3. Pediatric transplantation

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3.1 Pediatric transplantation overview

  • Review of pediatric transplant history, rejection, and immunosuppression.

  • Review of infections and antimicrobial prophylaxis.

  • Reviews medical and psychosocial complications and outcomes that arise from pediatric solid organ transplantation.

  • Review of immunosuppressive therapies and their role in pediatric transplantation.

  • Comprehensive overview of issues related specifically to pediatric transplantation to recognize the many and substantial differences between adults and children.

3.2 Liver transplantation
- Review article that discusses hepatic diseases and focuses on improvements in medical, surgical and anesthetic management, organ availability, immunosuppression, and post-operative complications. Future developments for management of long-term follow-up and prevention of immunosuppression-related complications are also discussed.

### 3.2.1 Pre-transplant Evaluation

- Current pediatric liver transplant evaluation practice guideline that focuses on pediatric issues at each level of the evaluation process.

### 3.2.2 Induction Therapy

- Retrospective review of 136 patients comparing induction with either rATG or basiliximab. rATG with or without 2 week steroid taper was associated with higher rates of treated BPAR compared to basiliximab with a 6 month steroid taper. There was no difference in incidence of PTLD, infections, steroid resistant rejection, graft/patient survival, or time to treated BPAR between the groups.

- Review article discussing various induction agents and focuses on basiliximab use in pediatric patients.

- Results of a retrospective review of 18 pediatric liver transplant recipients with follow-up of 2 years found similar rates of patient and graft survival and decreased rates of rejection compared to literature reports. There was no increased risk of PTLD or CMV in the study population.

- Results from a retrospective review of 10 high immunologic risk pediatric liver transplant recipients given alemtuzumab induction therapy. Results were compared to a historical control group that received conventional immunosuppression without induction therapy. Rate of rejection was similar between the groups, but significantly prolonged in the group that received alemtuzumab induction. Alemtuzumab also allowed for lower doses of tacrolimus and steroids for maintenance immunosuppression.

- Review article comparing anti-IL-2 induction to anti-lymphocyte antibody induction therapy in pediatric transplant.
3.2.3 Maintenance Therapy

- Results of a matched case-control trial of tacrolimus plus MMF compared to a historical cohort of patients receiving tacrolimus monotherapy or cyclosporine plus steroids. Incidence of BPAR did not differ between groups. GFR declined at similar rates in all groups. Increased risk of septicemia in tacrolimus plus MMF group. Study was limited by minor reductions in tacrolimus concentrations.

- Results from a 24 month prospective study of 56 pediatric liver transplant recipients. Patients received either basiliximab or no induction and were converted 1-6 months post-transplant from CNI with or without mycophenolate to everolimus with reduced exposure CNI. Recruitment was stopped early due to high rates of PTLD and serious infections related to treatment. eGFR was higher in the everolimus group.

- Addresses immunosuppression options in pediatric patients and issues unique to the pediatric patient population.

- This review provides an overview of the efficacy and safety of everolimus-based regimens in liver transplantation in the de novo and maintenance settings, as well as in special populations such as patients with hepatocellular carcinoma recurrence, hepatitis C virus-positive patients, and pediatric transplant recipients.

- Current practice guidelines for long-term medication management after pediatric liver transplantation addressing growth and nutritional management, psychosocial development, neurocognitive function, and adherence. Maintenance immunosuppression, acute and chronic rejection, and the management of adverse effects associated with immunosuppression such as the increased risk for diabetes, hyperlipidemia, hypertension, obesity, and metabolic syndrome are discussed.

- This review provides an overview of studies indicating patients treated initially with tacrolimus compared with cyclosporine have shown significantly lower incidences of rejection, hypertension, hyperlipidemia and cosmetic side effects.


- Retrospective analysis of 129 children on either cyclosporine (n=87) or tacrolimus (n=42) monotherapy to assess the advantages and disadvantages of both drugs at least five years post liver transplantation. There was no significant difference in the calculated glomerular filtration rate between children on cyclosporine and tacrolimus; cosmetic changes were found in more than one-third of the patients on cyclosporine and in 4.8% of the patients receiving tacrolimus; quality of life was excellent in both groups per self-assessment.


