

# Small bowel transplantation: Literature review 2003–2005

Botha JF, Horslen SP. Small bowel transplantation: Literature review 2003–2005.

Pediatr Transplantation 2006; 10: 7–16. © 2005 Blackwell Munksgaard

**Abstract:** The rapid expansion of the volume of peer reviewed publications in recent years, including a large increase in the number of new biomedical journals, makes it difficult for the practicing clinician to stay up to date with the medical literature. This review is part of a new series that will provide succinct summaries of the recent medical literature in the field of pediatric transplantation. In this review, we summarize important articles in the field of pediatric intestine transplantation that have been published over the last 2½ years (2003–2005). The review is intended to be comprehensive but not exhaustive.

**Jean F. Botha and Simon P. Horslen**

Division of Surgery, Department of Transplant, University of Nebraska Medical Center, Omaha, NE, USA and Children's Hospital & Regional Medical Center, University of Washington, Seattle, WA, USA

Key words: pediatric intestine transplant – literature review

Simon P. Horslen MB ChB, FRCPC, Children's Hospital & Regional Medical Center, Seattle, WA 98105, USA

Tel.: +1 206 987 2521

Fax: +1 206 987 2721

E-mail: simon.horslen@seattlechildrens.org

Accepted for publication 12 July 2005

## Registry data and large center experience

*Paper 1:* Mortality in candidates waiting for combined liver-intestinal transplants exceeds that for other candidates waiting for liver transplants. Fryer J, Pellar S, Ormond D, Koffron A, Abecassis M. *Liver Transplant* 2003;9:748–753.

The UNOS data set was examined between 1993 and 2001 for waiting list data for potential intestinal transplant candidates, particularly the subset of patient requiring combined liver/intestine transplant. These data were compared to waiting list data on all liver only transplant candidates. The majority of deaths on the intestine waiting list occurred in candidates listed for combined liver/intestine transplant (84%). Only 7% of the intestine waiting list deaths occurred in

the isolated intestine candidates. While there has been a steady decrease in the overall liver waiting list mortality since 1994, the mortality rate in liver/intestine transplant candidates has increased significantly. As the majority of patients on the intestinal list are pediatric, adult and pediatric groups were evaluated separately. In the pediatric group annual wait list mortality rates were significantly higher in the liver/intestine transplant candidates. Mortality rates were further analyzed based on the candidate's age at time of listing, as well as according to final UNOS status. Mortality rates were significantly greater for liver/intestine transplant candidates at all age groups.

*Comment:* Liver/intestine transplant candidates are a unique subset of liver transplant recipients who appear to be at a competitive disadvantage against liver-only candidates. The CPT-based criteria of the UNOS system failed to prioritize liver/intestine transplant candidates. The MELD/PELD system does not incorporate criteria that recognize the unique risk factor in these patients. The changes in the MELD/PELD that provides for an additional 10% per day mortality risk is an important step in the right direction; however, it is likely that additional measures will be required to address this problem.

Abbreviations: BAL, bronchoalveolar lavage; CHQ, Child Health Questionnaire; CMV, cytomegalovirus; CTP, Childs-Turcotte-Pugh score; EBV, Epstein-Barr virus; GrB, granzyme B; GVHD, graft vs. host disease; IgE, immunoglobulin E; ITR, Intestinal Transplant Registry; KM, Kaplan-Meier; MELD/PELD, model for end-stage liver disease/pediatric end-stage liver disease; MMF, mycophenolate mofetil; MVID, microvillous inclusion disease; PTLN, post-transplant lymphoproliferative disease; rATG, rabbit antithymocyte globulin; SMA, superior mesenteric artery; TPN, total parenteral nutrition; UCLA, University of California Los Angeles; UNOS, United Network for Organ Sharing.

## Botha and Horslen

*Paper 2:* 2003 Report of the Intestine Transplant Registry: A new era has dawned. Grant D, Abu-Elmagd K, Reyes J, Tzakis A, Langnas A, Fishbein T, Goulet O, Farmer D, on behalf of the Intestine Transplant Registry. *Ann Surg* 2005;241:607–613.

