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A Review of Induction with Rabbit Antithymocyte Globulin in Pediatric Heart Transplant Recipients

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Pediatric heart transplantation (pHTx) represents only a small proportion of cardiac transplants. Due to these low numbers, clinical data relating to induction therapy in this special population are far less extensive than for adults. Induction is used more widely in pHTx than in adults, mainly because of early steroid withdrawal or complete steroid avoidance. Antithymocyte globulin (ATG) is the most frequent choice for induction in pHTx, and rabbit antithymocyte globulin (rATG, Thymoglobulin®) (Sanofi Genzyme) is the most widely-used ATG preparation. In the absence of large, prospective, blinded trials, we aimed to review the current literature and databases for evidence regarding the use, complications, and dosages of rATG. Analyses from registry databases suggest that, overall, ATG preparations are associated with improved graft survival compared to interleukin-2 receptor antagonists. Advantages for the use of rATG have been shown in low-risk patients given tacrolimus and mycophenolate mofetil in a steroid-free regimen, in sensitized patients with pre-formed alloantibodies and/or a positive donor-specific crossmatch, and in ABO-incompatible pHTx. Registry and clinical data have indicated no increased risk of infection or post-transplant lymphoproliferative disorder in children given rATG after pHTx. A total rATG dose in the range 3.5–7.5 mg/kg is advisable.

MeSH Keywords: **Antilymphocyte Serum • Heart Transplantation • Pediatrics**

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Background

Children (<18 years old) account for approximately 14% of all heart transplants (HTx), with numbers rising gradually over the last decade [1]. Survival rates in pediatric heart transplantation (pHTx) have increased progressively over time, reaching more than 90% at 1 year, with the longest survival times in infants and children aged up to 5 years at time of transplant [1,2]. During the first post-transplant year, graft failure, rejection, infections, and multiple organ failure are major reasons for death, with cardiac allograft vasculopathy (CAV) becoming a more common cause in recent years [3].

There are substantial differences between adult and pediatric HTx recipients. Children transplanted for dilated cardiomyopathy are less likely to be sensitized due to previous blood transfusions than are adults [4–6], and sensitization due to pregnancy does not apply. However, children suffering from congenital heart disease (CHD) or on mechanical circulatory support have high levels of panel reactive antibody (PRA) (up to 27%) [7]. Two-thirds of children undergoing HTx in the USA have no PRAs [2]. Age also influences rejection risk. The youngest children (<6 years) have a lower risk for early or late acute rejection than do older children [2], while those aged more than 6 years show similar rates of rejection to those of younger adults [2]. Over-immunosuppression should be avoided in infants due to the higher risk of post-transplant lymphoproliferative disorder (PTLD) than in adults [2,8]. Lastly, the imperative to minimize long-term metabolic complications such as post-transplant diabetes mellitus (PTDM) is more pressing in children, since they will require immunosuppression for many decades, with the additional need to ensure that growth is as normal as possible. Immunosuppression regimens in pediatric transplant patients must be carefully planned to take into account their immunological status and long-term risks for immunosuppression-related complications, and minimized where possible [9].

Even though induction therapy is given more frequently in pHTx [9] than in adult HTx [2,10], and its use has increased in recent years [1,11], evidence-based prescribing criteria are lacking. Data from the International Society for Heart and Lung Transplantation (ISHLT) have shown that approximately 70% of children are now given induction therapy after heart transplantation, most frequently antithymocyte globulin (ATG) (~50% of patients), with less use of interleukin-2 receptor antagonist (IL-2RA) induction (~22%) [1]. The Pediatric Heart Transplant Study (PHTS), a multicenter US registry, recently reported similar rates of ATG and IL-2RA induction (48% and 35%), with 27% given no induction [11]. Evidence from the ISHLT [9] and PHTS [11] databases indicates that in children, ATG induction tends to be preferred to IL-2RA induction in younger patients (especially <6 months), in those with CHD, in patients requiring pre-transplant inotropic support or extracorporeal membrane oxygenation (ECMO), and in more sensitized patients or those with longer ischemic time [11,12].

Rabbit antithymocyte globulin (rATG, Thymoglobulin®) is the most frequently used ATG preparation. It is licensed for the prophylaxis of acute graft rejection in heart transplantation, with no age restriction. However, randomized trials comparing outcomes with rATG versus other induction agents – or versus no induction – have not been undertaken. This is largely due to the small number of pHTx procedures performed (<600 annually worldwide [9]). Data are instead derived from prospective or retrospective studies performed at single centers, usually with no comparator arm, and from registry analyses.

The authors of the present study all represent German-speaking HTx centers experienced in the use of rATG induction. Our group has previously published expert opinion articles concerning the appropriate use of rATG induction in adults undergoing HTx [8] and proposals for rATG dosing and early maintenance regimens in this setting [13]. Recognizing the important differences between adult HTx and pHTx and attempts towards patient-orientated tailored immunosuppressive regimens, we aimed to review available studies relating to rATG induction in pHTx, and to consider its role within modern immunosuppressive strategies in this unique population. Given the lack of large prospective trials, the present review is necessarily based on registry databases and studies with relatively weak designs. Moreover, given that almost 50% of all US pHTx procedures are undertaken at centers performing <10 pHTx per year, and an even higher proportion outside the US [9], it is helpful to share our limited experience with one another.

A literature search was performed in April 2017 using PubMed MeSH (medical subject headings) as the core database, with no time or language restrictions. Search terms included heart transplantation, pediatric, children, induction, antithymocyte, rabbit antithymocyte globulin, ATG, and thymoglobulin. Articles with no abstract in English were excluded. The reference lists of original articles and review articles were checked for additional citations. Studies in patients <18 years were considered to represent pHTx.

Evidence from Registry Analyses: Efficacy

The low number of pHTx places particular value on national and international transplant registries, which capture data from multiple centers. While informative, however, registry analyses have certain important weaknesses. To improve statistical power, data are often assessed over many years, despite changes in clinical practice over time. Patients given different lymphocyte-depleting or ATG preparations are often included

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in a single group – or, indeed, all induction therapies may be grouped together – disregarding differences between agents. There is also an absence of dosing information, an important factor because rATG doses have been reduced substantially in recent years [14]. Furthermore, the type of maintenance immunosuppression is not always taken into account and dose/exposure levels of maintenance therapies are not considered. Multivariate analyses or propensity scores approaches attempt to address some of these weaknesses and to minimize selection bias in prescribing induction agents, but, as in any observational study, all bias cannot be excluded.

