6	8.7	12.2	4.2	11.6	13.3	14.8	15.7	18.1	+
One year posttransplant											
Total sample size (N)	723	29	50	65	66	79	108	109	100	117	+
Percent using parenteral nutrition (%)	9.0	13.8	8.0	12.3	1.5	2.5	4.6	16.5	11.0	10.3	+
Three years posttransplant											
Total sample size (N)	402	23	38	50	52	61	91	87	+	+	+
Percent using parenteral nutrition (%)	5.2	4.3	2.6	2.0	1.9	3.3	6.6	10.3	+	+	+
Five years posttranplant											
Total sample size (N)	184	18	33	42	42	49	+	+	+	+	+
Percent using parenteral nutrition (%)	3.8	5.6	12.1	2.4	2.4	0.0	+	+	+	+	+

Source: SRTR analysis, data as of May 2009.
+ Insufficient follow-up available to present statistics for this year.
Notes: sample excluded recipients with prior transplants of any organ, those who received a kidney with their intestine transplant and those receiving dialysis treatments prior to transplant. Parenteral nutrition (PN) status reported only for those alive with a functioning graft at the specified follow-up period.

6–12 months after transplantation, this improves significantly. Indeed, at one year, nearly 90% of intestine recipients are independent of PN support.

Retransplantation outcomes

There have been a limited number of retransplantation procedures involving the intestine; a total of 131 over the ten years of this report (1999 to 2008) [Table 10.4]. In 2008, there were 20 intestine retransplants performed which represented 11% of all intestine transplants. As more experience is gained with primary intestinal transplantation, it is logical that retransplant procedures will also increase. Of the 131 intestine retransplantation recipients, nearly 50% were hospitalized at the time of subsequent transplantation. The primary indications for retransplantation (i.e. the causes of graft failure for the previous transplant) were acute and chronic rejection in 31% and 29%, respectively. While 24% died prior to hospital discharge, 72% were discharged alive with a functioning graft. Of concern, 35% were discharged home with PN support. In unsuccessful cases, graft failure and sepsis were reported as the leading causes of patient death and rejection as the leading cause of graft loss.

The only single-center report focused on intestinal retransplantation is from the University of Pittsburgh and includes 14 patients with a mean follow-up of 56 months (30). Rejection was the most common indication for retransplantation. Excellent patient and graft survival was reported following retransplant (71% and 55%, respectively). As retransplantation of the intestine becomes more common, more analysis is required to determine suitable candidates and improve overall outcomes.

Summary

Intestine transplant candidates have noted substantial improvements in time to transplant and waiting list mortality between 1999 and 2008. Areas for further progress include augmenting donor consent rates and utilization. A modest increase in the current utilization of 2%–3% of organ donors as intestine donors could significantly impact waiting list mortality or eliminate it altogether. Although the number of intestine only registrations is stable, the proportion overall receiving multiple allografts suggests that efforts at earlier referral, consensus on optimal timing for transplantation and continued efforts at intestine rehabilitation are still urgently needed. Short-term results with intestine transplantation have significantly improved over the decade but minimizing graft loss from chronic rejection and optimizing long-term immunosuppression management may improve long-term patient and graft survival. Finally, more data on long-term morbidity, nutritional autonomy and quality of life are needed to better determine the overall benefit that intestine transplantation affords patients.

Acknowledgments

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