The ITR maintained by Dr Grant in Toronto reports collecting data on 100% of intestinal transplants worldwide between April 1985 and May 2003. This amounts to 989 transplants in 923 patients with only four patients lost to follow-up. Sixty-one programs from all around the world have contributed data, but only 28 centers actually carried out intestinal transplants during the final 2 yr and 83% of intestinal transplants had been conducted in the 10 most active programs. The total number of cases has increased from 11 in 1990 to 140 in 2002. Just over 75% were carried out in the USA, 19% in Europe, 1.4% in Asia and 4% in Canada, South America and the Middle East combined. Short bowel syndrome is the most common indication that etiology differs from pediatric and adult patients. Sixty-one percent of the database were transplanted at or below 18 yr of age. Isolated intestinal transplants were more common in adults, 55% vs. 37% in children. Thirty-two living donor transplants have been carried out, including one identical twin and one triplet. Allograft and patient survival shows steadily improving results. Of recipients surviving more than 6 months, 81% are free of parental nutrition. An analysis of factors influencing survival in patients transplanted since the last ITR results were analyzed in 1998 was conducted. One-year graft and patient survival was 65% and 77%, respectively in those receiving isolated intestinal transplantation, 59% and 60% for combined liver small bowel transplantation and 61% and 66% for those with multivisceral transplantation. There was a notable shift to transplant more patients waiting at home. Prior to 2001, 52% of patients were waiting at home immediately prior to transplantation whereas in final 3 yr, 71% of patients were in this category. Median hospital stay was 42 days for intestinal transplantation alone and 51 days for both liver and small bowel and multivisceral transplant recipients. Factors not associated with patient or graft survival include primary diagnosis, donor type, transplant type, graft irradiation and maintenance immunosuppression. Significant factors associated with graft survival were home vs. hospital at the time of transplantation, induction antibody therapy (against IL-2R or T/B lymphocytes). Factors associated with improved patient survival were home vs. hospital, antibody induction, center size (the cut-off being those who have

performed > 10 transplants in total) and age of recipients.

*Comment:* With 100% participation and a relatively large number of patients, it provides an opportunity to examine factors affecting survival. Limitations in this database method were discussed and give insight into issues, not captured by the database, that have probable importance to the evolution of the field. This is a must read document that underlines the improving outcomes in what remains a very complex and difficult medical endeavor.

*Paper 3:* Evolutionary experience with immunosuppression in pediatric intestinal transplantation. Bond GJ, Mazariegos GV, Sindhi R, Abu-Elmagd KM, Reyes J. *J Pediatr Surg* 2005;40: 274–280.

The paper documents the evolution of immunosuppression in the Pittsburgh program. One hundred and twenty-two children received 129 intestinal transplants from July 1990 to December 2003. Immunosuppressive protocols were divided into three categories: (i) tacrolimus and steroids (n = 52, 1990–1995, 1997–1998), (ii) tacrolimus, steroids and induction therapy with either cyclophosphamide (n = 16, 1995–1997) or daclizumab (n = 24, 1998–2001) and (iii) induction with rATG and tacrolimus alone (n = 37, 2002–2003). Overall KM graft and patient actuarial survival was 76% and 81% at 1 yr, 60% and 62% at 3 yr and 51% and 61% at 5 yr, respectively. One-year graft/patient survival by groups was: (i) 62%/71%, (ii) 75%/77% and (iii) 100%/100%. Rejection rate in the first 90 days was 78% for group 1, 81% for group 2 patients with cyclophosphamide induction and 75% of group 2 receiving daclizumab and 49% for group 3. Of those experiencing acute rejection, severe acute rejection occurred in 38%, 54% and 27% of groups 1, 2 and 3, respectively. Chronic rejection rates were 8% and 13% in groups 1 and 2, with cases so far diagnosed in group 3. Maintenance immunosuppression in those patients with a functioning allograft in groups 1 and 2 (36 of 92) was tacrolimus twice a day with daily steroids. A third agent had been added in 37% of these patients. In group 3, 35 of 37 were alive. Eighteen patients were on tacrolimus only, two on sirolimus only, one patient with once daily tacrolimus and once daily sirolimus. Daily corticosteroids were being administered to 13 patients, four of whom were receiving once daily tacrolimus doses and nine were on twice daily tacrolimus. One patient was on tacrolimus and azathioprine. Bone marrow augmentation did not improve survival rejection

rates. In considering opportunistic infections, CMV rates ranged from 23% in group 1, 56% in group 2 with cyclophosphamide induction, 4% in group 2 with daclizumab induction and 11% in the most recent cohort. PTLD rates fell from 42% in group 1 to 18% in group 2 and 3% in group 3. GVHD occurred in 12%, 4% and 8% of the three groups, respectively. The discussion in the papers focused on the rationale for immunosuppressive reduction as a means of avoiding long-term complications and the hope of allowing tolerance to occur with steroid avoidance.

*Comment:* The experience of this pioneering program demonstrates improved survival outcomes with the evolution of their immunosuppression protocols. The most recent protocol with rATG induction and tacrolimus alone is encouraging at least in terms of 1-yr survival and it will be of interest to see if this also translates into longer term improved outcomes. They have shown that limiting immunosuppression is possible in intestinal transplant recipients and that steroid avoidance is possible for some patients.

*Paper 4:* Intestinal transplantation in children: A summary of clinical outcomes and prognostic factors in 108 patients from a single center. Kato T, Gaynor JJ, Selvaggi G, Mittal N, Thompson J, McLaughlin GE, Nishida S, Moon J, Levi D, Madariaga J, Ruiz P, Tzakis. *J Gastrointest Surg* 2005;9:75–89.