Any induction

Butts et al. recently published an analysis of data from the United Network for Organ Sharing (UNOS) registry, which assessed graft survival in 2792 primary pHTx recipients who did or did not receive induction therapy [15]. The study grouped all types of induction therapy (rabbit or equine ATG preparations, OKT3 or IL-2RA agents), and included patients transplanted over a 10-year time span (1994–2013). A robust statistical approach based on propensity-score-matched transplants was applied. The hazard ratio (HR) for graft loss was 0.88 (95% CI 0.75–1.01, p=0.07) with any induction versus no induction. In the subgroups of highly sensitized patients (204 patients with PRA >50%; HR 0.57 [95% CI 0.34–0.97]) and patients with CHD (n=1210; HR 0.78 [95% CI 0.64–0.96]), induction was associated with a lower risk for graft loss [15]. A recent study of pediatric heart transplant recipients registered with the US PHTS database also found lower patient survival in children without induction overall, on univariate analysis (p<0.04) [11]. Registry data are conflicting as to whether induction therapy of any type is associated with higher or lower rates of rejection compared to children given no induction [1,11], which may reflect variations in the extent to which analyses account for preferential use of induction in higher-risk children.

Interestingly, induction does not seem to affect short-term patient survival. However, ISHLT data from 2004 to 2013 showed no association with induction versus no induction and survival at 1 year after heart transplantation in children [3]. Strikingly, the most recently published data on pediatric heart transplant recipients registered with the ISHLT for the first time showed a small but significant association between induction therapy and CAV-free survival, which could potentially contribute to a longer-term survival advantage [1].

Induction by class

In the study by Butts et al., graft survival was compared for rabbit or equine ATG versus IL-2RA induction in 535 propensity-matched pairs of children [15]. Results showed a significantly higher risk of graft loss with IL-2RA induction (HR 1.34, 95% CI

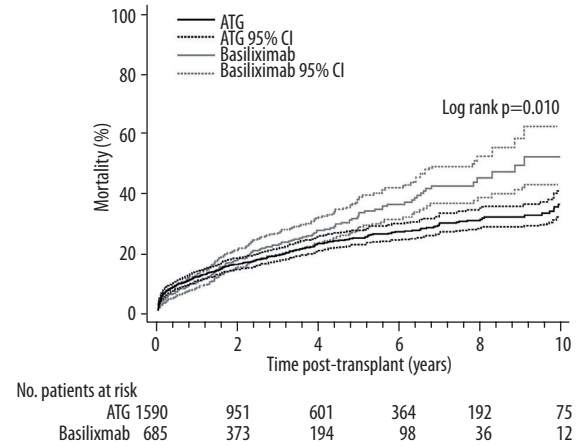

Figure 1. All-cause mortality in pediatric recipients of heart transplant during 2001–2013 who received either antithymocyte globulin (ATG) or basiliximab induction (OPTN data; Kaplan-Meier estimates) [14]. Multivariate analysis confirmed the higher mortality risk with basiliximab versus ATG induction (HR 1.27, 95% CI 1.02–1.67, p=0.030). The figure is reproduced with permission from Ansari D, Höglund P, Andersson B, Nilsson J. Comparison of basiliximab and antithymocyte globulin as induction therapy in pediatric heart transplantation: A survival analysis. J Am Heart Assoc 2015; 5(1). pii: e002790 [Available at: *http://jaha.ahajournals.org/content/5/1/e002790*] [16].

0.02–1.76; p=0.03). Consistent with this, an ISHLT analysis of pHTx, based on a more recent time period (2000–2012), also observed that ATG (of any type) was associated with improved survival versus those given IL-2RA induction, on univariate analysis (p=0.014), but no multivariate analysis was performed [9]. Lastly, another UNOS analysis compared 1612 patients given ATG induction after pHTx to 699 given the IL-2RA agent basiliximab [12]. Transplants between 2001 and 2013 were included, with a median follow-up of 2.7 years. Differences in recipient, donor, and transplant characteristics, and in maintenance immunosuppression, were included in a multivariate model. The results again showed basiliximab to be associated with an increased risk for mortality versus ATG, both on univariate analysis (Figure 1) and multivariate analysis (HR 1.27, 95% CI 1.02–1.67, p=0.030). The difference in mortality was due to increased graft failure (p=0.013), with no difference in deaths from cardiovascular causes, malignancy, or infections [12]. The same group performed a similar analysis in 9324 adult recipients of a HTx during 2001 to 2011 and also found basiliximab to be associated with increased mortality risk versus ATG over a median of 3 years of follow-up [16]. Taken together, these findings indicate that ATG induction is more effective than IL-2RA induction after HTx in children.

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rATG Induction with Conventional Immunosuppressive Regimens

There are limited data regarding use of rATG induction in children receiving a standard triple regimen [17–19], published in the late 1990s to early 2000s. Di Filippo and colleagues described their single-center experience in 30 children during 1984–2001 who were given rATG dosed according to platelet count, at a median cumulative dose of 8.0 mg/kg [17]. Maintenance therapy consisted of cyclosporine, azathioprine, and steroids [17]. During year 1, 15 patients (50%) experienced rejection, leading to graft loss in 3 patients, and 40% of patients experienced infection in month 1. Such high rATG dosing is no longer used, however, and cyclosporine-based triple regimens with azathioprine have been superseded. In general, rATG with standard triple therapy is used only selectively. The ISHLT comments that ATG may be beneficial in patients at high risk for acute rejection [20].

rATG and Steroid Minimization or Avoidance

Long-term steroid therapy after solid organ transplantation has a well-established association with increased metabolic abnormalities [21], adverse skeletal effects [22,23], and risk of infections [24,25]. Steroid avoidance has been shown to achieve significant benefits in pediatric transplant recipients, including improved growth [26–28]. Nevertheless, approximately 70% of children who undergo HTx are discharged from hospital on steroid therapy [2,9] and more than half of all children are still receiving steroids at 1 year after transplant [2,9]. Early, retrospective, single-arm studies of steroid-free maintenance therapy without induction therapy during the cyclosporine era described high early rates of rejection [29], or a lower rejection rate but only at the cost of high cyclosporine exposure and renal dysfunction [30]. Induction therapy appears essential to avoid or to minimize steroid exposure. An OPTN analysis from 1990 to 2010 found no significant difference in graft survival between patients discharged from hospital with or without steroids in a population of 462 propensity-matched pairs given induction therapy in 89% of cases (the type of induction was not stated) [31]. The ISHLT guidelines published in 2010 include the recommendation that 'routine use of induction therapy with a polyclonal preparation is indicated when complete steroid avoidance is planned after HTx' [20].

A retrospective 2-center experience with rATG and steroid-free therapy in children undergoing HTx has been described by Singh et al. [32] (Table 1). Fifty-five patients transplanted during 2005–2009 who had a negative donor-specific flow cytometry crossmatch (49 with PRA <10%, 6 PRA ≥10%) received rATG, oral tacrolimus, and mycophenolate mofetil (MMF)). rATG was given at a dose of 1.5 mg/kg for 5 days (range 3–6 days), with an intravenous dose of methylprednisolone. Five patients died from multi-organ failure during post-transplant hospitalization. Among the remaining 50 patients, 8 (16%) started steroids in response to rejection, development of donor-specific antibody (DSA), or persistent enteropathy. Freedom from rejection, defined as cellular rejection (ISHLT grade ≥2R) or antibody-mediated rejection (AMR) according to pre-defined criteria, was 92% at month 6, 87% at year 1, and 81% at year 2 (Figure 2) [32]. One patient, who was pre-sensitized, died from AMR after developing DSA; no other patients died after leaving hospital. In the absence of a control arm, no firm conclusions can be drawn, but these results are encouraging for steroid-free therapy with rATG induction in patients at low immunological risk.

