3. Pediatric transplantation

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3.1 Pediatric transplantation overview

Crowther B (2019). Immunosuppression in Pediatric SOT. Transplantation PedSAP 2019 Book 2. Retrieved from: https://www.accp.com/docs/bookstore/pedsap/ped2019b2_sample.pdf
- Review of pediatric transplant history, rejection, and immunosuppression.

Knackstedt ED, et al (2017). Infections in pediatric solid-organ transplant recipients. Seminars in Pediatric Surgery 2017; 26:199-205. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28964474
- Review of infections and antimicrobial prophylaxis

LaRosa C, et al (2011). Outcomes in pediatric solid-organ transplantation. *Pediatr Transplant*. 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.

Agarwal A, et al (2006). Immunosuppression in pediatric solid organ transplantation. *Semin Pediatr Surg.* 2006; 15:142-152. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16818135.
- Review of immunosuppressive therapies and their role in pediatric transplantation.

Magee JC, et al (2004). Pediatric transplantation. *Am J Transplant*. 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.

3.2 Liver transplantation

Spada M, et al (2009). Pediatric liver transplantation. *World J Gastroenterol*. 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 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

Squires RH, et al (2014). 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. *J Peditr Gastroenterol Nutr.* 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.

3.2.2 Induction Therapy

Newland DM, et al (2019). Analysis of rabbit anti-lymphocyte globulin vs basiliximab induction in pediatric liver transplant recipients. 2019; 23:e13573. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/petr.13573.

- 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 compard 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.

Turner AP, Knectle SJ (2013). Induction immunosuppression in liver transplantation: a review. *Transpl Int*. 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.

Shah A, et al (2006). Induction immunosuppression with rabbit antithymocyte globulin in pediatric liver transplantation. *Liver Transpl.* 2006; 12(8):1210-1214. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16868953.

- 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.

Kato T, et al (2006). Pediatric liver transplant with Campath 1H induction—Preliminary report. *Transplant Proc.* 2006; 38(10):3609-3611. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17175346.

- 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.

Di Filippo S, et al (2005). Anti-IL-2 receptor antibody vs. polyclonal anti-lymphocyte antibody as induction therapy in pediatric transplantation. *Pediatr Transplant.* 2005; 9(3):373-380. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1399-3046.2005.00303.x.

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

Ganschow, et al (2005). Long-term results of basiliximab induction immunosuppression in pediatric liver transplant recipients. *Pediatr Transplant*. 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.

3.2.3 Maintenance Therapy

Leiskau C, et al (2018). Side effects and efficacy of renal sparing immunosuppression in pediatric liver transplantation - A single center matched cohort study. Pediatr Transplant. 2018; 22:e13207. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/petr.13207.

- 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.

Ganschow R, et al (2017). Everolimus and reduced calcineurin inhibitor therapy in pediatric liver transplant recipients: Results from a multicenter, prospective study. *Pediatr Transplant*. 2017; 21(7):epub. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28714558.

- 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.

Miloh T, et al (2017). Immunosuppression in Pediatric Liver Transplant Recipients: Unique Aspects. Liver Transpl. 2017; 23(2):244-256. Retrieved from: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/lt.24677.

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

Ganschow R, Pollok JM, Jankofsky M, Junge G (2014). The role of everolimus in liver transplantation. *Clin Exp Gastroenterol*. 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 (2013). 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 Transpl*. 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 (2011). Safety and efficacy of tacrolimus in pediatric liver recipients. *Pediatr Transpl.* 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 (2006). Long-term evaluation of cyclosporine and tacrolimus based immunosuppression in pediatric liver transplantation. *Pediatr Transpl*. 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.

Kelly D, et al (2004). 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.

3.2.4 Management of Rejection

Dehghani SM, et al (2017). Acute Hepatic Allograft Rejection in Pediatric Recipients: Independent Factors. *Int J Organ Transplant Med*. 2017; 8(4):203-206. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5756902/.

- 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 disase, receipt of drugs/blood products, type of donor, Child score/class) were associated with development of ACR.

Martin SR, et al (2004). 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 ($RR = 0.62$, $p < 0.05$).

3.2.5 Transplantation considerations with specific hepatic diseases

Mieli-Vergani G, et al (2018). Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement. *J Pediatr Gastroenterol Nutr.* 2018; 66(2):345-360. Retrieved from: https://insights.ovid.com/crossref?an=00005176-201802000-00033.