This paper describes the complete experience with pediatric intestinal transplantation from the Miami group from August 1994 until April 2004. One hundred and twenty-four intestine transplants were carried out in 108 children. The group was divided into time periods: (i) early experience from 1994 to 1997. Immunosuppressive regimes during this period included OKT3 induction with maintenance tacrolimus and corticosteroids (n = 4), cyclophosphamide induction then tacrolimus and steroids (n = 3) and no induction with triple maintenance tacrolimus, MMF and steroids (n = 18). (ii) The early daclizumab experience from 1998 to 2000. Twenty-six patients received daclizumab induction with maintenance immunosuppression of tacrolimus and corticosteroids. (iii) The later daclizumab experience dated from 2001 to April 2004. Forty patients received daclizumab, tacrolimus and steroids. (iv) During the same period the fourth group was composed of 17 patients who received Campath-1H induction, followed by maintenance of tacrolimus alone in a steroid free immunosuppressive protocol. The range of etiology for the intestinal failure was consistent with other published series and the ITR with the majority transplanted for short bowel syndrome.

Multiple graft types were employed including isolating intestine, combined liver and small bowel with or without whole pancreas, multivisceral included stomach and modified multivisceral, which included stomach but excluded liver. Spleen was included in 23 cases, all of which were multivisceral or modified multivisceral allografts. Colon was included in 19 patients with a variety of other organ allograft types. Median age at transplant was 1.5 yr (range of 6 months to 17 yr). Median weight of the recipients was 10 kg (range 4.5–67 kg). The vast majority (97%) received ABO identical allografts and three received ABO compatible grafts. Liver graft reduction occurred in 17 cases. Primary abdominal closure occurred in almost 50% of cases. The results primarily focused on the incidence of rejection and infection and survival outcomes. Severe rejection was significantly less likely to occur in the multivisceral and modified multivisceral transplants compared to either the isolated intestinal transplants or the combined liver and small bowel grafts. There was no difference in rejection rates between these latter two groups. Actuarial patient survival was 59%, 52% and 41%, 1, 2 and 5 yr, respectively, for the group as a whole. The best 1-yr survival year were seen in the most recent cohort patients who receive the daclizumab induction protocol with 83% patient survival compared to 44% in the early experience, 54% in the first period of daclizumab use until 2000 and 41% with the Campath-1H induction protocol. Predictors of a favorable outcome in a Cox regression model included multivisceral or modified multivisceral graft, age at transplant, age > 1 yr and daclizumab induction. Deaths (n = 55) were divided according to the triggering event leading to death with 19 attributed to rejection, 19 to infection and 17 due to other complications. The hazard rate of death due to rejection was significantly lower for those receiving multivisceral and modified multivisceral grafts and for those receiving induction therapies of any type. The risk of death from infection related to younger age < 1 yr and to transplant prior to 2001. The risk of death from other causes was significantly associated with patients having not received daclizumab induction.

*Comment:* This is a comprehensive report of the experience and evolution of pediatric intestinal transplantation as conducted by one of the most experienced programs in the world. Interestingly, one conclusion was that it is not the liver that offers survival benefit to the allograft because the multivisceral and modified multivis-

ceral grafts had better outcomes than either the intestinal group alone or the liver/small bowel group. This has not generally been the experience of other groups and further analysis of this phenomenon is awaited.

**Case series and outcomes**

*Paper 5:* Isolated intestinal transplantation: Proof of clinical efficacy. Fishbein TEM, Kaufman SS, Florman SS, Gondolesi GE, Schiano T, Kim-Schluger L, Magid M, Harpaz N, Tschernia A, Leibowitz A, LeLeiko NS. *Transplantation* 2003;76:636–640.

This paper documents the Mount Sinai School of Medicine experience with isolated intestinal transplantation. Twenty patients underwent 28 isolated intestinal transplants. All transplants were performed with ABO matched organs into recipients who were all T and B cell compatible by lymphocytotoxic cross-match. Immunosuppression was initially based on tacrolimus, OKT3 and anti IL-2 induction and tapering steroids. Later sirolimus was added to the regimes and OKT3 no longer used. Target trough levels for tacrolimus and sirolimus are provided. Primary end-points were patient and graft survival, freedom from parenteral support and regression of liver disease. Patient and graft survival at 3 yr was 88% and 71%, respectively. All but one of the survivors are at home and free of any parenteral support. The addition of sirolimus has decreased the incidence of early rejection (<30 days) from 74% to 30%, graft survival, however, was not affected by the addition of sirolimus. Four recipients had ‘progressive liver dysfunction’, all of which resolved after isolated intestinal transplant.

*Comment:* This experience demonstrates the improved survival now attainable with isolated small bowel transplantation. While the addition of sirolimus has decreased the incidence of early rejection, there appears to be no impact on survival. The point at which liver disease becomes irreversible is very difficult to answer; unfortunately no information is given on the four patients with liver disease in terms of how many had bridging fibrosis pretransplant or how severe the fibrosis was.

*Paper 6:* Improved quality of life by combined transplantation in Hirschsprung’s disease with a very long aganglionic segment. Yann R, Yves A, Dominique J, Thierry Y, Olivier G, Florence L. *J Pediatr Surg* 2003;38:422–424.