In 2013, Marshall et al. published a retrospective observational single-center study comparing a historical cohort of 64 patients given an induction-free triple regimen versus a cohort of 39 patients given rATG induction with tacrolimus, MMF, and no oral steroids [33] (Table 1). Drug doses and exposure levels were not reported. PRA >10% was present in 14% of the historical control group and 10% of the new protocol group. The 2 groups were similar except for non-significant trends to shorter ischemia time (mean 187 versus 209 min) and more ABO-incompatible transplants (10% versus 2%) in the steroid-free group. The incidence of acute rejection in the first year post-transplant was significantly lower with steroid-free rATG/tacrolimus/MMF therapy than with induction-free cyclosporine-based triple therapy (36% versus 58%, p=0.042) [33] (Figure 3). However, determining the specific effect of rATG induction in this analysis is not possible because tacrolimus and MMF are more potent in suppressing rejection than cyclosporine and azathioprine [38,39], but rATG induction with tacrolimus and MMF maintenance therapy offered adequate steroid-free immunosuppression.

Retrospective, uncontrolled studies have been published describing the use of rATG induction to support early steroid withdrawal (<1 week), or entirely steroid-free regimens, with tacrolimus and MMF maintenance therapy after pediatric kidney transplantation [28,40–42]. These have reported rare or no acute rejection with good longitudinal growth and normal bone density, although, as in pHTx, prospective trials are lacking.

rATG Induction in Sensitized Patients

The ISHLT advises that pediatric recipients with pre-formed alloantibodies and a positive donor-specific crossmatch should receive induction therapy [20]. As described above, Butts and colleagues analyzed UNOS registry data from patients who underwent pHTx during 2003–2013 [15]. Their study included an analysis of graft survival in patients with PRA <10%, 10–50%,

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Table 1. Overview of selected clinical studies of rATG induction in subpopulations of pediatric heart transplant patients.

Study	Design	Follow-up	Population	n	rATG induction	Maintenance IS	Control regimen	Key outcomes	Comments
Steroid avoidance regimen									
Singh 2010 [32]	Retrospective Single arm 2 centers	Median 19 months	49 sensitized 6 non-sensitized	55	1.5 mg/kg (median 5 doses)	IV steroids (median 5 days) TAC MMF	–	5.4% cellular rejection[a] 9.1% AMR	Maintenance steroids required in 8/50 patients who survived beyond discharge
Marshall 2013 [33]	Retrospective Historical controls Single center	1 year	Standard risk	103	1.5 mg/kg ×5	IV steroids to day 5 TAC MMF	No induction CsA AZA Steroids	Acute rejection 36% *vs.* 58% (log rank p=0.42)	Similar rates of bacterial, fungal and viral infections
Sensitized patients									
Jacobs 2004 [34]	Retrospective Single center	Not stated	Sensitized[b] (n=8) Non-sensitized (n=52)	60	Dose not specified	CNI AZA or MMF Pulsed steroids to day 4		50% *vs.* 15.4% mortality	1/8 sensitized patients died after graft rejection; 3/8 deaths were unrelated to rejection
Pollock-BarZiv 2007 [35]	Retrospective Single arm Single center	Median 1.7 years	Sensitized[c]	13	1.5 mg/kg (2–7 days)	TAC MMF Steroids	–	ACR 53.8% AMR 46.2%	No hemodynamic compromise or impaired systolic function due to rejection except 1 rejection-related death
Holt 2007 [36]	Retrospective Single arm Single center	3 years	Sensitized[d]	13	Not specified[e]	CNI AZA or MMF Steroids to month 6	–	Acute rejection 92.3%	1 death due to ACR 1 death due to AMR
ABO-incompatible transplantation									
Daebritz 2007 [37]	Retrospective Single arm Single center	12–17 months	ABO-incompatible	3	3 mg/kg ×1 then 2 mg/kg/day adjusted by lymphocyte count	TAC MMF	–	No rejection	3/3 grafts functioning at year 1

ACR – acute cellular rejection; AMR – antibody-mediated rejection; AZA – azathioprine; CNI – calcineurin inhibitor; CsA – cyclosporine; IS – immunosuppression; IV – intravenous; MMF – mycophenolate mofetil; PRA – panel reactive antibodies; TAC – tacrolimus. [a] ISHLT graded 2R/3A; [b] Elevated PRA (>10%); [c] Elevated PRA (>10%) or positive T cell or B cell crossmatch (n=10; daily plasmapheresis ± IV immunoglobulin G was given to patients with positive crossmatch); [d] Elevated PRA (>10%) and positive T cell or B cell crossmatch (treated with pre- and post-transplant plasmapheresis); [e] Antithymocyte globulin (ATGAM) was used until 1995.

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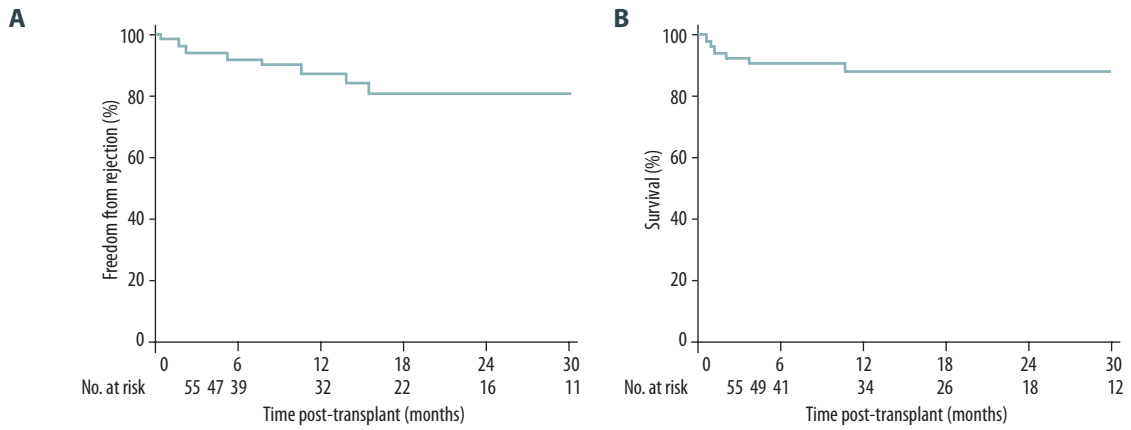

Figure 2. (**A**) Freedom from rejection and (**B**) survival in 55 pediatric heart transplant patients receiving rATG induction with tacrolimus and MMF maintenance therapy (a 2-center retrospective analysis). Rejection was defined as cellular rejection (ISHLT grade ≥2R) or antibody-mediated rejection (Kaplan-Meier estimates) [32].

