Prevention and Treatment of Severe Hemodynamic Compromise in Pediatric Heart Transplant Patients

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Contents

Abstract	705
1. Prevention of Rejection: An Overview of Immunosuppression	706
1.1 Maintenance Immunosuppression	706
1.1.1 Calcineurin Inhibitors	706
1.1.2 Antiproliferative Agents	707
1.1.3 Corticosteroids	708
1.2 Induction Therapy	708
1.2.1 T Cell Pool Depletion	708
1.2.2 Monoclonal Antibodies Against Interleukin-2 Receptors	709
1.2.3 Photopheresis	710
2. Treatment of Severe Hemodynamic Compromise	710
2.1 Hemodynamic Support	710
2.1.1 Heart Rate and Rhythm	710
2.1.2 Preload	710
2.1.3 Contractility	711
2.1.4 Afterload	711
2.1.5 Oxygen Consumption	711
2.1.6 Mechanical Support	711
2.2 Immunosuppression	711
2.2.1 Cellular Rejection	711
2.2.2 Humoral Rejection	712
2.2.3 Retransplantation	712
3. Conclusions	712

Abstract

Allograft rejection is a leading cause of severe hemodynamic compromise in pediatric heart transplant patients. A triple-drug immunosuppression regimen, which includes a calcineurin inhibitor, antiproliferative agent, and corticosteroid, suppresses the immune system at multiple different levels for optimal graft protection while minimizing the adverse effects of any one particular agent. Some pediatric centers also use induction therapy with anti-T cell antibodies immediately following transplantation as additional rejection prophylaxis. These antibodies augment immunosuppression by either depleting the T cell pool or blocking interleukin-2 receptors on activated T cells.

Despite the aggressive preventive measures outlined above, some pediatric heart transplant patients will develop severe hemodynamic compromise, most commonly due to fulminant rejection. Such patients require attention to, and optimization of, the four determinants of cardiac output (heart rate, preload, contractility and afterload) to stabilize the circulation until the rejection can be reversed. Careful administration of volume, diuretics, inotropes, and afterload-reducing agents will meet this goal. Patients with allograft rejection require augmentation of immune suppression to facilitate myocardial recovery.

Corticosteroids form the cornerstone of treatment for both cellular and vascular rejection. In patients with refractory cellular rejection, conversion to mycophenolate mofetil or tacrolimus may be appropriate if these agents are not already being used for maintenance immunosuppression. Critically ill patients may additionally benefit from muromonab-CD3 (OKT3) to augment lympholysis. Treatment employed specifically for humoral rejection is prescribed with the intention of suppressing new antibody formation, removing circulating antibody, and improving coronary blood flow. In addition to corticosteroids, cyclophosphamide and antithymocyte globulin or muromonab-CD3, along with plasmapheresis, may improve survival. Systemic heparinization should be considered to minimize coronary thrombosis in patients with humoral rejection. In the future, novel immunosuppressive agents may further assist in the prevention as well as treatment of severe hemodynamic compromise due to rejection in pediatric heart transplant recipients.

The development of severe hemodynamic compromise in pediatric heart transplant patients is associated with significant morbidity and mortality.^[1] A primary objective of medical personnel treating these patients is to prevent acute graft failure and the obligatory hemodynamic compromise that follows. To achieve this goal, a dedicated team including multiple physicians (with expertise in transplantation, cardiac catheterization, echocardiography, pathology, electrophysiology and critical care), nurse specialists, pharmacists, social workers, mental health professionals and, perhaps most importantly, the patient and family members, must work in unison over the lifetime of the patient.

Severe hemodynamic compromise may occur in the pediatric heart transplant patient from a variety of etiologies, most commonly secondary to allograft rejection or transplant coronary artery disease (TCAD). Meticulous evaluation and education of the patient and his/her caretakers before, during and following heart transplantation will minimize the chances of hemodynamic embarrassment, since late rejection in children is commonly associated with noncompliance.^[2] This review will focus on the role of immunotherapy for the prevention and treatment of rejection in pediatric heart transplant recipients, as well as drugs and other modalities used to support the circulation in such patients with severe hemodynamic compromise. This review will not include discussion of pretransplant factors, including pulmonary hypertension, elevated panel reactive antibody, and patient-donor graft matching, as well as post-transplant issues of primary graft failure and TCAD.