- Multicenter, open-label, parallel-group, randomized study compared a dual tacrolimus regimen with a cyclosporine-based triple immunosuppressant regimen pediatric liver transplant recipients. There was no difference between treatment groups with respect to patient survival or graft survival at month 12 after transplant. The acute rejection free rate at study end (Kaplan-Meier method) was 55.5% for patients on tacrolimus and 40.2% for patients on ciclosporin microemulsion (p=0.0288). Incidence of adverse events did not differ between groups.

### 3.2.4 Management of Rejection


- Retrospective review of 47 liver transplant recipients to identify risk factors for rejection. No suspected risk factor (recipient blood group, sex, age, familial history of disease, receipt of drugs/blood products, type of donor, Child score/class) were associated with development of ACR.


- Data from the 1092 patients who have received a first liver transplant since 1995 were analyzed for factors influencing patient survival, graft survival and acute rejection. Infection was the single most important cause of death and was a contributing cause in 39%, particularly with bacterial or fungal organisms. Risk factors for graft loss included fulminant liver failure and cadaveric technical variant grafts. Initial immunosuppression with tacrolimus reduced the probability of rejection (RR = 0.62, p < 0.05).

### 3.2.5 Transplantation considerations with specific hepatic diseases


- Review of autoimmune hepatitis and autoimmune sclerosing cholangitis, and the role of liver transplantation in management.
3.3 Kidney transplantation

special-considerations-in-pediatric-kidney-transplantation/.

- Review presents a comprehensive discussion of the unique issues in pediatric renal transplantation.


- Clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients intended to assist the practitioner caring for adults and children after kidney transplantation. Includes joint pediatric and adult recommendations and does not highlight specific pediatric recommendations.

3.3.1 Transplant Evaluation


- Updated recommendations for evaluation of kidney transplant patients with pediatric considerations.

3.3.2 Induction Therapy

• The SRTR database was used to assess outcomes in 7884 first-time pediatric kidney transplant patients. Patients who received lymphocyte-depleting induction were compared to those who did not. In African American patients, the risk of acute rejection in 1 year was lower in African American patients who received lymphocyte-depleting induction compared to those who did not. This difference was not significant in non-African American patients.


• Retrospective, descriptive study of pediatric renal transplant recipients receiving induction immunosuppression with alemtuzumab, daclizumab, and anti-thymocyte globulin. Graft survival at 1 year was better in the patients who received alemtuzumab (87.5%) compared to other induction agents (80%). Incidence of CMV infection was highest in the alemtuzumab group.


• Review provides an overview of induction therapies for renal transplantation including historic therapies such as total lymphoid irradiation and Minnesota antilymphocyte globulin, and current therapies with polyclonal and monoclonal antibodies and chemical agents, with special emphasis on children.

### 3.3.3 Maintenance Therapy


• Initial case series of six EBV seropositive adolescent patients (median age 15.5 years) switched to belatacept due to nonadherence to their immunosuppressive regimens a median of 7.5 months after kidney transplant.


• 2-year follow-up to the TWIST trial to assess whether improved growth persisted in the longer term. Results showed early corticosteroid withdrawal subjects grew better at 1 year (P = 0.001). At 2 years growth continued to be significantly better in prepubertal subjects (P = 0.004). Bacterial and viral infection was significantly more common in CW subjects at 1 year only. Corticosteroid withdrawal and corticosteroid continuation subjects received similar exposure to both tacrolimus and MMF at 1 and 2 years. No significant difference in patient or graft survival, rejection, estimated glomerular filtration rate, or other adverse events was detected.


• Review of outcomes of 92 pediatric renal transplant recipients converted from CNI to sirolimus immunosuppression after transplant. Median time of conversion post-transplant was 31.6 months. The majority of patients were transitioned due to progressive increasing SCr and biopsy proven chronic allograft nephropathy. Baseline proteinuria and eGFR were determined to be independent risk factors for graft loss. Two patients (1.1%) experienced BPAR. Seventy-three percent of converted patients experienced an adverse event.

