Pediatric Heart Transplant Immunosuppression

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Jessica A. Laks and Anne I. Dipchand

28.1 Introduction

Post-heart transplant immunosuppression has seen considerable evolution over the last 60 years. Steroids were the mainstay of transplant immunosuppression back in the 1960s while transplant was first being attempted; however, survival outcomes were poor which led to abandoning cardiac transplantation [1]. The discovery of cyclosporine led to renewed attempts at heart transplantation in the 1980s and eventually to our modern era approaches of combination antirejection medications [2]. The goal of our current immunosuppression regimens is to target different areas of the immune system in order to minimize both acute and chronic rejection while limiting side effects to the patients. This is done through specific peri-transplant immunosuppression regimens as well as maintenance immunosuppression with the most common approaches reviewed below and summarized in Table 28.1. As well, we will discuss the common immunosuppression side effects and complications.

J. A. Laks
Heart Institute, Johns Hopkins All Children's Hospital, St Petersburg, FL, USA
e-mail: jlaks1@jhmi.edu

A. I. Dipchand (✉)
University of Toronto, Labatt Family Heart Centre, Hospital for Sick Children, Toronto, ON, Canada
e-mail: anne.dipchand@sickkids.ca

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Table 28.1 Commonly used immunosuppression drugs, dosing and therapeutic ranges/monitoring used in heart transplant patients

Peri-Transplant Immunosuppression			
Generic Name	**Type**	**Typical Dosing Protocols**	**Monitoring**
Induction Therapy			
Rabbit anti-thymocyte globulin	Rabbit polyclonal	• Cumulative dose—3.5 mg/kg to 7.5 mg/kg IV • Given as 1.5 mg/kg/dose IV q24h for 3–5 days • Infused over >6 h	• Platelets, leukocytes, neutrophils and CD3+ counts
Basiliximab	Monoclonal IL-2 receptor antibody	• <35 kg: two 10 mg IV doses • ≥35 kg: two 20 mg IV doses – 1st dose given during OR and 2nd dose given POD 4	N/A
Peri-operative Therapy			
Methylprednisolone	Corticosteroid	• Intra-op dosing: 10-20 mg/kg IV – 1st dose on induction, 2nd dose on release of aortic cross-clamp • Post-op taper: – Day 1-4 – 2mg/kg IV once daily reducing by 0.5 mg/kg each day – Day 5 – 0.25 mg/kg IV	N/A
Maintenance Immunosuppression			
Generic Name	**Type**	**Typical Dosing Protocols**	**Monitoring**
Cyclosporine	Calcineurin inhibitor	• First 3-6 mos: 8-15 mg/kg/day enterally divided q12h • > 3-6 mos: 4-6 mg/kg/day enterally divided q12h • Affected by drugs that influence cytochrome P450 3A4 metabolizing pathway	• TDM via trough levels • General target levels (ng/mL): – 0–3 mos post-tx – 300-350 – 4-12 mos post-tx – 250-300 – >12 mos post-tx – 150-200 • Levels 2 hours post-dose (C2) more accurately estimate AUC and may result in lower doses