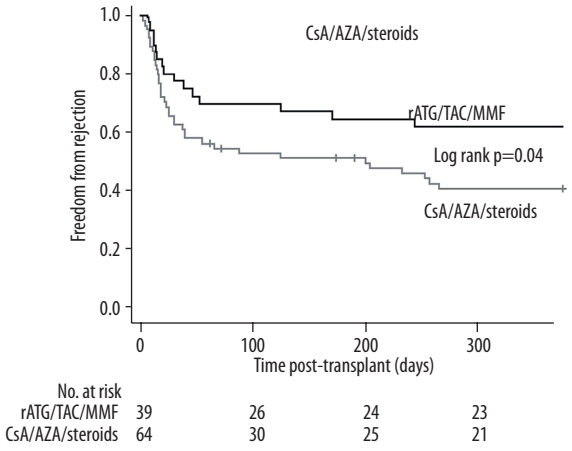

Figure 3. Freedom from rejection in the first year after pediatric heart transplantation in 64 patients given no induction with cyclosporine/azathioprine/steroids as maintenance therapy (2005–2008) versus 39 patients given rATG induction with tacrolimus/MMF and no oral steroids as maintenance therapy (2008–2010) (a single-center retrospective analysis) (Kaplan-Meier estimates) [33].

or >50%, based on 1369 propensity-matched pairs in which one patient was given induction and the other was induction-free. The HR values for graft survival for induction versus no induction increased dramatically in the highly sensitized patients (Table 2). Outcomes with ATG induction specifically were not assessed in the subgroups with different PRA levels.

Use of rATG induction in small series of sensitized children undergoing HTx has been described in the literature [34–36] (Table 1). The first report, in 2004, retrospectively assessed outcomes in 8 patients with PRA >10% and in 52 patients with non-elevated PRA (≤10%), all transplanted between 1995 and 2003 [42]. Immunosuppression comprised rATG (the dose was not specified), pulse steroids for 4 days, and intravenous immunoglobulin, with a calcineurin inhibitor (CNI) (usually cyclosporine) and either azathioprine or MMF. Overall mortality was higher in the sensitized group (50% versus 15.4%, p=0.043), but using this relatively intensive immunosuppressive strategy, only 1 graft in the sensitized group was lost to rejection. Pollock-BarZiv et al. subsequently reported use of rATG induction in HLA-sensitized patients with a more contemporary maintenance regimen [35]. In their series, 13 patients who underwent pHTx with PRA >10%, or with a positive

Table 2. Multivariate Cox regression analysis of graft loss in 1369 propensity-scoring matched pairs of pediatric heart transplant patients, according to PRA level (OPTN data 1994–2013).

PRA level	No. pairs	Hazard ratio (induction *vs.* no induction)	95% CI
<10%	1120	0.91	0.76–1.08
10–50%	147	0.86	0.51–1.45
>50%	102	0.57	0.34–0.97

CI – confidence interval; OPTN – Organ Procurement and Transplantation Network; PRA – panel reactive antibodies.

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T or B cell crossmatch, received rATG (1.5 mg/kg/day for 2–7 days), followed by triple therapy with tacrolimus, MMF, and steroids. All patients underwent plasma exchange peri-operatively, and 12 patients with a positive crossmatch underwent daily plasmapheresis for 12 days post-operatively. Five patients were also given weekly intravenous immunoglobulin and MMF (20 mg/kg/day) pre-transplant. Based on B cell counts, rituximab was administered in 9 patients and cyclophosphamide was administered in 2 early patients [35]. AMR developed in 9/13 patients and 7/13 patients had early acute cellular rejection, with no hemodynamic compromise or impaired graft function in any case, other than 1 patient who died due to severe acute rejection and AMR on day 11. No AMR developed after month 6, and none of the 9 patients who survived beyond month 9 were diagnosed with CAV, PTLD, or malignancy after a median follow-up of 1.7 years. Although AMR was relatively common early post-transplant, graft dysfunction or graft loss as a result was infrequent in this challenging patient group [35]. Similar results have been reported in a retrospective analysis by Holt et al., in a cohort of 13 pre-sensitized children (PRA >10%) who also had a positive T cell or B cell crossmatch [36]. Plasmapheresis was performed shortly before transplant and for 5–7 days post-transplant, with rATG (or in early patients, ATGAM) for 7–14 days (no dose was stated) and cyclophosphamide for 4 weeks. Maintenance therapy comprised cyclosporine or latterly tacrolimus, with azathioprine or MMF, plus steroids to month 6. In this series, 12 of the 13 patients experienced rejection, usually associated with hemodynamic compromise. One- and three-year survival rates were 85% and 73%: 1 death was considered to be due to acute cellular rejection and 1 due to AMR. rATG induction was only a single component in these complex regimens, so its specific role cannot be defined, but it is unlikely that randomized trials will be conducted in this setting and these results are encouraging.

ABO-Incompatible Transplants

ABO-incompatible transplantation has been pioneered in pHTx due to the imperative to save lives in severely ill children for whom transplantation cannot be delayed by waiting for an ABO-compatible graft. Such transplants have generally been performed in neonates, in whom the immune system is relatively immature. An analysis of transplants reported to the Pediatric Heart Study database during 1996–2008 assessed 85 ABO-incompatible transplants in patients aged up to 15 months, and compared outcomes to 417 ABO-compatible transplant recipients who were also aged ≤15 months [43]. One-year survival rates were similar in a risk-adjusted analysis [43]. This is in line with the findings of an analysis from the OPTN database that observed comparable survival to 3 years post-transplant [44].

rATG induction is widely used in ABO-incompatible HTx in children, and preliminary data from small series have been published (Table 1). As above, Pollock-BarZiv and colleagues included 6 ABO-incompatible patients in their cohort of sensitized patients, but did not present outcomes specifically in these 6 cases [35]. Daebritz et al. described 3 infants undergoing ABO-incompatible HTx who were managed with intraoperative plasmapheresis, rATG (3 mg/kg then 2 mg/kg, adjusted to reach a lymphocyte count of 200-400/μL), and intravenous methylprednisolone, using a maintenance regimen of tacrolimus, MMF, and steroids [37]. At 1 year, all 3 patients were rejection-free with good graft function. A larger series, involving 57 children aged 0.03–90 months who received 58 ABO-incompatible HTx, has been reported by Urschel et al., who surveyed 6 centers in Europe and the USA [45]. Graft survival was high (100% at year 1, 96% at year 5) with low rates of acute cellular rejection (7%) and AMR (12%). However, due to the nature of the analysis across 4 centers and over 9 years, management practices and immunosuppression varied widely. Only 34% of patients were given rATG and a further 27% were given equine ATG, so it is difficult to draw conclusions about the role or rATG.