Due to the limited number of pediatric heart transplants performed at any one center, the initial experience and clinical research for all of the drugs discussed in this review came from adult heart and other solid organ transplant recipients.

1. Prevention of Rejection: An Overview of Immunosuppression

1.1 Maintenance Immunosuppression

In the absence of adequate immunosuppression, antigens from

the allograft will be recognized by recipient CD4 T cells as foreign, triggering a host response that eventually leads to rejection (figure 1). The ideal immunosuppressive agent – one that selectively inhibits alloantigen immune responses, prevents chronic allograft rejection, and is free of major adverse effects – does not yet exist.^[3] Most pediatric programs currently use triple-drug immunosuppression regimens in the immediate postoperative period extending through at least the first 6 months following heart transplantation to prevent rejection (table I). The combination of a calcineurin inhibitor, antiproliferative agent, and corticosteroid suppresses the immune system at multiple different levels for optimal graft protection and minimizes the adverse effects of any one particular agent (figure 2). Intense immunosuppression is achieved immediately following transplant, when the risk of rejection is highest, and then tapered over the subsequent weeks and months, depending on the perceived risk of rejection for each individual patient. Generally, the same drugs administered immediately following transplant are also used for long-term immunosuppression, but at lower doses.

1.1.1 Calcineurin Inhibitors

Calcineurin is a key enzyme that is situated early in the signal transduction pathway between the T cell receptor and the interleukin (IL)-2 gene. Cyclosporine inhibits calcineurin,^[4] thus preventing the production of IL-2 and γ -interferon, effectively interrupting the T cell activation cascade.^[5] Cyclosporine has served as the cornerstone for solid organ transplant immunosuppression for more than two decades and is widely used by pediatric heart transplant centers. Problems with variable absorption of the Sandimmune® brand of cyclosporine have been diminished with the introduction of a microemulsion formulation marketed as Neoral® (Novartis).^[6-8] Generic forms of cyclosporine are under development.

Tacrolimus, another calcineurin inhibitor, has a similar mechanism of action to cyclosporine, but greater potency.^[4] Tacrolimus is used by a few pediatric heart transplant centers in place of cyclo-

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

Fig. 1. Cellular interactions that form the anti-allograft response: CD4 T cells recognize antigen through direct and indirect pathways, become activated, and undergo clonal proliferation. Activated CD4 T cells provide help for monocyte/macrophages, B cells, and cytotoxic CD8 T cells by secreting cytokines and by cell-cell contact-dependent mechanisms. Activated monocytes/macrophages release a range of noxious agents that mediate tissue injury. B cell alloantibody production ultimately results in complement mediated tissue destruction. Activated CD8 T cells kill graft cells in an antigen-specific manner through induction of apoptosis and cell lysis (reproduced from Denton et al.,^[3] with permission). **MHC** = major histocompatibility complex; **TCR** = T cell receptor.

sporine for initial maintenance immunotherapy, but tacrolimus is not approved by the US Food and Drug Administration for use in heart transplant recipients. Other programs may switch patients from cyclosporine to tacrolimus due to persistent rejection or unacceptable adverse effects of cyclosporine. In a multicenter trial comparing cyclosporine to tacrolimus in adult heart transplant recipients, less hypertension and hyperlipidemia were seen with tacrolimus.^[9] Because tacrolimus is associated with other toxicities, including anemia, renal insufficiency, and type 1 diabetes mellitus,^[10-12] most programs continue to prefer cyclosporine for primary therapy.^[13] Plasma levels of tacrolimus should be followed closely to avoid toxicity, particularly when the drug is administered intravenously.^[14]

1.1.2 Antiproliferative Agents

Antiproliferative agents prevent the expansion of alloactivated T and B cell clones. Azathioprine is a thiopurine which, following conversion to mercaptopurine, antagonizes several enzymes necessary for purine synthesis, thus inhibiting DNA and RNA production. Available since the 1960s, azathioprine may cause significant bone marrow suppression and is being used less often since the introduction of mycophenolate mofetil.