Tacrolimus	Calcineurin inhibitor	• < 40 kg: starting dose ~0.05-0.2 mg/kg/day enterally divided q12h • ≥ 40 kg: starting dose 1-2 mg enterally q12h • Affected by drugs that influence cytochrome P450 3A4 metabolizing pathway	• TDM via trough levels • General target levels (ng/mL): – 0–3 mos post-tx – 10-12 – 3–6 mos post-tx – 8-10 – 6–12 mos post-tx – 6-8 – 1–2 years post-tx – 5-7 • Targets dependent on clinical course
Azathioprine	Purine antimetabolite	• Pre-transplant: 3-5 mg/kg/dose IV or enterally x 1 • Post-transplant: 1-3 mg/kg/dose enterally daily	• Monitoring of levels not clinically available • Consider decrease or discontinue for WBC < 3000-4500
Mycophenolate mofetil	Purine biosynthesis	• 20-80 mg/kg (600-1200 mg/m^2/day) enterally divided q12h • Initial doses lower to mitigate GI side effects • Up-titration q2-3 days until target dose achieved • Maximum dose not to exceed 1.5 g twice daily	• MPA (MMF metabolite) therapeutic drug monitoring trough levels • Predominant role of monitoring is supportive (drug not titrated to levels) • MMF dose modifications for side effects: GI symptoms and/or severe neutropenia
Sirolimus (Rapamycin)	mTOR inhibitor	• <40 kg: loading dose 3 mg/m^2 enterally x 1, then 1 mg/m^2 enterally daily or divided q12h • ≥40 kg: loading dose 6 mg enterally x 1, then 2 mg enterally daily	• TDM via trough levels of 5–15 ng/mL
Everolimus	mTOR inhibitor	• Currently being studied	• TDM via trough levels of 3–8 ng/mL
Prednisone	Corticosteroid	• Variable use and dosing (institution and program-specific)	N/A

d/c discontinuation, *TDM* therapeutic drug monitoring, *GI* gastrointestinal, *MMF* mycophenolate mofetil, *AUC* area under the curve, *CNI* calcineurin inhibitor

28.2 Peri-Transplant Immunosuppression

28.2.1 Induction Therapy

Induction therapy is the administration of intensive immunosuppression during the perioperative period, with the rationale being that the risk of rejection is greatest early post-transplant. The overall goal is to reduce the frequency and intensity of acute rejection and allow for the delayed introduction of nephrotoxic maintenance immunosuppression drugs [3, 4]. Induction therapy has also been used as a successful prelude to steroid-free protocols [5]. Concerns about the effect of induction therapy on post-transplant infections or post-transplant lymphoproliferative disorder (PTLD) exist; however, no association has been firmly established in pediatric heart transplantation [6]. Induction therapy has been increasingly utilized over the last 15 years. According to data from the International Society for Heart and Lung Transplantation (ISHLT) registry, nearly 75% of pediatric heart transplant recipients received induction therapy from January 2010 to June 2018, which was a significant increase from 64% in 2005 to 2009 [7]. The two most common induction agents used are anti-lymphocyte or anti-thymocyte globulin and interleukin-2 receptor antagonists, which were used in 57% and 18% of pediatric heart transplant recipients, respectively.

28.2.2 Polyclonal Anti-Thymocyte Globulin

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG) are both polyclonal antibodies produced by injecting human lymphocyte or thymus tissue into another mammalian species and then harvesting and concentrating the resultant anti-human lymphocyte antibodies produced by that animal [8]. Rabbit ATG is the most frequently used preparation, although prior generations of products were also produced in horses [9]. Polyclonal antibodies have a broad specificity and target T cells, B cells, plasma cells, monocytes, and dendritic cells (DCs) [10]. They act in three major ways: activating or altering the function of lymphocytes, lysing lymphoid cells, and altering the traffic of lymphoid cells and sequestering them, which ultimately results in depletion of lymphoid effector cells [3, 9]. The underlying mechanism of action of ATG in depleting T cells is through complement-dependent lysis in the blood compartment and apoptosis and subsequent phagocytosis by macrophages in the lymphoid tissue. ATG has also been found to downregulate adhesion molecules and chemokine receptors inhibiting lymphocyte proliferation and recruitment to the allograft especially during periods of ischemia-reperfusion injury [10]. Side effects can be seen with ATG, as by triggering T cells and the subsequent release of tumor necrosis factor alpha (TNFα), interferon γ (IFN- γ), and other cytokines, symptoms of fever and chills can occur [3].