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

Sundaram SS, et al (2017). 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.

Oishi K, et al (2016). Liver transplantation for pediatric inherited metabolic disorders: considerations for indications, complications, and perioperative management. *Pediatr Transplant*. 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.

Liberal R, et al (2016). 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.

3.3 Kidney transplantation

Herbert SA, et al (2017). Special Considerations in Pediatric Kidney Transplantation. *Adv Chronic Kidney Dis.* 2017; 24(6):398-404. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29229171-special-considerations-in-pediatric-kidney-transplantation/.

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

Kasiske BL, et al (2009). KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Am J Transplant*. 2009; 9 (Suppl 3): 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.

3.3.1 Transplant Evaluation

Chadban SJ, Ahn C, Axelrod DA, et al (2020). KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Transplantation. 2020;104(4S1 Suppl 1):S11-S103. doi:10.1097/TP.0000000000003136

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

3.3.2 Induction Therapy

Crowson CN, et al (2017). Lymphocyte-depleting induction therapy lowers the risk of acute rejection in African American pediatric kidney transplant recipients. Pediatr Transplant. 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.

Velez C, et al (2011). Clinical Description and Evolution of Renal Transplant Pediatric Patients Treated with Alemtuzumab. *Transplant Proc.* 2011; 43(9):3350-3354. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/22099794-clinical-description-and-evolution-of-renal-transplant-pediatric-patients-treated-with-alemtuzumab/.

- 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.

Moudgil A, Puliyanda D (2007). Induction therapy in pediatric renal transplant recipients: an overview. Paediatr 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.

3.3.3 Maintenance Therapy

Lerch C, et al (2017). Belatacept after kidney transplantation in adolescents: a retrospective study. *Transpl Int*. 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.

Webb NJ, et al (2015). 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.

Monteverde ML, et al (2012). Conversion to sirolimus in pediatric renal transplant patients: A single-center experience. *Pediatr Transplant.* 2012; 16:582-588. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1399-3046.2012.01697.x.

- 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.

Grenda R, et al (2010). A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. *Am J Transplant*. 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.

Hymes LC, Warshaw BL (2005). Sirolimus in pediatric patients: results in the first 6 months post-renal transplant. *Pediatr Transplant*. 2005; 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 (2003). Tacrolimus vs. cyclosporine A as primary immunosuppression in pediatric renal transplantation a NAPRTCS study. *Pediatr Transplant*. 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.

3.3.4 Management of Rejection

Pearl MH, et al (2016). Bortezomib may stabilize pediatric renal transplant recipients with antibody-mediated rejection. *Pediatr Nephrol*. 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.

Ng YW, et al (2015). 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.

Billing H, et al (2012). IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2-year follow-up. *Transpl Int*. 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.

3.3.5 Transplantation considerations with specific renal diseases

Kang HG, et al (2016). Recurrence and treatment after renal transplantation in children with FSGS. *Biomed Res Int*. 2016; 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 (2011). Malformative uropathies and kidney transplantation. *Transplant Proc*. 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 (2003). Renal transplantation in children with lupus nephritis. *Am J Kidney Dis*. 2003;41:455-463. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/12552510-renal-transplantation-in-children-with-lupus-nephritis/.

- 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

Dipchand AI (2018). Current state of pediatric cardiac transplantation. *Ann Cardiothorac Surg*. 2018; 7(1): 31–55. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5827130/

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

Conway J, Dipchand AI (2010). Heart transplantation in children. *Pediatr Clin North Am*. 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 (2007). 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.

Rosenthal D, et al (2004). International Society for Heart and Lung Transplantation: Practice Guidelines for Management of Heart Failure in Children. *J Heart Lung Transplant*. 2004; 23(12):1313-1333. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15607659

3.4.1 Induction Therapy

Wagner SJ (2019). Less Is More in Post Pediatric Heart Transplant Care. *Ann Thorac Surg*. 2019; 107:165-72. Retrieved from: https://www.annalsthoracicsurgery.org/article/S0003-4975(18)31040-3/fulltext

- 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.

Carlo WF, et al (2019). Comparison of 10-year graft failure rates after induction with basiliximab or anti-thymocyte globulin in pediatric heart transplant recipients—The influence of race. race. *Pediatr Transplant*. 2019;23:e13366. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30735604

- 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.