Safety Issues

Risk of infection

Randomized trials of rATG induction versus IL-2RA induction in adult HTx recipients have shown no difference in the rate of infections overall, or for cytomegalovirus (CMV) infection in particular [46,47]. The only randomized trial of rATG induction following HTx is that of Yamani et al., which was conducted in adults [46]. The study compared rATG (total dose 6 mg/kg) and a steroid-free regimen versus no induction and standard steroids, both with tacrolimus and MMF, in 32 low-risk individuals [46]. The authors stated that there was no relevant difference in the incidence of infections during the first year post-transplant (no data were provided). CMV infection occurred in 19% of rATG-treated patients versus 25% of controls, with pneumonia in 6% and 13%, respectively. Marshall and colleagues observed a similar rate of bacterial, fungal, CMV, and EBV infections when they compared 39 children given rATG induction with tacrolimus and MMF versus 64 historical induction-free controls treated with cyclosporine, azathioprine, and steroids [33].

Registry data also indicate no increased risk for infection in children receiving rATG induction after HTx [48]. A PHTS analysis assessed 2374 children who underwent transplantation from 1999 to 2008 at 32 centers [48]. Of these, 1258 received induction therapy, including 246 who were given rATG. Overall, the proportion of patients given steroid maintenance therapy was lower in the induction group (39% versus 61% in patients

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Table 3. Observed incidence of infections by year 1 in pediatric heart transplant patients at 32 centers during 1993–2007 (Pediatric Heart Transplant Study) [48].

	rATG (n=247)	IL-2RA induction (n=242)	No induction (n=1111)
Bacterial	41 (16.6)	32 (13.2)	228 (20.5)
Fungal	5 (2.0)	3 (1.2)	54 (4.9)
Viral	21 (8.5)	36 (14.9)	150 (13.5)
CMV	8 (3.2)	6 (2.5)	73 (6.6)

rATG – rabbit antithymocyte globulin; IL-2RA – interleukin-2 receptor antagonist.

Table 4. Univariate analysis of risk for PTLD by year 3 after pediatric heart transplantation according to type of induction therapy at 32 centers during 1993–2007 (Pediatric Heart Transplant Study) [48].

	N	HR for PTLD (versus no induction*)	95% CI	P value
Any induction**	1,258	0.63	0.27–0.95	0.027
rATG	246	0.31	0.10–0.98	0.046
IL-2RA induction	244	0.45	0.16–1.23	0.120

* 1,116 patients had no induction; ** Induction comprised rATG (n=329), IL-2RA (n=244), antithymocyte serum (ATS, n=231), antithymocyte globulin excluding rATG (n=329) and OKT3 (n=194).

with no induction). The incidences of viral, fungal, or bacterial infections over the first year post-transplant were all lower in the rATG-treated group than in those given no induction, as was the incidence of CMV infection (Table 3) [48]. It is possible that these lower rates of infection may be related to reduced steroid exposure or a lower requirement for anti-rejection steroid therapy in the cohort given rATG induction (mean 1.06 versus 1.33 rejection episodes in the no-induction group; p<0.001), but this cannot be confirmed.

It seems reasonable to conclude that rATG induction does not increase the risk for infection in children after HTx.

Post-transplant lymphoproliferative disorder

PTLD is a well-recognized and potentially fatal complication after solid organ transplantation. It affects approximately 0.8% of kidney transplant recipients [49] but occurs more frequently (>1.0%) after HTx [50]. Children are at greatly increased risk for PTLD versus adults [2,51] and PTLD is the most common form of post-transplant malignancy in children [52]. The incidence of PTLD after pHTx has been reported to be 8% at 5 years post-transplant, most frequently affecting the gastrointestinal tract and respiratory system [53]. This increased risk is believed to be due to primary EBV infection of seronegative children [54]: 40–50% of patients aged <18 years are EBV-negative at time of transplant [48,55]. OPTN data show the 5-year incidence rate of PTLD to be approximately 4% in children receiving a HTx during 2001–2011, rising to 6% in EBV-negative children [2]. EBV contributes to the development of PTLD in more than 70% of cases [56], and EBV seronegativity is an independent predictor for PTLD [48,57]. One large-scale OPTN analysis (n=5169) found that 65% of pHTx patients who developed PTLD were EBV-negative compared to 42% of those without PTLD (p<0.001) [55]. Multivariate analysis showed a diagnosis of PTLD to be associated with more than a 3-fold increase in mortality risk [55].

The relative rarity of PTLD makes an accurate assessment of the effect of specific immunosuppressive agents difficult. Registry analyses, which offer the large populations necessary for evaluation, frequently span periods when rATG dosing was higher than at present, and do not always control for the maintenance regimen. Registry analyses published in the mid-2000s that explored an association between PTLD and induction with rATG in adult or pediatric kidney transplantation reported mixed findings [58–60]. Dharnidharka and colleagues found no significant increase in risk of PTLD between children given rATG induction after kidney transplantation (n=685) versus no induction (n=2433) in OPTN data from 1987 to 2003 [58].

In pHTx, an analysis of ISHLT data from 2000 to 2011 found no effect of induction therapy overall on risk of malignancy in 565 children [9]. Gajarski et al. investigated the effect of induction on risk for PTLD in 2375 children (<18 years) receiving HTx during 1993–2007, using data from the Pediatric Heart

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Transplant Study [48]. Overall, induction of any type was associated with a lower risk for PTLD versus no induction (Table 4). When different induction agents were assessed separately, rATG was associated with a significantly lower risk for PTLD than with no induction (Table 4). It is possible that this reduction in risk may have arisen from the general trend towards less intensive maintenance therapy in recent years, when induction was used more widely. More specifically, rATG induction may also have been used to facilitate CNI-sparing or steroid-sparing therapy, potentially lowering the risk for PTLD. Hayes and colleagues have also examined factors for PTLD in a series of 1462 pHTx patients registered with the OPTN in a less recent cohort (1987–2003) [55]. In their analysis, rATG was grouped with other lymphocyte-depleting agents (anti-Lymphocyte globulin [ALG] and ATG). On multivariate analysis, there was no significant relation between rATG/ALG/ATG and risk for PTLD (HR 1.03, 95% CI 0.72–1.49; p=0.866). Induction *per se,* or rATG in particular, does not seem to increase risk for PLTD.

Individual studies of PTLD under rATG induction in pHTx patients are limited by small population sizes. Several retrospective analyses in patients given rATG have reported no cases [17,28,38,42] or only a single case [19,33,61,62] of PTLD. There is tentative evidence, however, concerning the question of whether lower rATG dosing reduces the risk for PTLD. Aliabadi et al. performed a retrospective single-center analysis in which outcomes in 523 HTx patients (including 19 patients aged 5–18 years) were assessed according to cumulative rATG dose (<4.5 mg/kg, 4.5–7.5 mg/kg, or >7.5 mg/kg) [63]. There were no cases of PTLD in patients given a total dose of up to 7.5 mg/kg. The mean time to tumor development, including PTLD, was significantly shorter in the group given more than 7.5 mg/kg rATG (mean 32 months) than in those given <4.5 mg/kg (63 months) or 4.5–7.5 mg/kg (47 months) (p=0.031). An earlier systematic review of 5 studies in adult HTx patients found the incidence of PTLD to be 0.50% (2/402) in patients given a total rATG dose <7.5 mg/kg compared to 1.55% (7/452) with a total dose ≥7.5 mg/kg [48]. In children, Schubert et al. analyzed 72 patients who had undergone HTx at their center during 1986 to 2007 and found the mean number of rATG doses to be 4.3 in those with PTLD versus 2.7 in those without PTLD, but doses were not stated and the analysis included rATG given to treat rejection as well as induction [64]. Based on these data, albeit largely derived from adult patients, rATG dosed at today's levels (typically no more than 7.5 mg/kg) would not be expected to increase the risk for PTLD.

rATG Dosing and Monitoring in Pediatric Heart Transplantation

Our group recently published a review that concluded, based on 2 published studies [33,61], that a maximum total rATG dose of 7.5 mg/kg is adequate in children at standard immunological risk receiving CNI-based maintenance therapy [13]. A lower cumulative dose (but not less than 3.5 mg/kg) may be sufficient in younger, lower-risk patients who are receiving CNI therapy, in view of the increased risk for PTLD in the youngest recipients [8,13], although this has not been assessed clinically. The duration of rATG infusion should not be less than 6 h [13].