This is a report of three patients with very long segment Hirschsprung’s disease. The goal was to assess the quality of life after liver/small bowel and right colon transplant and some form of

pull-through procedure after transplantation. All three patients underwent combined liver/small bowel and right colon transplant. The first patient underwent a Swenson procedure 4 months after transplant and the remaining two patients underwent a Duhamel procedure 1 yr and 8 months after transplant, respectively. All three patients had covering loop ileostomies closed soon after the pull-through operation. All three patients are alive and have been weaned from nutritional assistance, having 1–4 bowel movements per day. All patients are continent during the day with one patient using diapers at night.

*Comment:* This report demonstrates the feasibility of combining the right colon with an intestinal allograft and then using the colonic segment to perform a pull-through procedure and restore continence in children with near total intestinal aganglionosis.

*Paper 7:* New perspectives for children with microvillus inclusion disease: Early small bowel transplantation. Ruemmele FM, Jan D, Lacaille F, Cezard J-P, Canioni D, Phillips AD, Peuchmaur M, Aigrain Y, Brousse N, Schmitz J, Revillon Y, Goulet O. *Transplantation* 2004;77:1024–1028.

This paper documents the Paris group’s experience with small bowel transplantation for children with MVID. Twelve children were evaluated, of which seven underwent either isolated small bowel transplant (three) or combined liver/small bowel transplant (four). Of note, five patients received a concomitant right colon as part of the graft. Overall survival was excellent with 86% actuarial patient and graft survival at 3 yr (one patient died in the operating room at the time of transplant). When compared to the five patients who were not transplanted, the outcome was dramatically better with transplantation. Nutritional recovery was also very good, with all six survivors weaned from parenteral nutrition, although not supported by any data, the authors state that subnormal to normal growth velocity has been achieved at 6 months post-transplant. The two patients not receiving colon grafts took longer to be weaned from PN (270 and 1000 days); the first patient requiring total colectomy before being able to be weaned, leading this group to recommend associated colonic grafting in children being transplanted for MVID, also suggesting that this should be employed in patients with other epithelial cell disorders (tufting enteropathy).

*Comment:* This experience demonstrates the survival advantage for intestinal transplantation in patients with MVID. While the authors make

an argument for adding a segment of colon to the graft, we do not have a similar experience with ongoing diarrhea, necessitating total colectomy.

*Paper 8:* Quality of life after pediatric intestinal transplantation: The perception of pediatric recipients and their parents. Sudan D, Horslen S, Botha J, Grant W, Torres C, Shaw B Jr, Langnas A. *Am J Transplant* 2004;4:407–413.

Quality of life was examined in pediatric patients surviving with intact intestine allograft function more than 1 yr after transplantation in patients aged 5 and 18 yr. The study was based on a postal survey using the CHQ, a standardized and validated tool specifically developed to assess physical and psychosocial function of children and assesses 14 health-related domains. Twenty-nine patients fulfilled the inclusion criteria and were asked to complete form CF87 of the CHQ and, at the same time, the parental proxy form PF50 was completed by a parent. Twenty-two families, 76% of group, responded with completed forms. Demographic factors of families that did not respond were compared to those completing the questionnaire. All factors were similar except that six of seven were male whereas among the respondents males accounted for nine of 22 patients ( $p = 0.037$ ). In all domains, pediatric intestine transplant recipients reported no significant difference in any of the domains compared to norms established in a cohort of healthy US school children. However, parental proxy responses showed parents of intestine recipients perceived significantly lower function in six of 14 domains, i.e. physical function, role limitation due to physical problems, general health perception, negative impact in terms of emotion and time and a negative effect on family activities. Parents reported no significant difference in child's level of bodily pain, general behavior, mental health, self-esteem or family cohesion compared with the sample norms. Overall, parental assessments were lower than the patient's own perception of health and function. Comparisons were also made to other cohorts that have been published using the CHQ and included children with chronic renal disease on dialysis and parental proxy responses from parents of liver transplant recipients and a Danish cohort of parents of children with diabetes. The paper has a detailed discussion of the limitations and possible biases of this study and acknowledges that this only examines the quality of life that the patients with the best outcome from intestinal trans-

plant, i.e. those with significant length of survival and intact allograft function.

*Comment:* Within the limitations of this study, this paper demonstrates that a good quality of life after intestinal transplantation is achievable for pediatric patients. As long-term survival improves intestinal transplant recipients, quality life issues have moved to the fore in line with the trend in other solid organ transplant groups such as liver, kidney and heart.

#### Pathology and laboratory studies

*Paper 9:* A schema for histologic grading of small intestine allograft acute rejection. Wu T, Abu-Elmagd K, Bond G, Nalesnik MA, Randhawa P, Demetris AJ. *Transplantation* 2003;75:1241–1248.