Dosing of ATG varies in clinical practice; however, the literature has shown that a total cumulative dose of 3.5–7.5 mg/kg appears to be adequate for children at standard immunological risk receiving calcineurin inhibitor (CNI)-based maintenance therapy [11]. Dosing can be tailored according to overall risk of the patient

based on factors including age, immunologic risk (e.g., presence of pre-transplant donor-specific antibodies (DSA) or a positive crossmatch), prior cardiac surgery, and retransplantation, among other factors. However, a total dose below 3.5 mg/kg is not recommended [11, 12]. Hematological triggers of platelets, leukocytes, neutrophils, lymphocytes, and CD3+ counts are used in adults for dose modification or discontinuation and can also be applied to children [11].

28.2.3 Monoclonal Interleukin-2 Receptor Antagonists

Interleukin-2 (IL-2) is a key autocrine growth factor that induces T cell proliferation [3]. IL-2 receptor antagonists bind to the alpha subunit of the IL-2 receptor complex and block binding, thus preventing IL-2 receptor-mediated lymphocyte activation and proliferation [9]. Basiliximab is a chimeric monoclonal antibody against CD25 (IL-2 receptor alfa) and also inhibits an additional proliferation signal mediated via IL-15. Full receptor saturation can occur after a single dose with effects after two intravenous doses lasting 4–6 weeks in children [13].

28.2.4 Basiliximab Vs Anti-Thymocyte Globulin

As the use of induction therapy continues to rise in pediatric heart transplant patients, studies over the last few years have begun to compare the use of basiliximab and ATG. An analysis of pediatric heart transplant patients from the United Network for Organ Sharing (UNOS) database reviewed 2275 patients who received induction therapy with 685 receiving basiliximab and 1590 receiving ATG [4]. Basiliximab was associated with poorer long-term survival at 5 and 10 years (68% vs 76% at 5 years [$p < 0.001$] and 49% vs 65% at 10 years [$p < 0.001$], respectively). Basiliximab was associated with higher risk of death secondary to graft failure ($p = 0.013$) but not death attributable to cardiovascular causes, infection, or malignancy. Compared to ATG, use of basiliximab remained significantly associated with all-cause mortality after multivariate analysis (hazard ratio, 1.27; 95% CI, 1.02–1.57; $p = 0.030$) [4]. A study analyzing ISHLT registry data confirmed many of these findings with improved 5- and 10-year graft survival for ATG on conditional 1-year survival analysis (87.4% vs 82.1% at 5 years and 71.0% and 58.3% at 10 years [$p < 0.01$], respectively) [14]. The basiliximab cohort was more likely to experience rejection prior to discharge (17.5% vs 13.3%, $p = 0.04$) and had a higher likelihood of being discharged home on steroid maintenance (90% vs 60%, $p < 0.01$). PTLD and death due to infection did not differ between the two groups; however, infection prior to discharge did occur more frequently in the ATG cohort (23.2% vs 21.1%, $p = 0.03$) [14]. An analysis of the PHTS database comparing the impact of induction therapy on outcomes after stratifying patients by diagnosis and risk found that overall, patients who did not receive any induction therapy had lower survival ($p < 0.01$) [15]. Both ATG and IL-2 receptor antagonists were associated with an improved freedom from first rejection in patients transplanted for cardiomyopathy ($p < 0.01$).

28.2.5 Perioperative Steroids

Exact protocols, dosing, and timing of administration of perioperative IV steroids are difficult to find in the literature; however, the majority of pediatric heart transplant programs give IV methylprednisolone in the perioperative period for 2–5 days including a rapid wean to either maintenance steroids or a steroid-free regimen [9]. Timing of the initial methylprednisolone dose often aligns with the initiation of cardiopulmonary bypass and/or the release of the aortic cross-clamp. Often, methylprednisolone will be co-administered with ATG induction therapy to prevent ATG infusion reactions [16]. Practice patterns within the pediatric heart transplant community support the use of perioperative IV corticosteroids as evidenced by the fact that the term "steroid avoidance" does not mean complete avoidance but rather is generally defined as complete withdrawal of steroids from the immunosuppression protocol after the induction period [5, 9].