Mycophenolate mofetil is a prodrug of mycophenolic acid, which selectively inhibits inosine monophosphate dehydrogenase in the de novo pathway of guanine nucleotide synthesis, thus impairing proliferation of lymphocytes.^[15,16] Mycophenolate mofetil also inhibits antibody production by plasma cells^[17] and the glycosylation of lymphocyte adhesion molecules, thus reducing the binding of these cells to activated endothelial cells.^[18] When compared with adult heart transplant recipients randomized to receive azathioprine, those on mycophenolate mofetil for initial maintenance immunosuppression had less rejection and a lower 1-year mortality rate when analyzed on a treated basis; however, no difference was detected on the intention-to-treat analysis.^[19] Another study revealed no difference in adult patients randomized to mycophenolate mofetil or azathioprine 3 months following transplant in terms of rejection or early complications.^[20] Early pediatric data support a role for the use of mycophenolate mofetil in heart transplant recipients, although drug levels may need to be monitored.^[21,22] A multicenter, randomized trial will be necessary to determine if mycophenolate mofetil is superior to azathioprine.

Sirolimus is a novel immunosuppressive agent that inhibits cytokine-induced signal transduction distal to calcineurin, and

Table I. Standard maintenance triple-drug immunotherapy

Drug	Brand name	Starting dose	Therapeutic level (trough)	Specific adverse effects
Calcineurin inhibitors				
Cyclosporine	Sandimmune® ^a Neoral®	5 mg/kg IV over 18 hours, or 0.05-0.1 mg/kg/h once urine output is adequate	Depends on assay used and time since transplant	Renal insufficiency, hypertension, seizures, hyperlipidemia, gingival hyperplasia, hypertrichosis
Tacrolimus	Prograf® (FK 506)	0.1 mg/kg IV od	10-15 µg/L	Renal insufficiency, anemia, diabetes, vasculitis
Anti-proliferative agents				
Azathioprine	Imuran®	1-2 mg/kg PO od	N/A; follow CBC	Bone marrow suppression
Mycophenolate mofetil	CellCept®	20 mg/kg PO bid	>3 µg/L; follow CBC	Vomiting, diarrhea
Sirolimus	Rapamycin®		N/A; follow CBC	Bone marrow suppression, hyperlipidemia
Corticosteroids				
Methylprednisolone, prednisone	Solu-Medrol®, Deltasone®	10 mg/kg IV od, rapid taper	N/A	Peptic ulcer, aseptic necrosis of the hip, osteoporosis, cataracts, glucose intolerance, hypertension, short stature, hyperlipidemia, Cushingoid features

a The use of tradenames is for product identification purposes only and does not imply endorsement.

bid = twice daily; **CBC** = complete blood count; **h** = hours; **IV** = intravenously; **N/A** = not available; **od** = once daily; **PO** = orally.

inhibits several kinases critical to cellular division.^[23,24] Sirolimus has been shown to decrease early rejection when used with or without calcineurin inhibitors for primary immunosuppression in adult renal transplant recipients.^[25,26] Experience with sirolimus in adult heart transplant patients is limited but suggests that the drug may allow for dose reduction or discontinuation of calcineurin inhibitors in patients with renal insufficiency.^[27] As experience with this drug grows in the adult population, it will most likely become part of the armamentarium of immunosuppressive agents used by physicians caring for pediatric heart transplant recipients, particularly those with renal compromise. However, hyperlipidemia related to sirolimus may limit widespread use of this drug in heart transplant recipients.