This paper describes a standard histological grading system for the diagnosis of intestinal allograft acute rejection from the transplant program at the University of Pittsburgh. Between 1990 and 1999, 52 adult patients underwent 55 intestinal transplant procedures from which over 3000 small bowel allograft biopsies were available for evaluation. Biopsy sections were stained with hematoxylin–eosin and several levels were routinely examined. Each specimen was characterized based on architecture, crypt injury, inflammation, fibrosis, granulation tissue and exudate, as well as evidence of viral infection, luminal organisms and submucosal abnormalities. Apoptotic bodies were identified and quantified. All biopsies were reviewed twice or more by at least two pathologists. The grading system recognized the following five categories: no rejection, indeterminate for acute rejection, mild, moderate and severe rejection. The grading system was then evaluated for inter- and intra-operator reliability. Correlation with clinical outcomes and treatment was assessed by selecting 65 post-transplant small bowel biopsy specimens at random that had been reviewed in a blinded manner by four pathologists, using the agreed histological grading criteria. All four cases of severe rejection based on histological criteria were associated with an unfavorable outcome, either graft loss or patient death. Of 14 episodes of moderate acute rejection, two episodes required OKT3 treatment. Two episodes were prolonged beyond 21 days of immunosuppressive therapy and one allograft was removed for chronic rejection prior to the resolution acute rejection. The remaining nine episodes of moderate acute rejection responded to treatment. Unfavorable outcomes were much less apparent in those diagnosed with mild or lesser

degrees of acute rejection. In terms of reliability of grading, a consensus diagnosis was reached by all participating pathologists in 60 of 65 cases, the five cases without a consensus were differentiating between mild or indeterminate for acute rejection, or indeterminate for acute rejection or no rejection. All cases of severe or moderate acute rejection achieved unanimous diagnosis. Good intra-observer agreement was also noted when slides were reviewed in a blinded manner by the same pathologists on two separate occasions with intervals of approximately 6 months.

*Comment:* This histological grading system has evolved in and is used in a very similar manner by, most of the major intestinal transplant programs and is applicable to both adult and pediatric patients. This paper clearly demonstrates the utility of the grading system and its ability to predict unfavorable outcomes in those with more severe grades of acute intestinal rejection.

*Paper 10:* Chronic rejection of small bowel grafts: Pediatric and adult study of risk factors and morphologic progression. Parizhskaya M, Redondo C, Demetris A, Jaffe R, Reyes J, Ruppert K, Martin L, Abu-Elmagd K. *Pediatr Dev Pathol* 2003;6:240–250.

Careful study was made of all patients identified with chronic rejection of intestinal allografts at the Pittsburgh programs up to August 2001. Thirty-four patients had partial or complete resection of their intestinal allograft and 15 of these patients showed histological features of chronic rejection in the resected small bowel. Twelve received isolated small bowel graft with inclusion of donor colon in two. The remaining received composite liver and small bowel allograft. Immunosuppression depended on the year of transplant; the evolution of the immunosuppressive protocols in Pittsburgh has been documented elsewhere. The study population was defined on the criteria of chronic vasculopathy in the mesenteric vessels of the resected graft. All prior mucosal biopsies were then identified and reviewed in an attempt to identify features of early chronic rejection. The recipients who developed chronic rejection tended to be older; 67% were between 16 and 39 yr, whereas only 25% without chronic rejection were in this age group. Donor age and gender of recipient did not seem to be associated with outcome; however, chronic rejection was more likely to appear in non-Caucasian recipients. Recipients of combined small bowel and liver allografts experienced significantly less chronic rejection than those recipients of an isolated small bowel graft.

The occurrence of early acute rejection within 30 days of transplantation and a higher total number of acute rejection episodes were associated with a greater risk of progression to chronic rejection. Sixty percent of patients who had severe acute rejection developed chronic rejection. The time to diagnosis of chronic rejection ranged from 69 to almost 3000 days post-transplantation. The early histopathological findings of chronic rejection tended to be non-specific, but may include patchy, mild fibrosis of the lamina propria, focal loss of crypts. Granulation-type stroma could be seen separating the deep portions of the crypts from the muscularis mucosae. Late changes on mucosal biopsy may include loss of villous architecture, chronic ulcers with exudates and granulation tissue, wide-spread loss of crypts with pyloric glands metaplasia and regenerative changes in remaining crypts. On resection specimens and full thickness biopsies the primary focus is on changes within large and medium-sized arteries of the submucosa, subserosa and mesentery immediately adjacent to the bowel. Arterial changes could not be evaluated in endoscopic biopsies because of the presence of minimal submucosa. Outcomes for patients diagnosed with chronic rejection are uniformly poor; 10 of 15 subsequently died and all remaining patients are TPN dependent.

*Comment:* This is the most detailed analysis of chronic rejection in small bowel allografts and although a descriptive and correlative study, provides important information for an important causes of late graft loss.

*Paper 11:* Granzyme B and perforin as predictive markers for acute rejection in human intestinal transplantation. D'Errico A, Corti B, Pinna AD, Altamari A, Gruppioni E, Gabusi E, Fiorentino M, Bagni A, Grigioni WF. *Transplant Proc* 2003;35:3061–3065.