28.3 Maintenance Immunosuppression

Maintenance therapies are used to prevent acute rejection over the long term. Triple and dual therapy are the most commonly employed regimens and work by inhibiting T cell activation via differing pathways [16].

28.3.1 Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Calcineurin inhibitors have been the pillar of maintenance immunosuppression since cyclosporine revolutionized the field in the early 1980s [9, 16]. Calcineurin is a component of the T cell receptor (TCR) signaling pathway, which is responsible for activation and proliferation of the T cell. Cyclosporine and tacrolimus both inhibit T cell activation through calcineurin inhibition but through different steps in the activation pathway. Cyclosporine is a lipophilic molecule that binds to cyclophilins, which then complexes with calcineurin and inhibits its activity. Tacrolimus or FK506 is a macrolide antibiotic that binds to the FK-binding proteins, which then complexes with calcineurin and inhibits its activity. Pediatric data on the efficacy of cyclosporine and tacrolimus is limited [17].

There has been a trend towards an increasing use of tacrolimus over cyclosporine in pediatric heart transplant recipients based on pediatric ISHLT registry data. In the 2008 registry report, 41% of patients were receiving cyclosporine, and 56% were receiving tacrolimus at 1-year post-transplant compared to 84% of patients receiving tacrolimus at 1-year post-transplant in the 2019 registry report [16, 18]. This is likely a result of a number of factors including ease of tacrolimus administration and monitoring as well as the cosmetic influences of cyclosporine causing hirsutism and gingival hyperplasia, resulting in compliance issues especially in the teenage years [16].

28.3.2 Antiproliferative Agents: Azathioprine and Mycophenolate Mofetil

Antiproliferative agents are typically the second maintenance agent in dual- and triple-drug regimens and work by blocking B and T cell proliferation via different pathways [16]. Azathioprine is a prodrug that is metabolized to 6-mercaptopurine, which is converted to its active metabolite and subsequently interferes with nucleic acid synthesis inhibiting T and B lymphocytes [19]. Mycophenolate mofetil (MMF) is an antimetabolite that interrupts purine metabolism in T and B lymphocytes [16].

Azathioprine was primarily used in early clinical trials; however, MMF use in pediatric heart transplant patients has increased over the years with ISHLT registry data demonstrating that 94% of patients were discharged on MMF in the most recent era and 81% of patients remained on MMF at 1-year post-transplant [18]. The shift from azathioprine to MMF has been a result of large adult studies including a randomized controlled trial demonstrating that patients who received MMF over azathioprine (in addition to cyclosporine and corticosteroids) had a significant reduction in mortality at 1 year (18 [6.2%] vs 33 [11.4%], $p = 0.031$) and a significant reduction in the requirement for rejection treatment (65.7% vs 73.1%, $p = 0.026$) [20]. Similarly, an analysis of the joint UNOS/ISHLT registry database for outcomes of adult heart transplant patients treated with azathioprine versus MMF found that actuarial survival was greater in patients treated with MMF compared to azathioprine (1 year, 96% vs 93%; 3 years, 91% vs 86%, $p = 0.0012$) [21].

Pediatric studies also support the beneficial effects of MMF. Dipchand et al. reported a single-center experience on 21 pediatric heart transplant patients on calcineurin inhibitors who were switched from azathioprine to MMF [22]. The rationale for switching included rejection (66%), inability to wean steroids (14%), ABO donor-recipient mismatch (10%), coronary artery vasculopathy (CAV) (5%), and immunosuppressant side effects (5%). Of those switched for rejection, 93% demonstrated resolved or improved rejection and corticosteroids were reduced or discontinued in 48% [22]. Another single-center experience reported significantly less rejection when treating pediatric heart transplant patients with MMF in combination with a calcineurin inhibitor compared with azathioprine or corticosteroids [23].