Randomized, multicenter study investigated the impact of early steroid withdrawal on mean change in height standard deviation score (SDS) and the safety and efficacy of two immunosuppressive regimens during the first 6 months after transplantation. Children received tacrolimus, MMF, two doses of daclizumab and steroids until day 4 (TAC/MMF/DAC, n=98) or tacrolimus, MMF and standard-dose steroids (TAC/MMF/STR, n=98). Early steroid withdrawal significantly aided growth at 6 months more so in prepubertal than pubertal children. This was accompanied by significantly better lipid and glucose metabolism profiles without increases in graft rejection or loss.


4-year experience of 66 children receiving deceased or living donor transplants on a maintenance immunosuppression regimen of sirolimus 3 mg/m² in addition to prednisone and tacrolimus or cyclosporine. Patient survival was 100% and graft survival was 65 of 66. Seven children experienced acute rejection episodes responsive to increased doses of corticosteroid. Sirolimus was discontinued in 20% for adverse events that included poor wound healing and non-infectious pneumonitis. The study concluded a sirolimus-based regimen that is combined with both an interleukin-2 receptor antibody and a calcineurin inhibitor may be excessive immunosuppression for pediatric renal transplant recipients.


A NAPRTCS database review looked at primary immunosuppression in 986 pediatric kidney transplant patients. Patients receiving tacrolimus, mycophenolate and steroids were compared to those receiving cyclosporine, mycophenolate, and steroids. At both 1 and 2 year post-transplant, there was no difference in time to first rejection, risk for rejection, or risk for graft failure. However, tacrolimus treated patients were less likely to require antihypertensive therapy at both 1- and 2-years post-transplant. Tacrolimus patients also had higher estimated mean GFR at both 1- and 2-years post-transplant.

3.3.4 Management of Rejection


An examination of seven pediatric kidney transplant recipients to determine the benefit of a therapeutic protocol using bortezomib for refractory C4d positive antibody-mediated rejection. All patients tolerated bortezomib. One patient had allograft loss. Five had improvement of histological findings of AMR, C4d staining, and/or acute cellular rejection. Reduction in HLA DSAs was more effective for class I than class II.


A review of the pathophysiology, diagnosis, and management of antibody mediated rejection presented with a pediatric patient case.


Antihumoral therapy with IVIG and rituximab significantly reduced or stabilized the progressive loss of transplant function in pediatric patients from 7.6 mL/min/1.73 m² to 2.1 mL/min/1.73 m² (p=0.0013) with chronic antibody mediated rejection over an observation period of 2 years. This
effect was thought to be due to decreased circulating DSA and reduced intrarenal complement activation.

### 3.3.5 Transplantation considerations with specific renal diseases

- Review article discussing risk for disease recurrence for children with FSGS who undergo kidney transplantation. Treatment strategies are also presented.

- Retrospective study describing characteristics and outcomes of 47 patients who underwent kidney transplantation for renal disease caused by congenital anomalies of the kidney and urinary tract. Rejection and graft survival were comparable to patients transplanted for kidney disease from other causes.

- Study of the UNOS database comparing 254 children with lupus to 7672 without. Allograft survival was not different between the groups, but in multivariate analysis, patients with lupus were 1.8 times more likely to die than patients without lupus (95% CI, 1.14 to 2.74; P = 0.01).

### 3.4 Heart transplantation

- Review of data registries, recipients demographics, waitlist support, outcomes, and immunosuppression.

- Review article that provides general information on pediatric heart transplantation in children, including indications, pretransplant assessment, transplant surgery, complications, and outcomes.

- Guidelines for the development and refinement of indications for heart transplantation for patients with congenital heart disease and pediatric cardiomyopathies in addition to indications for pediatric heart retransplantation.


#### 3.4.1 Induction Therapy

- Single center retrospective study of 49 pediatric cardiac recipients compared induction steroids with protocol biopsies to those who receive no steroids or biopsies. No difference in survival, In
the group with no steroids or biopsies there was less rejection, less hypertension, and less insulin dependence.