In the presence of the granule pore-forming protein, perforin, GrB is one of the molecular mediators of apoptosis by cytotoxic T-lymphocytes and NK cells. The aim of this study was to determine whether the expression for GrB or perforin correlated with the appearance of histologically determined acute allograft rejection. Thirteen patients transplanted with an intestine either alone or in combination with other abdominal organs was undertaken in two centers in Italy in 2002 and 2003. Immunohistochemical staining for GrB and perforin, as well as for other lymphocyte markers, was performed on the leukocyte populations identified in mucosal allograft biopsies, taken to evaluate the possibility of rejection. A grading system was established depending upon the expression of GrB and

perforin in the lymphocytes. Grade 0 was assigned to mucosal biopsies with less than 10% positive lymphocytes, Grade 1 for samples with 10–25% positive lymphocytes, Grade 2 for samples showing 25–50% positive and Grade 3 for samples showing more than 50% positivity. This scoring system was then correlated with histological finds. There was a highly significant correlation between GrB and perforin scores with the histological severity of rejection. All patients with severe acute rejection and eight of 10 with moderate acute rejection had GrB/perforin expression Grade 3 and the remaining two with moderate rejection had Grade 2. However, those with mild acute rejection ranged between grading scores of 1, 2 and 3. Those samples that were histologically negative or indeterminate for rejection all showed Grade 0 GrB/perforin expression scores with the exception of those taken from one patient who subsequently developed severe acute rejection.

*Comment:* An interesting study although published in a non-peer reviewed journal. Parameters, other than histological, by which to assess acute rejection, particularly when the need to differentiate rejection from the effects of viral infection is in question, have been long sought. It is to be hoped that utility of GrB and perforin expression will be evaluated in this context.

### Surgical modifications

*Paper 12:* Living related small bowel transplantation donor surgical technique. Testa G, Panaro F, Schena S, Holterman M, Abcarian H, Benedetti E. *Ann Surg* 2004;240:779–784.

This is a technical paper describing the perioperative management of living small bowel donors. Over a 5-yr period, nine adults underwent resection of 150–200 cm of distal ileum for the purpose of small bowel donation. The authors describe in detail the donor selection, vascular anatomy and surgical technique. Briefly, 150–200 cm of ileum, 20 cm proximal to the ileocecal valve is used. The vascular pedicle is based on the terminal branch of the SMA, just distal to the take off of the ileocolic artery. This preserves all the vascular supply to the remaining jejunum and proximal ileum. There was no mortality or significant morbidity, no significant weight loss or increase in the number of bowel movements. No donor developed macrocystic anemia.

*Comment:* While the authors demonstrate the feasibility of live donor small bowel transplantation as a realistic solution for patients with irreversible intestinal failure, they quote wait list mortality figures up to 60% in these patients. In reality, however, the patients that die on the wait

list are young children with associated liver disease. Isolated bowel transplant from a live donor is unlikely, therefore, to have a major impact on reducing wait list mortality.

*Paper 13:* Non-composite simultaneous liver and intestinal transplantation. Fishbein T, Florman S, Gondolesi G, Decker R. *Transplantation* 2003;75:564–565.

This is a case report describing the rationale and technical details of non-composite simultaneous liver and small bowel transplantation. The usual technique of combined liver and small bowel transplantation involves inclusion of the donor duodenum and head of pancreas (or whole pancreas) with the liver and intestine as first described by the Omaha group. This technique obviates the need for hepatic artery and bile duct anastomoses, which in very small patients is associated with complications. Fishbein et al. proposes this modification because there are limited options for removal of the intestine alone when severe exfoliation rejection occurs as the combined organ bloc shares its vascular supply.

*Comment:* This technique is not suitable for pediatric liver and small bowel recipients because of the need to anastomose very small hilar structures. As for adult recipients, exfoliative rejection is rarely seen in liver/small bowel recipients and it may be that the potential benefits of this procedure may not justify the additional risks.

*Paper 14:* Transplantation of the abdominal wall. Levi DM, Tzakis AG, Kato T, Madariaga J, Mittal NK, Nery J, Nishida S, Ruiz P. *Lancet* 2003;361:2173–2176.

This paper describes the novel technique of transplanting the anterior abdominal wall associated with either an isolated intestinal or multivisceral organ transplant. The abdominal wall graft is a full thickness myocutaneous free flap consisting of one or both rectus abdominis muscles, the investing fascia and overlying skin and subcutaneous tissue. Vascular supply is based on the inferior epigastric vessels left in continuity with the femoral and iliac vessels. The technical details of procurement and transplantation are detailed in the paper. Eight recipients of either isolated intestinal or multivisceral grafts underwent either simultaneous or staged abdominal wall transplantation. Six patients are alive, five with viable abdominal wall grafts. Two grafts were lost to infarction, the remaining patient died with a functional abdominal wall graft. Of the five surviving grafts, two have experienced rejection of the skin without concomitant rejection of the intestinal graft. Two

further patients had rejection of their bowel grafts, but not the abdominal wall grafts.

*Comment:* Most patients with short bowel syndrome who are listed for intestinal transplantation have shrunken peritoneal cavities due to complete resection of the mid gut associated with severe scarring of the abdominal wall from multiple previous laparotomies, ostomies, infectious and enterocutaneous fistula. While abdominal wall transplantation is a novel technique to overcome the challenges that some of these patients pose in terms of getting suitable abdominal wall closure, its true utility is really unknown. The question is whether or not this allows the use of larger donors thereby increasing the donor pool for these recipients and how this would differ from simple reduction of the graft.