1.1.3 Corticosteroids

Corticosteroids are nonspecific anti-inflammatory agents that act by several mechanisms, including decreasing synthesis of cytokines and cell surface molecules necessary for immune function.^[28] Corticosteroids up-regulate IκBα protein synthesis, which binds nuclear factor-κB in the cytoplasm, preventing this key regulator of inflammatory genes from translocating to the nucleus.^[29,30] Corticosteroids also inhibit phospholipase A₂ activity, thus decreasing the inflammatory response to acute rejection. Corticosteroids are used immediately after transplant by all pediatric heart transplant programs; however, continuation of low dose corticosteroids >1 year following transplant is controversial in the patient who has been relatively free of rejection. Due to the adverse effects of corticosteroids in growing children, and the possible association with TCAD,^[13] many pediatric centers at-

tempt to discontinue corticosteroids within the first year following transplant.^[31,32]

1.2 Induction Therapy

Induction therapy generally refers to the administration of anti-T cell antibodies immediately following transplantation to prevent acute rejection. These antibodies provide additional immunosuppression by either depleting the T cell pool or blocking the secretion of IL-2 from these cells. Photopheresis is an alternative induction therapy. Induction therapy is considered in patients at highest risk of rejection, such as children, sensitized patients, and those undergoing a retransplant. In addition, the use of induction therapy may allow the delayed initiation of calcineurin inhibitors in patients with renal insufficiency.^[3] Nevertheless, the generalized use of induction therapy following pediatric heart transplant is controversial as only half of the programs in the US administer an induction agent in low risk patients.

1.2.1 T Cell Pool Depletion

Both monoclonal and polyclonal antibody preparations may be used to effect T cell pool depletion in pediatric heart transplant recipients (table II). Muromonab-CD3 (Orthoclone OKT3®) is a murine monoclonal antibody directed against the CD3 receptor on T cells.^[33,34] T cells are rapidly cleared from the peripheral circulation following the administration of muromonab-CD3.^[35] Muromonab-CD3 also modulates the receptor complex on T cells, which inhibits their ability to recognize foreign antigens, thus inhibiting CD4 proliferation and CD8 cytotoxicity, and B cell proliferation.^[36,37] Muromonab-CD3 often causes a cytokine re-

lease syndrome after initial doses,^[38-41] which may be minimized by pre-medication with corticosteroids, antipyretics and antihistamines. The development of human anti-mouse antibodies to muromonab-CD3 may be problematic in terms of drug efficacy and development of vascular rejection.^[42,43] When substituted for cyclosporine for the first few days following adult heart transplantation, muromonab-CD3 appeared to be equally efficacious for preventing rejection at 6 months,^[44] a strategy that allows for the delayed initiation of calcineurin inhibitors and their associated nephrotoxicity. However, other adult heart transplant programs reported that muromonab-CD3 induction therapy may be associated with an increased risk of post-transplant lymphoproliferative disease^[45] or infection.^[46] No controlled trials of muromonab-CD3 for induction therapy in pediatric heart transplant recipients have been published.

Antithymocyte globulin is a polyclonal antibody preparation derived from the hyperimmune serum of animals inoculated with human thymus lymphocytes. Commercially available preparations include Thymoglobulin®, which is prepared using rabbits, and Atgam®, which is produced using horses. Although the mechanism of action of antithymocyte globulin has not been fully elucidated, administration leads to prompt lymphocytolysis and impairment of proliferative responses of T cells.^[37] In the cyclosporine era, antithymocyte globulin has been used for in-

duction therapy and reported in retrospective studies in adult^[47] and pediatric^[48] heart transplant recipients, and appears to be at least as efficacious as muromonab-CD3. However, because of the significant adverse effects associated with polyclonal antibody preparations and the newer, more specific and well tolerated monoclonal antibodies, the use of antithymocyte globulin is falling out of favor.

1.2.2 Monoclonal Antibodies Against Interleukin-2 Receptors

New induction strategies involve the administration of monoclonal antibodies against IL-2 receptors. High affinity IL-2 receptors are only functionally present on activated T cells. Monoclonal antibodies directed against these receptors will block alloantigen activated T cell clonal expansion and generation of cytotoxic T cells, while sparing resting T cells.^[3] Theoretically, this focused approach may minimize adverse effects of global T cell depletion seen with muromonab-CD3 and antithymocyte globulin.