28.3.3 Proliferation Signal Inhibitors: Sirolimus and Everolimus

Proliferation signal inhibitors (PSI) are used in immunosuppressive therapies for prevention of both acute and chronic rejection. Sirolimus is a macrolide antibiotic with a structure similar to that of tacrolimus. It binds to FK-binding protein-12, inhibiting a protein kinase, the mammalian target of rapamycin (TOR), which results in inhibition of the clonal expansion of T cells. Activation of TOR also signals proliferation of smooth muscle cells and endothelial cells in response to growth factors [16, 19]. Everolimus is an analog of sirolimus that differs by one hydroxyl group at position 40 of the molecule. It arrests the cell cycle of lymphocytes and inhibits IL-2- and IL-15-mediated T and B cell proliferation [16].

PSIs, specifically sirolimus, have been used for alternative maintenance immunosuppression, predominantly for its renal-sparing effects and to promote regression of or prevent CAV. An early pediatric single-center experience with sirolimus demonstrated it to be a valuable immunosuppressant for the management of rejection and significant renal dysfunction with improvement on follow-up biopsies and glomerular filtration rates [24]. Balfour et al. studied the renal function of 15 pediatric heart transplant patients taking calcineurin inhibitors who had sirolimus introduced to their immunosuppressant regimen. Patients were given a lower dose of calcineurin inhibitor with it completely discontinued in five patients. Renal function significantly improved in the patients within 30 days without a meaningful increase in rejection [25]. More recent data comparing utility and safety of total replacement of a calcineurin inhibitor with PSIs versus calcineurin inhibitor minimization with concomitant use of PSIs revealed on a multivariate analysis that improvement of renal function was primarily seen in patients with PSI usage within 5 years of transplantation especially in those with the total replacement strategy ($p = 0.049$) [26]. Asante-Korang et al. conducted a single-center, retrospective study of 19 patients converted from calcineurin inhibitors to either sirolimus ($n = 15$) or everolimus ($n = 4$) [27]. There were four treatment failures for rash, bone marrow suppression, rejection and renal transplantation, and one patient with recurrent rejection necessitating resumption of tacrolimus. Median creatinine was found to be higher pre-switch ($p = 0.016$), and median eGFR was lower pre-switch ($p = 0.0004$) indicating that conversion from calcineurin inhibitor to PSI can be safely accomplished [27].

A prospective study on the use of everolimus as primary immunosuppressive therapy followed 36 pediatric heart transplant patients over a 4-year period. Median calculated GFR increased from 40.7 to 48.7 ml/min, although this was not statistically significant. Median arterial blood pressure as well as triglyceride and cholesterol levels did not change significantly. Overall, this study demonstrated that calcineurin inhibitor-free immunosuppression with everolimus is an effective and safe approach [28]. However, PSIs remain second line in most pediatric heart transplant program protocols pending further experience in pediatrics.

28.3.4 Corticosteroids

Corticosteroids have been a fundamental part of heart transplant immunosuppression since its inception. Corticosteroids are nonspecific immunosuppressive medications affecting the number, distribution, and function of all types of leukocytes as well as endothelial cells [19]. The major effect on lymphocytes is through binding to nuclear factor kappa B and inducing an inhibitory protein. This prevents translocation of nuclear factor kappa B into the nucleus and transcription of pro-inflammatory cytokines [9]. Corticosteroids are associated with a number of detrimental adverse effects including impaired constitutional growth, facial swelling, acne, weight gain, osteopenia, avascular necrosis, fractures, gastritis, abnormal hair growth, adrenal insufficiency, hypertension, and psychiatric conditions [9, 16, 19].