A small number of centers use CD3 monitoring, or absolute lymphocyte count, to guide rATG dosing. Where this approach is applied, the ISHLT guidelines advise targeting a CD3 count in the range 25–50 cells/mm^3 or an absolute total lymphocyte count <100–200 cells/mm^3 [20]. Data on immune monitoring in pHTx are scant but a retrospective study compared CD3-guided rATG dosing in 32 patients versus 17 historical controls given fixed rATG dosing (1.5 mg/kg, usually for 5 days) [65]. The patient group managed with CD3 monitoring received a significantly lower total rATG dose (median 3.2 versus 7.4 mg/kg, p<0.001), with no difference in rates of rejection, patient survival, or infection. This dosing strategy merits further study. Peri-operative initiation of rATG during HTx in children, with subsequent doses titrated according to lymphocyte count, has also been reported by 1 center, but evaluation is difficult due to the single-arm nature of the study [61].

Hematological values should be monitored and taken into account during rATG dosing, with the dose lowered – or even discontinued – in response to thrombocyte, lymphocyte, and neutrophil counts. Thrombocytopenia is a particular risk due to the thrombocytopenic effect of circularly bypass. Our group has previously proposed thresholds for platelet, leukocyte, neutrophil, and lymphocyte counts in adult HTx patients to prompt rATG dose reduction, halving, or withdrawal [13]. These thresholds can also be applied in pHTx. According to these proposals, the rATG dose should be lower, halved, or discontinued if the thrombocyte count declines to 75 000/mm^3, 5000–75 000 mm^3 or <50 000 mm^3, respectively [13].

One unresolved question is whether rATG therapy should be reduced or temporarily interrupted in the presence of elevated pulmonary pressures, but reliable evidence is lacking and case reports are rare [66,67]. An FDA investigation of horse ATG between 2004 and 2012 identified only 2 drug adverse event reaction reports related to pulmonary pressure.

Limitations

We are aware of the inherent weaknesses in registry analyses, notably the long observation periods spanning changes in clinical practice, missing data, and the absence of relevant information such as dosing data, which makes comparison difficult. Despite these issues, it seems unrealistic to undertake

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Table 5. Overview of suitability for rATG induction in different clinical situations according to the authors' experience and opinion.

Clinical situation	Suitability of rATG induction
Non-sensitized patients receiving triple therapy*	Consider in patients at high risk of rejection**
Steroid-free immunosuppression from time of pHTx	Recommended
Early steroid withdrawal (<1 week)	Possible
Pre-sensitized patients	Recommended
ABO-compatible neonates	Possible
T cell or B cell crossmatch pHTx	Recommended
ABO-incompatible pHTx	May be advisable (more data required)
Donor EBV-positive, recipient EBV-negative	Not recommended

* Standard CNI therapy, an antimetabolite and maintenance steroids; ** e.g. poor HLA mismatch, black race, retransplantation, risk of non-adherence.

prospective, randomized, controlled trials to achieve sufficient numbers to provide adequate statistical power in studies of patients undergoing pHTx.

Conclusions

pHTx represents a small but crucial part of the solid organ transplant program. Comparative trials are rare in this population, and decision-making about immunosuppression frequently has to be based on limited data or clinical experience and expertise. By necessity, data from adult HTx or other types of organ transplantation may need to be considered, despite the distinctive risk profiles of children receiving a HTx. While recognizing the highly limited evidence-base in this population, we tentatively propose our recommendations for rATG induction in pediatric heart transplantation (Table 5). Based on the available data, the following points seem realistic: (1) Registry analyses indicate that, in general, rATG induction is associated with improved graft survival versus IL-2RA induction. (2) Polyclonal induction therapy is recommended when steroid avoidance is attempted, and early steroid withdrawal (<1 week) or steroid avoidance in low-risk patients is feasible with rATG induction, tacrolimus, and MMF without loss of immunosuppressive efficacy versus steroid-containing regimens. (3) Induction therapy is recommended in sensitized patients or those with a positive crossmatch, and small series have suggested relatively good outcomes, with acceptable rates of graft loss due to acute cellular rejection or AMR, when rATG induction is included in early, aggressive management strategies. (4) ABO-incompatible transplantation, while still rare, has been reported to be achieved successfully in children receiving rATG induction. (5) The risk for infection, including CMV, does not appear to be increased with rATG induction. (6) PTLD does not seem to be frequent in children given rATG induction at a total dose ≤7.5 mg/kg, and a lower dosage (minimum 3.5 mg/kg) may be adequate.

Conflicts of interest

Martin Schweiger has received speaker's honoraria from Novartis and Sanofi-Genzyme. Andreas Zuckermann has received research grants from Astellas, Roche, Novartis, One Lambda, Chiesi and Sanofi, is a member of the speakers' bureaus for Novartis, Sanofi-Genzyme, Biotest, and One Lambda, and is a member of advisory boards for Sanofi Genzyme and Sandoz and Biotest. Andres Beiras-Fernandez has received research grants from Sanofi and Orion Pharma and has received speaker's honoraria from Sanofi Genzyme and Boehringer Ingelheim. Michael Berchtold-Herz has no conflicts of interest to declare. Udo Boeken has no conflicts of interest to declare. Jens Garbade has no conflicts of interest to declare. Stephan Hirt has no conflicts of interest to declare. Manfred Richter has received speaker's honoraria from Novartis and Sanofi-Genzyme. Arjang Ruhpawar has no conflicts of interest to declare. Jan Dieter Schmitto has no conflicts of interest to declare. Felix Schönrath has received speaker's honoraria from Abbott, Astra Zeneca, Bayer HealthCare, Novartis, and Sanofi-Genzyme. Rene Schramm has no conflicts of interest to declare. Uwe Schulz has received speaker's honoraria from Sanofi-Genzyme, Novartis, and Hexal, travel grants from Biotest and Actelion, and a research grant from Actelion. Markus J. Wilhelm has received honoraria from Sanofi Genzyme. Markus J. Barten has received speaker's honoraria from Therakos as well as honoria as a member of advisory boards for Sanofi, Novartis Pharma, and Biotest.