Daclizumab and basiliximab are two commercially available chimeric mouse-human monoclonal antibodies that bind to IL-2 receptors on activated T cells. Data from well-designed adult studies on renal transplant revealed excellent tolerance and a lower incidence of cellular rejection for the initial 6 months in patients receiving basiliximab^[49,50] or daclizumab^[51] as induction agents

Fig. 2. Stages of T cell activation: multiple targets for immunosuppressive agents: Signal 1: stimulation of T cell receptor results in calcineurin activation, a process inhibited by cyclosporine and tacrolimus. Calcineurin dephosphorylates nuclear factor of activated T cells, enabling it to enter the nucleus and bind to the interleukin-2 promoter. Corticosteroids inhibit cytokine gene transcription in lymphocytes and antigen-presenting cells by several mechanisms. Signal 2: costimulatory signals are necessary to optimize T cell interleukin-2 gene transcription, prevent T cell anergy, and inhibit T cell apoptosis. Experimental agents, but not current immunosuppressive agents, interrupt these intracellular signals. Signal 3: interleukin-2 receptor stimulation induces the cell to enter the cell cycle and proliferate. Signal 3 may be blocked by interleukin-2 receptor antibodies or sirolimus, which inhibits second messenger signals induced by interleukin-2 receptor ligation. Following progression into cell cycle, azathioprine and mycophenolate mofetil interrupt DNA replication by inhibiting purine synthesis (reproduced from Denton et al.,^[3] with permission). **CyA** = cyclosporine; **IL-2** = interleukin-2; **NFAT** = nuclear factor of activated T cells; **P** = phosphate.

Table II. Induction agents

Drug	Brand name	Dose	Specific adverse effects
Muromonab-CD3	Orthoclone OKT3® ^a	<30kg: 2.5mg IV od x 5-14 days >30 kg: 5mg IV od x 5-14 days	Cytokine release syndrome
Antithymocyte globulin	Atgam® Thymoglobulin®	5-15 mg/kg IV od x 7-14 days 1.5 mg/kg IV od x 7-14 days	Phlebitis, fever/chills, thrombocytopenia, serum sickness, anaphylaxis
Basilixumab	Simulect®	12 mg/m ² /dose IV on POD 0 and 4	None reported
Daclizumab	Zenapax®	1 mg/kg IV within 24h of transplant, q2wk x five total doses	None reported

^a The use of tradenames is for product identification purposes only and does not imply endorsement.

h = hours; **IV** = intravenously; **od** = once daily; **POD** = postoperative day; **q2wk** = every 2 weeks.

in addition to cyclosporine based immunotherapy. In a controlled study of adult heart transplant recipients, daclizumab decreased the incidence and severity of rejection, and was well tolerated without cytokine release syndrome or an increased incidence of infection or post-transplant lymphoproliferative disorder.^[52] We have been using basiliximab as induction therapy for all pediatric heart transplant recipients at our institution since January 2001 because of the more favorable administration schedule (see table II). The efficacy of daclizumab and basilixumab when combined with tacrolimus and/or mycophenolate mofetil in heart transplant recipients is unknown at this time.

1.2.3 Photopheresis

Photopheresis is an alternative induction technique available at selected medical centers. Patient leucocytes are extracorporeally exposed to ultraviolet light and methoxalen, and then reinfused into the patient, where the irradiated leucocytes die over a few weeks and also cause an autologous suppressor response to nonirradiated T cells of similar clones.^[53] Preliminary adult data have shown that adding photopheresis to standard triple-drug immunosuppression may decrease rejection in the first 6 months following heart transplantation, and may inhibit the development of transplant coronary artery disease.^[54,55] Photopheresis for induction therapy for pediatric heart transplant patients has not been reported.

2. Treatment of Severe Hemodynamic Compromise

Despite the aggressive measures outlined above, 11% of pediatric heart transplant patients will develop late severe hemodynamic compromise, most commonly due to fulminant rejection.^[1,56] This clinical scenario represents a medical emergency as such patients are at high risk of mortality irrespective of age, biopsy score, or time from transplant. These patients should be stabilized at outlying medical facilities and then transported as soon as feasible to pediatric tertiary care centers with expertise in heart transplantation and critical care medicine. In patients

with suspected fulminant rejection and hemodynamic compromise, the administration of high dose intravenous corticosteroids should not be delayed until a definitive diagnosis is made by echocardiogram or myocardial biopsy.