- This study was a retrospective study of 5,464 pediatric heart recipients. Authors concluded that black recipients who received thymoglobulin had improved long-term graft survival compared to those who received basiliximab or no induction.


- Retrospective study of 3158 pediatric heart recipients who received induction with basiliximab or antithymocyte globulin compared graft survival. Authors concluded antithymocyte globulin is associated with improved late graft survival.


- Pediatric heart transplant recipients receiving rATG have an associated improved graft survival compared to patients receiving interleukin-2 receptor antagonists. The benefit of rATG was shown in low-risk patients receiving tacrolimus and mycophenolate mofetil in a steroid-free regimen, patients who were sensitized with pre-formed alloantibodies and/or a positive donor-specific crossmatch, and in ABO-incompatible heart transplant recipients.


- Induction therapy with anti-thymocyte antibody (ALA) or interleukin-2 receptor antagonist (IL2-RA) is associated with decreased rejection but did not directly influence survival. Patients deemed low risk my benefit from induction therapy, particularly IL-2RA may be correlated with a decrease in infection and rejection.


- Analysis of 2,792 pediatric heart recipients using UNOS database to investigate the effects of induction immunosuppression on graft survival. No difference was seen in graft survival when comparing patients who received induction to those who did not. In the subgroup analysis, a benefit was seen for patients with a PRA greater than 50% and congenital heart disease.


- Analysis of 2,275 pediatric heart recipients using UNOS database to compare long-term mortality between basiliximab and thymoglobulin. Authors concluded basiliximab was associated with increased mortality when compared to thymoglobulin.


- 461 patients enrolled in the Pediatric Heart Transplant Study Group between January 1993 and December 1995 were divided into three groups based on induction (OKT3, rabbit polyclonal
antithymocyte globulin serum [ATS], no induction), evaluated, and followed for up to 36 months. Overall mortality and death due to rejection was lowest in the ATS group. Induction did not affect cumulative infections, deaths due to infection, or the frequency of malignancies. Cumulative rejection and freedom from rejection death were lowest in centers using ATS.

3.4.2 Maintenance Therapy


early-outcomes-for-low-risk-pediatric-heart-transplant-recipients-and-steroid-avoidance-a-multicenter-

- Multicenter, prospective cohort study of 240 pediatric heart transplant recipients analyzing 1 year outcomes of patients without pre-transplant DSAs. Patients received thymoglobulin induction and were maintained on tacrolimus and/or mycophenolate. Steroids were not continued beyond 1 week post-transplant. Survival was 94.5%. Freedom from any rejection was 67.5%.


- Retrospective study of 13 patients continued on mTOR inhibitors in the perioperative period. Authors identified a surgical wound complication in one patient.


- Sirolimus was used in less than 10% of patients at 1 year post-transplant. Overall outcomes of sirolimus treated and non-treated patients were similar with respect to survival and major transplant adverse events. Further study of sirolimus in pediatric heart transplant patients is needed.


- Immunosuppression free of CNIs and corticosteroids appears to be a safe alternative in pediatric heart transplant patients with significant renal insufficiency. Furthermore, this strategy can significantly reverse renal insufficiency, even late after transplantation.


- Maintenance steroid use at 30 days post-transplant was not associated with enhanced graft survival after pediatric heart transplant. Maintenance steroid patients had a higher incidence of rejection with severe hemodynamic compromise and infection. These risks should be taken into consideration when determining maintenance steroid use for pediatric recipients of heart transplants.


- Current practice guidelines for the management of heart transplant recipients. Specific pediatric recommendations are included.

- 55 patients (median age of 7.1 years) entered a steroid-avoidance immunosuppression protocol consisting of thymoglobulin induction followed by a 2-drug, tacrolimus-based, corticosteroid-free regimen. Freedom from rejection was 92% at 6 months and 87% at 1 year. Post-transplant survival was 91% at 6 months and 88% at 12 and 24 months. There was 1 death due to rejection (antibody-mediated) 8 months after transplantation.