Butts RJ, et al (2018). Comparison of basiliximab vs antithymocyte globulin for induction in pediatric heart transplant recipients: An analysis of the International Society for Heart and Lung Transplantation database. *Pediatr Transplant*. 2018;22:e13190. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/petr.13190

- 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.

Schweiger M, Zuckermann A, Beiras-FernandezA, et al (2018). A Review of Induction with Rabbit Antithymocyte Globulin in Pediatric Heart Transplant Recipients. Ann Transplant. 2018;23:322-333. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29760372.

- 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.

Castleberry C, Pruitt E, Ameduri R, et al (2018). Risk Stratification to determine the Impact of Induction Therapy on Survival, Rejection, and Adverse Events after Pediatric Heart Transplant: A Multi-Institutional Study. J Heart Lung Transplant. 2018;37(4):458-466. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28619384.

- 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.

Butts R, et al (2017). Effect of Induction Therapy on Graft Survival in Primary Pediatric Heart Transplantation: A Propensity Score Analysis of the UNOS Database. *Transplantation*. 2017;101(6):1228–1233. Retrieved from: https://www.ncbi.nlm.nih.gov/m/pubmed/27362312/#fft

- 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.

Ansari et al (2016). Comparison of Basiliximab and Anti-Thymocyte Globulin as Induction Therapy in Pediatric Heart Transplantation: A Survival Analysis. *J Am Heart Assoc*. 2016;5:e002790. Retrieved from: https://www.ahajournals.org/doi/10.1161/JAHA.115.002790

- 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.

Boucek RJ Jr, et al (1999). Induction immunotherapy in pediatric heart transplant recipients: a multicenter study. *J Heart Lung Transplant*. 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.

3.4.2 Maintenance Therapy

Lamour JM, et al (2019). Early outcomes for low-risk pediatric heart transplant recipients and steroids avoidance: A multicenter cohort study (Clinical Trials in Organ Transplantation in Children - CTOTC-04). *J Heart Lung Transplant.* 2019; 38(9):972-981. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31324444-early-outcomes-for-low-risk-pediatric-heart-transplant-recipients-and-steroid-avoidance-a-multicenter-cohort-study-clinical-trials-in-organ-transplantation-in-children-ctotc-04/.

- 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%.

Heble A, et al (2018). Safety of mTOR inhibitor continuation in pediatric heart transplant recipients undergoing surgical procedures. *Pediatr Transplant*. 2018;22:e13093. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5811366/

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

Rossano JW, Jefferies JL, Pahl E, et al (2017). Use of sirolimus in pediatric heart transplant patients: A multi-institutional study from the Pediatric Heart Transplant Study Group. J Heart Lung Transplant. 2017;36(4):427-433. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28029575

- 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.

Sierra CM, Tan R, Eguchi J, et al (2016). Calcineurin inhibitor- and corticosteroid-free immunosuppression in pediatric heart transplant patients. Pediatr Transplant. 2016. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27658616

- 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.

Auerbach SR, Kukreja M, Gilbert D, et al (2015). Maintenance steroid use at 30 days post-transplant and outcomes of pediatric heart transplantation: A propensity matched analysis of the Pediatric Heart Transplant Study database. J Heart Lung Transplant. 2015;34(8):1066-72. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Maintenance+steroid+use+at+30+days+post-transplant+and+outcomes+of+pediatric+heart+transplantation%3A+A+propensity+matched+analysis+of+the+Pediatric+Heart+Transplant+Study+database.

- 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.

Costanzo MR, et al (2010). The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 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 (2010). Safety and early outcomes using a corticosteroid-avoidance immunosuppression protocol in pediatric heart transplant recipients. *J Heart Lung Transplant*. 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 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

Das B, Dimas V, Guleserian K, et al (2017). Alemtuzumab (Campath-1H) therapy for refractory rejections in pediatric heart transplant recipients. Pediatr Transplant. 2017;21(1). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27862703

- 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.

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. 2010. 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.

Thrush PT, et al (2016). A multi-institutional evaluation of antibody-mediated rejection utilizing the Pediatric Heart Transplant Study database: Incidence, therapies and outcomes. *J Heart Lung Transplant*. 2016;35:1497–1504. Retrieved from: https://www.sciencedirect.com/science/article/pii/S1053249816301929

- 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

Tabarsi N, et al (2017). 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 (2016). Current expectations for cardiac transplantation in patients with congenital heart disease. *World J Pediatr Congenit Heart Surg*. 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 pediatric mechanical circulatory support.

