11.0. Pediatric transplantation overview

Magee JC, et al. Pediatric transplantation. American Journal of Transplantation. 2004;4:54-71. Retrieved from: http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2004.00398.x/full.

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

LaRosa C, et al. Outcomes in pediatric solid-organ transplantation. Pediatric Transplantation. 2011;15:128-41. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21309962.

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

Liver transplantation

Spada M, et al. Pediatric liver transplantation. World Journal of Gastroenterology. 2009;15: 648-674. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653434/.

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

Pre-transplant Evaluation

Squires RH, et al. Evaluation of the Pediatric Patient for Liver Transplantation: 2014 Practice Guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Journal of Pediatric Gastroenterology and Nutrition. 2014;59:112-131. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25222807.

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

Induction Therapy

Turner AP, Knectle SJ. Induction immunosuppression in liver transplantation: a review. Transplant International. 2013;26:673-683. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23651083.

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

Ganschow, et al. Long-term results of basiliximab induction immunosuppression in pediatric liver transplant recipients. Pediatric Transplantation. 2005;9:741-745. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16269045.

- Results from a long-term follow-up (up to 46 months) of 54 patients found a significant reduction in acute graft rejection as well as similar incidences of chronic rejection, PTLD, graft and patient survival in the treatment group (those patients who received basiliximab induction therapy) compared to the control group. There were no adverse effects observed, which could be related to the antibody treatment.

Maintenance Therapy

Kelly DA, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transplantation. 2013;19:798-825. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23836431.

- 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.

Kelly D. Safety and efficacy of tacrolimus in pediatric liver recipients. Pediatric Transplantation. 2011;15:19-24. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21176018.

- 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.

Hasenbein W, et al. Long-term evaluation of cyclosporine and tacrolimus based immunosuppression in pediatric liver transplantation. Pediatric Transplantation. 2006;10:938-942. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17096762.

- 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.

Ganschow R, Pollok JM, Jankofsky M, Junge G. The role of everolimus in liver transplantation. Clinical and Experimental Gastroenterology. 2014;7:329-343. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25214801.

- 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.

Kelly D, et al. Tacrolimus and steroids versus ciclosporin microemulsion, steroids and azathioprine in children undergoing liver transplantation: randomized European multicentre trial. Lancet. 2004;364:1054-1061. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15380964.

- 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.

Bulut OP, et al. Immunosuppression and challenges in pediatric liver transplant recipients. Journal of Transplantation Technologies and Research. 2013;3:1-6. Retrieved from: https://www.omicsonline.org/2161-0991/2161-0991-3-121.pdf.

- This review discusses immunosuppressive agents for pediatric liver transplantation and the unique issues that must be addressed when managing pediatric liver transplant recipients.

Management of Rejection

Martin SR, et al. Studies of Pediatric Liver Transplantation 2002: patient and graft survival and rejection in pediatric recipients of a first liver transplant in the United States and Canada. Pediatric Transplantation. 2004;8:273-283. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15176966.

- 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, $p < 0.05$).

Transplantation considerations with specific hepatic diseases

Oishi K, et al. Liver transplantation for pediatric inherited metabolic disorders: considerations for indications, complications, and perioperative management. Pediatric Transplantation. 2016;20:756-69. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27329540.

- Review article that discusses the use of liver transplantation for various inborn errors of metabolism, including, but not limited to, urea cycle disorders, alpha-1 antitrypsin deficiency, cystic fibrosis, and Wilson disease. Medical management after liver transplantation in these complex disorders is also discussed.

Sundaram SS, et al. Biliary atresia: indication and timing of liver transplantation and optimization of pretransplant care. Liver Transplantation. 2017;23:96-109. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27650268.

- Review article which discusses timing of liver transplantation in children with biliary atresia, including a specific discussion for the multidisciplinary team regarding optimization of nutrition and growth prior to transplantation is included. Information on management of complications such as portal hypertension and spontaneous bacterial peritonitis prior to transplantation is also provided.

Liberal R, et al. Recurrence of autoimmune liver disease and inflammatory bowel disease after pediatric liver transplantation. Liver Transplantation. 2016;22:1275-1283. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27257963.

- Review article describing incidence of disease in pediatric liver transplant patients who receive transplants for autoimmune liver diseases. Considerations for immunosuppression are discussed.

Kidney transplantation

Kasiske BL, et al. (2009). KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. American Journal of Transplantation, 9 Suppl, S1-155. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/19845597.

- 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.

Gulati A, Sarwal MM. (2010). Pediatric renal transplantation: an overview and update. Current Opinion in Pediatrics, 22, 189-196. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20125027.

- Review presents a comprehensive discussion of the major issues in pediatric renal transplantation, the newer immunosuppression approaches to limit toxicities of therapies in children and some critical issues that remain to be addressed, specific to the care of the transplanted child.

Induction Therapy

Moudgil A, Puliyanda D. Induction therapy in pediatric renal transplant recipients: an overview. Paediatric Drugs. 2007;9:323-341. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17927304.

- 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.

Crowson CN, et al. Lymphocyte-depleting induction therapy lowers the risk of acute rejection in African American pediatric kidney transplant recipients. Pediatric Transplantation. 2017;21:e12823. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27699934.

- 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.

Maintenance Therapy

Grenda R, et al. A randomized tiral to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. American Journal of Transplantation. 2010;10:828-836. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20420639.