### **Post-transplant complications**

*Paper 15:* Infectious enteritis after intestinal transplantation: Incidence, timing and outcome. Ziring D, Tran R, Edelstein S, McDiarmid SV, Gajjar N, Cortina G, Vargas J, Renz JF, Cherry JD, Krogstad P, Miller M, Busuttill RW, Farmer DG. *Transplantation* 2005;79:702–709.

The UCLA group reviewed their experience with intestine transplantation between 1991 and 2003 looking for cases of infectious enteritis and attempted to characterize these cases. During the study period 33 patients underwent 37 intestine transplants, 13 of whom developed evidence of infectious enteritis. These cases became the subjects of the analysis. In all, there were 20 episodes of infectious enteritis in the 13 recipients. Perioperative broad spectrum antibiotics were administered for 2–3 days after intestine transplantation and subsequently only as dictated by clinical condition. Immunosuppression consisted of triple maintenance therapy with tacrolimus MMF and corticosteroids. Induction in the first four patients utilized OKT3 and subsequently IL-2 receptor antagonists dactilizumab or basiliximab. The antiviral prophylactic protocol employed has been previously documented by this group and consisted of 100 days of IV ganciclovir followed by an indefinite period of oral acyclovir. Evaluation for infectious disease was based on changes in clinical signs and symptoms. Routine cultures were not generally used. The episodes of infectious enteritis occurred at a median of 76 days from the date of transplantation with very large range. Interestingly, 33% enteritis episodes were associated with acute rejection with a median time from enteritis to rejection of 36 days (range 0–52 days). Viral enteritis was diagnosed on 14 occasions in 12 patients with rotavirus account-

ing for eight infections, five in children, adenovirus in four pediatric patients and CMV and EBV in one case each. It was noted that prolonged viral carriage, for up to 6 wk, could occur with rotavirus enteritis. Adenoviral cases had histological changes that resembled acute rejection and, in fact, one allograft was removed for what was believed to be a refractory case of acute rejection. Subsequent cultures and immunohistochemical studies indicated adenoviral enteritis. The remaining cases of infectious enteritis included three cases of parasitic enteritis with *Giardia* and two with *Cryptosporidium* and three episodes of *Clostridium difficile* in two patients. It was demonstrated that infectious enteritis was more likely to occur in pediatric recipients of intestinal allografts and curiously 77% of cases occurred in males.

*Comment:* This paper discusses the importance of diagnosing infectious enteritis in bowel transplant recipients and differentiating it from acute rejection. The authors suggest an increased risk of infectious enteritis in intestinal patients compared with recipients of other solid organ donor transplants. Treatment of enteritis usually involves limitation of immunosuppression whereas treatment of acute rejection necessitates increased immunosuppressive medication. Misdiagnosis and treatment in either direction places the allograft and the patient at significant risk.

*Paper 16:* Adenovirus infection in pediatric small bowel transplantation recipients. Pinchoff RJ, Kaufman SS, Magid MS, Erdman DD, Gondolesi GE, Mendelson MH, Tane K, Jenkins SG, Fishbein TM, Herold BC. *Transplantation* 2003;76:183–189.

A retrospect review of adenoviral infection in 22 children who underwent intestine transplantation at Mount Sinai Hospital, NY, from 1999 to 2001. Fourteen patients had viral cultures obtained looking for adenovirus infection and all 14 demonstrated evidence of adenovirus. Twelve had at least one positive intestinal adenoviral culture. One had histological evidence of adenoviral disease confirmed on electron microscopy, but viral cultures remain negative and one patient had adenovirus cultured from liver biopsy, but not from intestinal biopsy specimens. Six of 14 patients had adenovirus identified in samples other than intestinal biopsies including urine, BAL, liver, upper airways and bone marrow. Histological evidence of viral enteritis was seen in eight patients. Correlation was made between other infections and presence of adenovirus, as well as the occurrence of rejection and immunosuppressive levels in these patients. The

patients with positive histology were defined as having invasive adenoviral diseases as opposed to just adenoviral infection in those with negative histology. Risk factors were analyzed for the development of invasive disease and associations were found with duration of positive cultures, virus isolated from multiple sites and the cumulative dose of steroids in the 10 days prior to positive cultures. Four of 14 patients died, three had adenoviral disease and one had infection only. Adenoviral disease was thought to be directly related to the death in two patients, the other two died, sometime after clearance of adenovirus, from other causes. Four of five survivors with histological proven adenoviral enteritis developed features of rejection concurrent with, or subsequent to, the adenoviral infection. Potential opportunities for nosocomial transmission were identified in three of 10 patients.

*Comment:* Adenovirus is increasingly recognized as a serious pathogen in intestinal transplant patients. The differentiation between enteritis and rejection can be difficult, but is of utmost importance. This paper points out the importance of specifically looking for evidence of adenoviral infection in a systematic manner.