Prednisone use in the pediatric population is decreasing with ISHLT registry data demonstrating that 66% of recipients were discharged on prednisone in the most recent era (January 2010–June 2018) compared to 74% in the previous era (January 2005–December 2009) [18]. Single-center pediatric studies have reported that corticosteroids can be avoided in pediatric heart transplant recipients with negative donor-specific crossmatch and induction with ATG with 92% freedom from rejection at 6 months and 87% at 1 year, and overall post-transplant survival rates of 91% at 6 months and 88% at 1 year [5]. Analysis of the Organ Procurement and Transplantation Network (OPTN) database for patients undergoing heart transplant between 1990 and 2010 for conditional 30-day graft loss and death based on maintenance steroid use showed no difference between propensity-matched cohorts [29]. This led the authors to conclude that a steroid-free regimen avoids complications of steroid use without compromising graft survival. A similar analysis was performed using the PHTS database for patients transplanted between 1993 and 2011 revealing no difference in graft loss or graft loss secondary to rejection. At 1-year post-transplant, there was no difference in freedom from rejection or malignancy, but there was higher incidence of rejection with severe hemodynamic compromise and infection in the steroid-free cohort [30].

A multicenter, prospective, cohort study reported 1-year outcomes among recipients without pre-transplant DSAs who received induction with ATG and maintenance immunosuppression with tacrolimus and MMF and no steroid use beyond 1 week [31]. Patients without DSAs at transplant and managed with a steroid-free protocol had excellent short-term survival (94.5%) and a low risk of first-year diabetes and PTLD.

28.4 Side Effects of Immunosuppression

Each immunosuppressive regimen has a different set of risks and benefits. It is important to have an understanding of the adverse effects associated with each medication and how to manage them.

28.4.1 Gastrointestinal Symptoms

Gastrointestinal symptoms are generally a side effect of MMF and can lead to nausea, vomiting, diarrhea, abdominal pain, and weight loss [9]. These symptoms are generally responsive to a decrease in dosage; however, at times, it requires discontinuation of MMF [19].

28.4.2 Myelosuppression

Myelosuppression is a universal side effect seen in almost all immunosuppressant medications, and complete blood counts should be monitored. Azathioprine

specifically can cause complete bone marrow failure with leukopenia, anemia, and thrombocytopenia [16]. Patients with polymorphisms in the TPMT gene can especially be affected with alterations in the metabolism of azathioprine resulting in marrow toxicity and life-threatening reactions [32]. These side effects are generally dose-dependent, however, and usually resolve within 7–10 days of dose reduction [19]. MMF is more commonly associated with anemia and neutropenia; however, thrombocytopenia does occur [19]. Sirolimus is also associated with thrombocytopenia, anemia, and leukopenia. The thrombocytopenia seen with sirolimus tends to be dose related and reversible, and severe thrombocytopenia is rare [19].

28.4.3 Diabetes Mellitus

New-onset diabetes mellitus (NODM) is a significant complication as it contributes to a number of factors that affect graft function and survival, including coronary artery disease, chronic kidney disease, and peripheral vascular disease. Tacrolimus and corticosteroid use at discharge were found to be independent risk factors for the development of NODM in adult heart transplant recipients [33]. Hyperglycemia is especially common at higher doses of tacrolimus and in certain subgroups including women and black race. As well, NODM has been shown to be more common when tacrolimus is combined with azathioprine over MMF [34]. Once patients develop NODM on tacrolimus, switching to a CNI-free regimen is unlikely to reverse the course; however, weaning corticosteroids can provide adequate glycemic control. A pediatric study reviewing NODM in heart transplant recipients from the OPTN database did not find immunosuppressive medications to be an independent risk factor [35]. The major modifiable risk factor identified in this study was obesity highlighting the importance of diet, exercise, and preventative intervention strategies. Transplantation before the year 2000 was also an independent risk factor for NODM in this study, and the authors speculate that this is related to the decreased use of maintenance corticosteroids after this era [35].