- 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.

Webb NJ, et al. Corticosteroid-free Kidney Transplantation Improves Growth: 2-Year Follow-up of the TWIST Randomized Controlled Trial. Transplantation. 2015;99:1178-1185. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25539467.

- 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.

Hymes LC, Warshaw BL. (2005) Sirolimus in pediatric patients: results in the first 6 months post-renal transplant. Pediatric Transplantation, 9, 520-522. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16048606.

- 4 year experience of 66 children receiving deceased or living donor transplants on a maintenance immunosuppression regimen of sirolimus 3 mg/m^2 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.

Neu AM, et al. Tacrolimus vs. cyclosporine A as primary immunosuppression in pediatric renal transplantation a NAPRTCS study. Pediatric Transplantation. 2003;7:217-22. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/12756047.

- 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 year2 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.

Lerch C, et al. Belatacept after kidney transplantation in adolescents: a retrospective study. Transplant International. 2017; doi:10.1111/tri.12932. https://www.ncbi.nlm.nih.gov/pubmed/28166398.

- 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.

Management of Rejection

Ng YW, et al. Antibody-mediated rejection in pediatric kidney transplantation: pathophysiology, diagnosis, and management. Drugs. 2015;75:455-472. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25813498.

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

Pearl MH, et al. Bortezomib may stabilize pediatric renal transplant recipients with antibody-mediated rejection. Pediatric Nephrology. 2016;8:1341-1348. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27048228.

- 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.

Billing H, et al. IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2-year follow-up. Transplant International. 2012;11:1165-1173. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22897111.

- 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 m^2 to 2.1 mL/min/1.73 m^2 ($p=0.0013$) 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.

Transplantation considerations with specific renal diseases

Kang HG, et al. Recurrence and treatment after renal transplantation in children with FSGS. Biomedical Research International. 2016; doi: 10.1155/201/6832971. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4860214/.

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

Ounissi M, et al. Malformative uropathies and kidney transplantation. Transplantation proceedings. 2011;43:437-440. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21440727.

- 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.

Gipson DS, et al. Renal transplantation in children with lupus nephritis. American Journal of Kidney Diseases. 2003;41:455-463. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/12552510.

- 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).

Heart transplantation

Conway J, Dipchand AI. Heart transplantation in children. Pediatric Clinics of North America. 2010;57:353-373. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20371041.

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

Canter CE, et al. Indications for Heart Transplantation in Pediatric Heart Disease. Circulation. 2007;115:658-676. Retrieved from: http://circ.ahajournals.org/content/115/5/658.

- 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.

Induction Therapy

Boucek RJ Jr, et al. Induction immunotherapy in pediatric heart transplant recipients: a multicenter study. Journal of Heart and Lung Transplantation. 1999;18:460-469. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/10363691.

- 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.

Maintenance Therapy

Costanzo MR, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. Journal of Heart and Lung Transplantation. 2010;29:914-956. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20643330

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

Singh TP, et al. Safety and early outcomes using a corticosteroid-avoidance immunosuppression protocol in pediatric heart transplant recipients. Journal of Heart and Lung Transplantation. 2010;29:517-522. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20061164

- 55 patients (median age of 7.1 years) entered a steroid-avoidance immunosuppression protocol consisting of thymoglobin 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.

Management of Rejection

Taylor D, et al. (2010). The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients, task force 2: immunosuppression and rejection. ISHLT Guidelines for the Care of Heart Transplant Recipients. Retrieved from: https://www.ishlt.org/ContentDocuments/ISHLT_GL_TaskForce2_110810.pdf

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

Transplantation in specific cardiac diseases

Tabarsi N, et al. Meta-analysis of the effectiveness of heart transplantation in patients with a failing Fontan. Am J Cardiol. 2017;119:1269-1274. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28233535.

- 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.

Kirklin JK, et al. Current expectations for cardiac transplantation in patients with congenital heart disease. World Journal for Pediatric and Congenital Heart Surgery. 2016;7:685-695. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27834759.

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

Pediatric Lung Transplantation

Faro A, et al. American Society of Transplantation Executive Summary on Pediatric Lung Transplantation. American Journal of Transplantation. 2007;7:285-292. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17109726

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

Solomon M, et al. Pediatric lung transplantation. Pediatric Clinics of North America. 2010;57:375-391. https://www.ncbi.nlm.nih.gov/pubmed/20371042.

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

Olsen MC, et al. ECMO for pediatric lung transplantation. ASAIO Journal. 2017; doi: 10.1097/MAT.0000000000000534. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28125461.

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

Induction

Hayes D, et al. A contemporary analysis of induction immunosuppression in pediatric lung transplant recipients. Transplant International. 2014;27:211-218. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24236829

- 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.

Pediatric Intestinal Transplantation

Avitzur Y, Grant D. Intestine transplantation in children: update 2010. Pediatric Clinics of North America. 2010;57:415-431. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20371045

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

Maintenance immunosuppression

Barau C, et al. Pharmacokinetics of mycophenolic acid and dose optimization in children after intestinal transplantation. Ther Drug Monit. 2017;39:37-42. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27898598.

- 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.

Miscellaneous

Immunizations

Rubin LG, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clinical Infectious Diseases. 2014;58:309-318. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24421306

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