*Paper 17:* Graft versus host disease in intestinal transplantation. Mazariegos GV, Abu-Elmagd K, Jaffe R, Bond G, Sindhi R, Martin L, Macedo C, Peters J, Girnita A, Reyes J. *Am J Transplant* 2004;4:1459–1465.

All 250 intestinal transplant recipients at the University of Pittsburgh School of Medicine and the Children's Hospital of Pittsburgh up to December 2003 were retrospectively reviewed for GVHD. Twenty-three patients (six adults, 17 children) were identified as having clinical signs suggestive of GVHD. Median time from transplant to presentation of GVHD features was 1.2 months (range of 2–96 months). Three patients presented with GVHD symptoms about a week after graft enterectomy and cessation of immunosuppression. Clinical signs included skin rash in 17, oral mucosal ulceration in two, diarrhea in three, lymphadenopathy in one and native liver dysfunction in one. More than one clinical feature is present in four patients. No risk factor achieved clear statistical significance, but four factors may be suggestive with p-values of 0.1 or less. These included isolated intestine transplantation, splenectomy, a positive cross-match and allograft irradiation. Fourteen of 23 cases had histological support for the diagnosis of GVHD and were discussed under heading of confirmed cases. Donor-cell chimerism was gen-

erally increased in this population. The histological findings in the confirmed cases included basal vacuolation and keratinocyte necrosis in nine, crypt cell apoptosis and epithelial cell necrosis of oral mucosa in one. Two of the 14 patients with confirmed GVHD died. One infant with an immune deficiency disorder and another in an adult with disseminated lymphoma. All remaining cases of confirmed and suspected GVHD resolved, four spontaneously and the others with steroid therapy.

*Comment:* Early animal studies into intestinal transplantation raised the fears the GVHD might become a major clinical issue. As it has turned out, this has not been the case, however, this paper shows the incidence of GVHD in the largest cohort of intestine recipients so far reported of less than 10% and that the condition, on the whole, responds to therapy.

*Paper 18 :* Sclerosing peritonitis after intestinal transplantation in children. Macedo C, Sindhi R, Mazariegos GC, Abu-Elmagd K, Bond GJ, Reyes J. *Pediatr Transplant* 2005;9:187–191.

This paper describes three children with long-term graft dysfunction and/or graft loss after isolated intestinal or combined liver small bowel transplantation. Each patient had two episodes of acute rejection, which happened at least 2 yr prior to the diagnosis of sclerosing peritonitis. No factors were identified that differentiated these three patients from other long-term survivors. All presented with vomiting and intermittent abdominal pain. On barium enema all showed an abrupt cut-off between native colon and the allograft ileum. At laparotomy, all had serositis with dense fibrous adhesions and contraction of the mesentery. No evidence of inflammation or fibrosis of the native bowel was found. Surgical resection was undertaken, but only one patient survived long-term. Histology of resection specimens show diffused lymphoplasmacytic infiltration with minimal mucosal inflammation and no significant apoptotic activity and no evidence of infection. Chronic inflammation was present, characterized by giant cells originating from macrophages, histiocytes and granulation tissue. Edema of small bowel loops between strictures was also noted. In one patient there was evidence vasculopathy, with medial hypertrophy and intimal fibrosis, consistent with chronic allograft rejection. Other causes of sclerosing peritonitis were discussed, but an immunological mechanism related to the allograft was proposed given the absence of the infection and the sparing of the native bowel. Although chronic rejection could

## Botha and Horslen

not be confirmed in two cases, the precise mechanism remains unclear.

*Comment:* This condition has been seen by other programs. The frequency of occurrence and the mechanisms of injury need to be elucidated because resection is frequently not a long-term solution and outcomes have generally been poor.

*Paper 19 : De novo food allergy after intestinal transplantation: A report of three cases. Chehade M, Nowak-Wegrzyn A, Kaufman SS, Fishbein TM, Tschernia A, Leleiko NS. J Pediatr Gastroenterol Nutr 2004;38:545–547.*

Three patients developing food allergy following intestinal transplantation were described. Although *de novo* allergic reactions following transplantation procedures have been previously described in liver and bone marrow transplantation, this is the first report in intestine recipients. The three patients developed allergy to peanuts in the first, multiple food (including clam, egg and pork) in second and third had severe reactions to milk and eggs. All three had evidence

of immediate IgE antibody-mediated symptoms and two had allergy work-up included skin testing and measurement of food-specific IgE antibodies. The authors expressed the opinion that these allergies were in some way a result of transplantation and discussed theories that have been proposed for the development of atopic responses in transplant recipients. This includes alterations in T-helper lymphocyte responses to immunosuppressive medications and a theory of transfer of atopy by the presence of donor–recipient chimerism. A final theory was proposed related more specifically to intestine transplantation; the allograft may have increased mucosal permeability to potential allergenic food proteins, thus increasing the antigenic exposure and likelihood of an IgE-mediated response evolving.

*Comment:* It will need larger cohort data to establish the true incidence of acquired allergy following transplantation and whether there is greater risk in intestinal transplant patients than recipients of other types of transplants.