3.4.5 Miscellaneous

Sparks JD, et al (2019). New-onset diabetes after pediatric heart transplantation: A review of the Pediatric Heart Transplant Study. *Pediatr Transplant*. 2019;23:e13476. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31124221

- 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.

Dipchand AI, et al (2018). Incidence, characterization, and impact of newly detected donor-specific anti-HLA antibody in the first year after pediatric heart transplantation: A report from the CTOTC-04 study. *Am J Transplant.* 2018; 18:2163-2174. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.14691.

- 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.

Webber S, et al (2018). Pediatric heart transplantation across a positive crossmatch: First year results from the CTOTC-04 multi-institutional study. *Am J Transplant.* 2018; 18:2148-2162. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.14876.

- Prospective analysis of 1 year outcomes of sensitized (CDC positive/negative and DSA positive/negative) vs. non-sensitized pediatric heart transplant recipients. Immunosuppression was standardized between groups, with the CDC crossmatch positive patients receiving pre-operative antibody removal, IVIG, and maintenance steroids. The primary endpoint (composite of death, re-transplantation, or rejection with hemodynamic compromise) was not statistically significant between groups (nonsensitized: 6.7%, sensitized crossmatch positive: 18.2%, sensitized crossmatch negative: 10.7%; p=0.2354). Freedom from AMR and ACR was lower in the positive crossmatch group.

3.5 Lung Transplantation

Olsen MC, et al (2017). 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.

Benden C, et al (2017). Pediatric lung transplantation. *J Thorac Dis*. 2017 Aug; 9(8): 2675–2683. Retrived from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5594176/

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

Burcham P, et al (2017). Immunosuppression Drug Therapy in Lung Transplantation for Cystic Fibrosis. *Pediatr Drugs*. 2017;19(4):339-346. Retrived from: https://www.ncbi.nlm.nih.gov/pubmed/28547678

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

Goldfarb SB, et al (2016). The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Lung and Heart–Lung Transplantation Report—2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. 2016;35(10):1196-1205. Retrieved from: https://www.jhltonline.org/article/S1053-2498(16)30300-X/fulltext

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

Solomon M, et al (2010). Pediatric lung transplantation. *Pediatr Clin North Am*. 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.

Faro A, et al (2007). American Society of Transplantation Executive Summary on Pediatric Lung Transplantation. *Am J Transplant*. 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.

3.5.1 Induction

Hayes D, et al (2014). A contemporary analysis of induction immunosuppression in pediatric lung transplant recipients. *Transpl Int*. 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.

3.6 Intestinal Transplantation

Barau C, et al (2017). 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.

Avitzur Y, Grant D (2010). Intestine transplantation in children: update 2010. *Pediatr Clin North Am*. 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.

3.7 Miscellaneous

3.7.1 Immunizations

Danziger-Isakov L, et al (2019). Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. *Clin Transplant*. 2019 Apr 19. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ctr.13563

- AST IDCOP Guidelines for vaccinations

Suresh S, et al (2019). Live vaccines after pediatric solid organ transplant: Proceedings of a consensus meeting, 2018. *Pediatr Transplant*. 2019 Nov;23(7):e13571. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31497926

- 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.

Dulek DE, de St Maurice A, Halasa NB (2018). Vaccines in pediatric transplant recipients-Past, present, and future. Pediatr Transplant. 2018;22(7):e13282. doi:10.1111/petr.13282

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

Rubin LG, et al (2014). 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58:309-318. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24421306

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

3.7.2 Posttransplant lymphoproliferative disorder

L'Huillier AG, et al (2019). Posttransplant lymphoproliferative disorder in pediatric patients: Survival rates according to primary sites of occurrence and a proposed clinical categorization. *Am J Transplant*. 2019 Oct;19(10):2764-2774. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30884098

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

Weintraub L, et al (2014). Identifying Predictive Factors for Posttransplant Lymphoproliferative Disease in Pediatric Solid Organ Transplant Recipients With Epstein-Barr Virus Viremia. *J Pediatr Hematol Oncol.* 2014; 36(8):e481-486. Retrieved from: https://insights.ovid.com/article/00043426-201411000-00025.

- 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.

Schober T, et al (2013). Characteristics of Early and Late PTLD Development in Pediatric Solid Organ Transplant Recipients. *Transplantation.* 2013; 95:240-246. Retrieved from: https://insights.ovid.com/crossref?an=00007890-201301150-00035.

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