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References:

1. Rossano JW, Dipchand AI, Edwards LB et al: The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant, 2016; 35(10): 1185–95
2. Colvin M, Smith JM, Skeans MA et al: OPTN/SRTR 2015 Annual Data Report: Heart. Am J Transplant, 2017; 7(Suppl. 1): 286–356
3. Dipchand AI, Rossano JW, Edwards LB et al: The Registry of the International Society for Heart and Lung Transplantation: Eighteenth Official Pediatric Heart Transplantation Report – 2015; Focus theme: Early graft failure. J Heart Lung Transplant, 2015; 34(10): 1233–43
4. Hung SY, Lin TM, Chang MY et al: Risk factors of sensitization to human leukocyte antigen in end-stage renal disease patients. Hum Immunol, 2014; 75(6): 531–35
5. Scornik JC, Meier-KrieschE HU: Blood transfusions in organ transplant patients: Mechanisms of sensitization and implications for prevention. Am J Transplant, 2011; 11(9): 1785–91
6. Taner T, Gandhi MJ, Sanderson SO et al: Prevalence, course and impact of HLA donor-specific antibodies in liver transplantation in the first year. Am J Transplant, 2012; 12(6): 1504–10
7. Dipchand AI, Kirk R, Edwards LB et al; International Society for Heart and Lung Transplantation. The Registry of the International Society of Heart and Lung Transplantation: Sixteenth Official Pediatric Transplant Report – 2013; Focus, theme: Age. J Heart Lung Transplant, 2013; 32(10): 979–88
8. Malik S, Kassaï B, Cochat P: Overview of pediatric organ transplantation: Current opinion and future perspectives on immunosuppression. Curr Opin Organ Transplant, 2015; 20(5): 527–35
9. Lund LH, Edwards LB, Kucheryavaya AY et al; International Society for Heart and Lung Transplantation: The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report – 2013; Focus theme: Age. J Heart Lung Transplant, 2013: 32(10): 951–64
10. Ansari D, Höglund P, Andersson B, Nilsson J: Comparison of basiliximab and anti-thymocyte globulin as induction therapy in pediatric heart transplantation: A survival analysis. J Am Heart Assoc, 2015, 5(1): e002790
11. Castleberry C, Pruitt E, Ameduri R et al: 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, 2017 [Epub ahead of print]
12. Zuckermann A, Schultz U, Deuse T et al: Thymoglobulin induction in heart transplantation: Patient selection and implications for maintenance immunosuppression. Transpl Int, 2014; 28(3): 259–69
13. Barten MJ, Schultz U, Beiras-Fernandez A et al: A proposal for early dosing regimens in heart transplant patients receiving Thymoglobulin and calcineurin inhibition. Transplant Direct, 2016; 2(6): e81
14. Mohty M, Bacigalupo A, Saliba F et al: New directions for rabbit antithymocyte Globulin (Thymoglobulin(®)) in solid organ transplants, stem cell transplants and autoimmunity. Drugs, 2014; 74(14): 1605–34
15. Butts R, Davis M, Savage A et al: Effect of induction therapy on graft survival in primary pediatric heart transplantation: A propensity score analysis of the UNOS database. Transplantation, 2017; 101(6): 1228–33
16. Ansari D, Lund LH, Stehlik J et al: Induction with anti-thymocyte globulin in heart transplantation is associated with better long-term survival compared with basiliximab. J Heart Lung Transplant, 2015; 34(10): 1283–91
17. Di Filippo S, Boissonnat P, Sassolas F et al: Rabbit antithymocyte globulin as induction immunotherapy in pediatric heart transplantation. Transplantation, 2003; 75(3): 354–58
18. Boucek RJ Jr., Naftel D, Boucek MM et al: Induction immunotherapy in pediatric heart transplant recipients: A multicenter study. J Heart Lung Transplant, 1999; 18(5): 460–69
19. Parisi F, Danesi H, Squitieri C et al: Thymoglobuline use in pediatric heart transplantation. J Heart Lung Transplant, 2003; 22(5): 591–93
20. Costanzo MR, Dipchand A, Starling R et al: The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant, 2010; 29(8): 914–56
21. Knight SR, Morris PJ: Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. Transplantation, 2010; 89(1): 1–14
22. Pearce G, Tabensky DA, Delmas PD et al: Corticosteroid-induced bone loss in men. Clin Endocrinol Metab, 1998; 83(3): 801–6
23. Cremer J, Strüber M, Wagenbreth I et al: Progression of steroid-associated osteoporosis after heart transplantation. Ann Thorac Surg, 1999; 67(1): 130–33
24. De Maria R, Minoli L, Parolini M et al: Prognostic determinants of six-month morbidity and mortality in heart transplant recipients. The Italian Study Group on Infection in Heart Transplantation. J Heart Lung Transplant, 1996; 15(2): 124–35
25. Gorensek MJ, Stewart RW, Keys TF et al: Decreased infections in cardiac transplant recipients on cyclosporine with reduced corticosteroid use. Cleve Clin J Med, 1989; 56(7): 690–95
26. Weaver DJ Jr., Selewski D, Janjua H, Iorember F: Improved cardiovascular risk factors in pediatric renal transplant recipients on steroid avoidance immunosuppression: A study of the Midwest Pediatric Nephrology Consortium. Pediatr Transplant, 2016; 20(1): 59–67
27. Delucchi A, Valenzuela M, Lillo AM et al: Early steroid withdrawal in pediatric renal transplant: Five years of follow-up. Pediatr Nephrol, 2011; 26(12): 2235–44
28. Warejko JK, Hmiel SP: Single-center experience in pediatric renal transplantation using thymoglobulin induction and steroid minimization. Pediatr Transplant, 2014; 18(8): 816–21
29. Canter CE, Moorhead S, Saffitz JE et al: Steroid withdrawal in the pediatric heart transplant recipient initially treated with triple immunosuppression. J Heart Lung Transplant, 1994; 13(1 Pt 1): 74–79; discussion 79–80
30. Leonard H, Hornung T, Parry G, Dark JH: Pediatric cardiac transplant: Results using a steroid-free regimen. Pediatr Transplant, 2003; 7(1): 59–63
31. Auerbach SR, Gralla J, Campbell DN et al: Steroid avoidance in pediatric heart transplantation results in excellent graft survival. Transplantation, 2014; 97(4): 474–80
32. Singh TP, Faber C, Blume ED et al: Safety and early outcomes using a corticosteroid-avoidance immunosuppression protocol in pediatric heart transplant recipients. J Heart Lung Transplant, 2010; 29(5): 517–22
33. Marshall CD, Richmond ME, Singh RK et al: A comparison of traditional versus contemporary immunosuppressive regimens in pediatric heart transplantation. J Pediatr, 2013; 163(1): 132–36
34. Jacobs JP, Quintessenza JA, Boucek RJ et al: Pediatric cardiac transplantation in children with high panel reactive antibody. Ann Thorac Surg, 2004; 78(5): 1703–9
35. Pollock-BarZiv SM, Den Hollander N, Ngan BY et al: Pediatric heart transplantation in human leukocyte antigen-sensitized patients. Circulation, 2007; 116(11 Suppl. 11): I172–78
36. Holt DB, Lublin DM, Phelan DL et al: Mortality and morbidity in pre-sensitized pediatric heart transplant recipients with a positive donor crossmatch utilizing peri-operative plasmapheresis and cytolytic therapy. J Heart Lung Transplant, 2007: 26(9): 876–82
37. Daebritz SH, Schmoeckel M, Mair H et al: Blood type incompatible cardiac transplantation in young infants. Eur J Cardiothoracic Surg, 2007; 31(3): 339–43
38. Penninga L, Møller CH, Gustafsson F et al: Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: Systematic review with meta-analyses and trial sequential analyses of randomised trials. Eur J Clin Pharmacol, 2010; 66(12): 177–87
39. Eisen HJ, Kobashigawa J, Keogh A et al: Three-year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. J Heart Lung Transplant, 2005; 24(5): 517–25
40. Barletta GM, Kirk E, Gardner JJ et al: Rapid discontinuation of corticosteroids in pediatric renal transplantation. Pediatr Transplant, 2009; 13(5): 571–78
41. Li L, Chaudhuri A, Chen A et al: Efficacy and safety of Thymoglobulin induction as an alternative approach for steroid-free maintenance immunosuppression in pediatric renal transplantation. Transplantation, 2010; 90(12): 1516–20
42. Lau KK, Haddad MN, Berg GM et al: Rapid steroid discontinuation for pediatric renal transplantation: A single center experience. Pediatr Transplant, 2007: 11(5): 504–10
43. Henderson HT, Canter CE, Mahle WT et al: ABO-incompatible heart transplantation: Analysis of the Pediatric Heart Transplant Study (PHTS) database. J Heart Lung Transplant, 2012; 31(2): 173–79