2.1 Hemodynamic Support

Cardiogenic shock represents a state of imbalance between oxygen delivery and consumption; thus, interventions are undertaken to improve cardiac output and oxygen delivery while minimizing oxygen consumption. As in any other patients with cardiogenic shock, pediatric heart transplant patients with severe hemodynamic compromise require immediate attention and optimization of the four determinants of cardiac output: heart rate, preload, contractility and afterload.^[57] Additional efforts are directed at decreasing oxygen consumption so that a balance is maintained between supply and demand. The use of invasive hemodynamic monitoring is critical for optimal resuscitation of these patients.

2.1.1 Heart Rate and Rhythm

Pediatric heart transplant recipients with rejection may develop significant tachyarrhythmias or bradyarrhythmias. Tachyarrhythmias may be particularly poorly tolerated in a patient with TCAD and limited coronary flow reserve.^[58] An accurate diagnosis is obtained using electrocardiograms occasionally aided by transesophageal recordings. Although beyond the scope of this article, pharmacologic and/or electrical treatment of these arrhythmias is similar to the principles that would be applied to non-transplant patients.^[59]

2.1.2 Preload

The Frank-Starling mechanism describes the relationship between preload and stroke volume. Optimal overlap of actin and myosin filaments, or end diastolic stretch, will maximize stroke volume.^[60] Preload is estimated using central venous or Swan-Ganz pulmonary artery catheters. In the underfilled ventricle, crystalloid or colloid is used to increase preload. In patients who

have volume overload, loop diuretics are administered to decrease preload.

2.1.3 Contractility

Contractility is the load-independent ability of muscle to generate force.^[60] Contractility is extremely difficult to accurately measure in the clinical setting as commonly used estimates of cardiac function are effected by loading conditions. Nonetheless, contractility is usually estimated by echocardiography, and may be augmented by using one, or a combination of the intravenous inotropes listed in table III.^[61-67] These agents are initiated and titrated with a goal of increasing contractility, decreasing afterload, and avoiding excessive tachycardia.

2.1.4 Afterload

In the intact ventricle, afterload is the sum of wall stress and vascular impedance, both of which are impractical to measure in the clinical setting.^[60] In the failing heart, increased afterload maintains perfusion pressure but places additional strain on the injured heart. Efforts should be made to lower afterload provided that systemic blood pressure is maintained (table III).

2.1.5 Oxygen Consumption

Positive pressure mechanical ventilation will serve to decrease left ventricular afterload,^[68-70] as well as decrease work of breathing, and thus oxygen consumption. Adequate sedation will also decrease oxygen consumption, and occasionally neuromuscular blockade is necessary to stabilize the patient.

2.1.6 Mechanical Support

Patients who still have signs of inadequate end organ perfusion despite optimization of hemodynamics and immunomodulation (see below), and are thought to have reversible ventricular dysfunction, may be considered for mechanical cardiac support. However, the reported pediatric experiences with extracorporeal membranous oxygenation and ventricular assist devices are lim-

ited to nontransplant patients, or those in the immediate post-transplant period.^[71,72] Limited adult experience with mechanical support in the setting of rejection is discouraging.^[73]

2.2 Immunosuppression

Concurrent with the measures outlined above, augmentation of immune suppression to facilitate myocardial recovery is crucial in the treatment of pediatric heart transplant patients with severe hemodynamic compromise due to rejection. Obtaining a myocardial biopsy is helpful to differentiate cellular from humoral rejection if the patient is hemodynamically stable. Because the severity of rejection found on biopsy does not always correlate with hemodynamic changes, the immunotherapy prescribed depends on several other factors, including severity of symptoms, time since transplant, grade of rejection on prior biopsies, and baseline immunosuppression. Adolescent patients will often admit to noncompliance with medications.^[2]

2.2.1 Cellular Rejection

Cellular rejection is the most common form of rejection seen in pediatric heart transplant recipients, and is graded based on criteria endorsed by the International Society for Heart and Lung Transplantation.^[74] The cornerstone of treatment for cellular rejection is pulsed dose corticosteroids.^[56] Patients with severe hemodynamic compromise may have grade 3 or 4 rejection on myocardial biopsy, and will receive methylprednisolone 10 mg/kg/day IV for 3 to 5 days. The use of a corticosteroid taper is controversial, but is generally used in our institution in patients with severe hemodynamic compromise requiring inotropic therapy.^[75] A follow-up myocardial biopsy may be obtained in 7 to 10 days.