28.4.4 Impaired Wound Healing

Impaired wound healing has been reported to be associated with PSIs. This is a result of these medications inhibiting the translation of transcription factors such as vascular endothelial growth factor (VEGF) resulting in reduced angiogenesis and interference with wound healing [27]. Adult heart transplant studies using primary initiation of everolimus have not shown significant differences in overall rates of wound dehiscence or sternal complications; however, the combined rate of serious incisional complications was increased [36]. This has led to some discouraging the de novo use of PSIs due to the high percentage of early withdrawal. However, a recent pediatric study demonstrated only 1 wound infection out of 13 surgical procedures, suggesting that sirolimus can be used or continued in pediatric patients undergoing major surgical procedures during the perioperative period [37]. These

results may be associated with the fact that in many studies, only BMI is significantly associated with wound healing complications and elevated BMI may play a more significant role than PSIs [36].

28.4.5 Hyperlipidemia

Hyperlipidemia and hypertriglyceridemia are seen with the use of PSIs. Despite elevated triglyceride levels, adult heart transplant studies show that everolimus is efficacious in preventing CAV when compared to other immunosuppressive medications [38]. In the single-center, retrospective pediatric study of conversion from CNI to PSIs as primary immunosuppressive therapy, median LDL, total cholesterol, and triglyceride levels increased from before to after the switch [27]. These increases were all statistically significant; however, it did not seem to affect graft function or development of CAV. Overall, the authors suggest that all patients over the age of 10 years be prescribed HMG-CoA reductase inhibitors and that patients on PSIs should be monitored and may require additional lipid-lowering medications [27].

28.4.6 Chronic Kidney Disease (CKD)

Calcineurin inhibitors can cause nephrotoxicity by limiting renal blood flow caused by constriction of the afferent arterioles in the glomerulus [39]. The effect on the kidneys can be exacerbated by dehydration, as well as concomitant use with NSAIDs, ACE inhibitors, and multiple other drugs. Given the widespread development of CKD in heart transplant recipients on CNIs and the associated morbidity and mortality, multiple adult and pediatric studies have focused on modifications to the immunosuppression regimens. A single-center, retrospective pediatric review evaluated the effect on renal function of a CNI minimization protocol using sirolimus in pediatric heart transplant recipients with CNI-induced renal insufficiency and demonstrated improved renal function as measured by GFR at 2 years ($p = 0.018$) [40]. Another pediatric single-center experience demonstrated improvement in renal function in two out of three patients who underwent minimization of tacrolimus and addition of sirolimus for renal dysfunction [24].

28.4.7 Post-Transplant Lymphoproliferative Disorder (PTLD)

The risk of malignancies develops over time post-transplant with 16% of survivors developing malignancy at 15 years post-transplant according to ISHLT registry data [18]. The majority of the malignancies are lymphomas or PTLD. Primary Epstein-Barr virus (EBV) infections after transplantation and insufficient EBV-directed cellular immunity have been linked as key pathogenic mechanisms for PTLD development [41]. Pediatric studies on PTLD have demonstrated that higher maximum EBV load ($p = 0.004$) and longer duration of induction therapy ($p = 0.02$) were

associated with increased risks of PTLD [42]. That being said, no specific immunosuppressive agents or regimens have been specifically linked to an increased risk for the development of PTLD. Most programs aim to minimize risk by using the lowest amount of immunosuppression deemed safe based on an individual patient's risk profile and clinical picture. Reduction or temporary discontinuation of immunosuppression at the time of PTLD diagnosis is used by most centers as a component of initial treatment in order to allow one's native immunoregulation to reverse lymphoproliferation [42, 43].

28.5 Conclusions

Post-transplant immunosuppression has evolved over the years for pediatric heart transplant recipients. In general, the majority of pediatric heart transplant recipients receive induction therapy with ATG followed by maintenance immunosuppression with a combination of tacrolimus and MMF. Many centers continue to use corticosteroid maintenance; however, there is increasing use of steroid-free and rapid steroid weaning protocols. There is also a rise in programs converting patients to PSI-based regimens demonstrating that the evolution in this field is ongoing. As transplant clinicians, it is imperative to not only be aware of the different regimens that exist but to also carefully balance drug side effects and comorbidities. The ultimate goal is to establish a regimen that optimizes the pediatric heart transplant recipient's quality of life and overall patient and graft survival.

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