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

44. Patel ND, Weiss ES, Scheel J et al: ABO-incompatible heart transplantation in infants: analysis of the united network for organ sharing database J Heart Lung Transplant, 2008; 27(10): 1085–89
45. Urschel S, Larsen IM, Kirk R et al: ABO-incompatible heart transplantation in early childhood: An international multicenter study of clinical experiences and limits. J Heart Lung Transplant, 2013; 32(3): 285–92
46. Yamani MH, Taylor DO, Czerr J et al: Thymoglobulin induction and steroid avoidance in cardiac transplantation: Results of a prospective, randomized, controlled study. Clin Transplant, 2008; 22(1): 76–81
47. Mattei M, Redonnet M, Gandjbakhch I et al: Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. J Heart Lung Transplant, 2007; 26(7): 693–99
48. Gajarski RJ, Blume ED, Urschel S et al; Pediatric Heart Transplant Study Investigators: Infection and malignancy after pediatric heart transplantation: The role of induction therapy. J Heart Lung Transplant, 2011; 30(3): 299–308
49. Sampaio MS, Cho YW, Shah T et al: Association of immunosuppressive maintenance regimens with posttransplant lymphoproliferative disorder in kidney transplant recipients. Transplantation, 2012; 93(1): 73–81
50. Marks WH, Ilsley JN, Dharnidharka VR: Posttransplantation lymphproliferative disorder in kidney and heart transplant recipients receiving Thymoglobulin: A systematic review. Transplant Proc, 2011; 43(5): 1395–404
51. Opelz G, Döhler B: Lymphomas after solid organ transplantation: A collaborative transplant study report. Am J Transplant, 2004; 4(2): 222–30
52. Feng S, Buell JF, Chari RS et al: Tumors and transplantation: The 2003 third annual ASTS state-of-the-art winter symposium Am J Transplant, 2003; 3(12): 1481–87
53. Webber SA, Naftel CD, Fricker FJ et al: Lymphoproliferative disorders after paediatric heart transplantation: A multi-institutional study. Lancet, 2006; 367(9506): 233–39
54. Hanto DW, Frizzera G, Gajl-Peczalska KJ, Simmons RL: Epstein-Barr virus, immunodeficiency, and B cell lymphoproliferation. Transplantation, 1985; 39(5): 461–72
55. Hayes D Jr., Breuer CK, Horwitz EM et al: Influence of post-transplant lymphoproliferative disorder in children after heart transplantation. Pediatr Cardiol, 2015; 369(8): 1748–53
56. San-Juan R, Comoli P, Caillard S et al., ESCMID Study Group of Infection in Compromised Hosts: Epstein-Barr virus-related post-transplant lymphoproliferative disorder in solid organ transplant recipients. Clin Microbiol Infect, 2014; 20(Suppl. 7): 109–18
57. Katz BZ, Pahl E, Crawford SE et al: Case-control study of risk factors for the development of post-transplant lymphoproliferative disease in a pediatric heart transplant cohort. Pediatr Transplant, 2007; 11(1): 58–65
58. Dharnidharka VR, Stevens G: Risk for post-transplant lymphoproliferative disorder after polyclonal antibody induction in kidney transplantation. Pediatr Transplant, 2005; 9(5): 622–26
59. Kirk AD, Cherikh WS, Ring M et al: Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. Am J Transplant, 2007; 7(11): 2619–25
60. Bustami RT, Ojo AO, Wolfe RA et al: Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant, 2004; 4(1): 87–93
61. Pollack-BarZiv SM, Allain-Rooney T, Manlhiot C et al: Continuous infusion of thymoglobulin for induction therapy in pediatric heart transplant recipients; Experience and outcomes with a novel strategy for administration. Pediatr Transplant, 2009; 13(5): 585–89
62. Goland S, Czer LS, Coleman B et al: Induction therapy with Thymoglobulin after heart transplantation: Impact of therapy duration on lymphocyte depletion and recovery, rejection, and cytomegalovirus infection rates. J Heart Lung Transplant, 2008; 27(10): 1115–21
63. Aliabadi AZ, Grömmer M, Dunkler D et al: Impact of rabbit antithymocyte globulin dose on long-term outcomes in heart transplant patients. Transplantation, 2016; 100(3): 685–93
64. Schubert S, Abdul-Khaliq H, Lehmkuhl HB et al: Diagnosis and treatment of post transplantation lymphoproliferative disorder in pediatric heart transplant patients. Pediatr Transplant, 2009; 13(1): 54–62
65. Thrush PT, Gossett JG, Costello JM et al: Role for immune monitoring to tailor induction prophylaxis in pediatric heart recipients. Pediatr Transplant, 2014; 18(1): 79–86
66. Parikh BK, Bhosale GP, Shah VR: Anti-thymocyte globulin induced non-cardiogenic pulmonary edema during renal transplantationIndian J Crit Care Med, 2011; 15(4): 230–32
67. Jodele S, Hirsch R, Laskin R et al: Pulmonary arterial hypertension in pediatric patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy. Biol Blood Marrow Transplant, 2013; 19(2): 202–7

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