3.4.3 Management of Rejection


- Despite substantial improvements in survival after pediatric heart transplantation, refractory rejection remains a major cause of morbidity and mortality. We have utilized ALE (Campath-1H) in six consecutive patients with refractory rejection. These rejection episodes persisted despite conventional treatment, which included intravenous methylprednisolone, rituximab, immunoglobulin G, and antithymocyte globulin. In our series, after ALE therapy, LV SF increased from 22%±5% to 33%±5% (P=.01). However, in our series, ALE therapy neither led to persistent LV function recovery nor could it prevent subsequent antibody-mediated rejection.


- Current practice guidelines for the management of immunosuppression and rejection in heart transplant recipients. Specific pediatric recommendations are included.


- Review of 179 patients and 246 antibody mediated rejection episodes from pediatric heart transplant study database data including incidence, treatment, and outcomes.

3.4.4 Transplantation in specific cardiac diseases


- Meta-analysis of 12 studies including 351 patients. Early and mid-term mortality after transplantation in younger patients after Fontan was acceptable and comparable to published mortality data of heart transplantation for other forms of congenital heart disease.


- Review article discussing challenges and outcomes in cardiac transplantation in patients with congenital heart disease, including pediatric mechanical circulatory support.

3.4.5 Miscellaneous

● Retrospective evaluation of 2185 pediatric heart recipients to identify risk factors and outcomes for new onset diabetes after transplant. Older age, black race, higher BMI, and steroid use were found to increase risk.


● Prospective analysis of 237 pediatric heart transplant recipients on the incidence of newly detected DSAs and their clinical impact. One-third of the patients developed DSAs and most were detected within the first 6 weeks after transplant. This suggests memory response may play a larger role in this population that de novo DSA production. Sensitizing events were determined to be a risk factor for patients developing DSAs post-transplant.


3.5 Lung Transplantation


● Review of use of ECMO and relevant management for pediatric lung transplant recipients before and after transplantation.


● Review article of indications for transplant and management of recipients.


● Review of immunosuppression regimens for adult and pediatric lung recipients with cystic fibrosis.


● Review of indications, immunosuppression, complications, and survival for pediatric lung transplant.


● Review article of pediatric lung transplantation including indications, evaluation, operative procedure, graft dysfunction, and outcomes.

• Consensus statement that highlights challenges in pediatric lung transplantation and provides guidance for the field. Discussion of induction and maintenance immunosuppression are included.

3.5.1 Induction


- A review of UNOS including 330 pediatric lung transplant recipients, 54% of whom received induction therapy. Induction agents included basiliximab, alemtuzumab, antilymphocyte globulin, and antithymocyte globulin. There was not a difference in survival in patients who did or did not receive induction, but there was a trend toward a protective effect with induction.

3.6 Intestinal Transplantation


- A pharmacokinetic study of 8 patients who received intestinal transplants. Mycophenolate was initiated at low median starting doses and had to be increased to reach target AUC levels of 30 mg·h·L. Starting doses of 600 mg/m2 twice daily are recommended based on this evaluation.


- Review article describing pediatric intestinal transplantation, including listing criteria, surgical techniques, management, monitoring, complications, and outcomes.

3.7 Miscellaneous

3.7.1 Immunizations


- AST IDCOP Guidelines for vaccinations


- Guidance by a consortium of experts on the use of live-attenuated viral vaccines after solid organ transplant. Includes recommendations for MMR and VV vaccines.


- Provides review of recent immunization studies performed in pediatric transplant patients.


- Evidenced-based guideline for vaccination of immunocompromised adults and children.

3.7.2 Posttransplant lymphoproliferative disorder


- Retrospective study of 82 pediatric solid organ transplant recipients with PTLD.

- Retrospective analysis of 350 pediatric solid organ transplant recipients seeking to identify predictive risk factors of development of PTLD in patients with EBV viremia. Identified risk factors include: younger age at time of transplant, increased immunosuppression prior to EBV viremia, higher peak EBV, and presence of symptoms.


- Review of German multicenter pediatric PTLD registry data including 127 patients. Evaluates characteristics of patients who developed early and late PTLD.