Based on uncontrolled data in adult patients with refractory rejection,^[76-79] pediatric heart transplant recipients with rejection and hemodynamic compromise requiring inotropic support in our institution receive muromonab-CD3 (0.1 mg/kg/day for 10 to 14

Table III. Selected intravenous agents useful in pediatric heart transplant patients with severe hemodynamic compromise

Drug	Administration range (μ g/kg/min)	Mechanism of action	Predominant clinical effect
Dobutamine	1-20	β_1 -agonist	Inotrope, mild chronotropy
Dopamine	1-3	Dopaminergic agonist	Renal vasodilator
	4-10	β_1 -agonist	Inotrope
	11-20	α -agonist $>\beta$	Vasoconstriction
Epinephrine (adrenaline)	0.03-1	α , β_{1+2} -agonist	Inotrope, chronotrope, β_2 vasodilation at lower doses, vasoconstriction at higher doses
Milrinone	0.25-0.75 +/- loading dose	Phosphodiesterase-III inhibitor	Inotrope, vasodilator
Nitroprusside	0.5-10	Nitric oxide donor	Vasodilation
Enalaprilat	0.01-0.3 mg/kg IV q6h	Angiotensin converting enzyme inhibitor	Systemic vasodilation

α = α receptor; β = β receptor; IV= intravenously; q6h = every 6 hours.

days). The efficacy of muromonab-CD3 in this setting has been questioned.^[80]

Augmentation of maintenance immunosuppression should be considered in patients with hemodynamic compromise. Mycophenolate mofetil may be substituted for azathioprine,^[81] and tacrolimus may replace cyclosporine.^[82,83] Methotrexate has also been found to be efficacious in a small, uncontrolled pediatric study of infants with 'life-threatening' rejection^[84] Methotrexate is a folic acid analog that blocks the conversion of dihydrofolic acid to tetrafollic acid, thus inhibiting purine synthesis and cell division. Neutropenia and gastritis are common adverse effects.

2.2.2 Humoral Rejection

Humoral rejection in heart transplant recipients is confirmed when biopsies reveal endothelial swelling and vasculitis by light microscopy, as well as vascular deposition of immunoglobulin and complement by immunofluorescence.^[85] When compared with cellular rejection, humoral rejection occurs earlier following transplant, causes more hemodynamic compromise, and is associated with earlier development of TCAD and higher mortality.^[85-87] Humoral rejection may be graded based on criteria published by Olsen et al.^[88] Graft dysfunction is exacerbated by thrombosis and vasospasm of coronary arteries. Although most of the literature on humoral rejection in heart transplantation is based on adult patients, humoral rejection has been reported in children from our center.^[89]

Treatments employed for humoral rejection are prescribed with the intention of suppressing new antibody formation, removing circulating antibody, and improving coronary blood flow. Often a combination of agents are employed to reduce new antibody formation, including high dose corticosteroids, cyclophosphamide (starting at 2 mg/kg/day), antithymocyte globulin, and muromonab-CD3.^[86,88,90]

Antibody removal for humoral rejection is accomplished with plasmapheresis, the efficacy of which has been reported in an animal model,^[91] and several adult case reports and small, uncontrolled series.^[86,88,92-95] We reported seven episodes in five young transplant patients with severe late left ventricular failure, negative immunofluorescence, and variable grade cellular rejection on myocardial biopsy.^[96] Despite not meeting strict criteria for humoral rejection, these critically ill patients were all successfully treated with aggressive multimodal immunomodulation, including corticosteroids, muromonab-CD3, cyclophosphamide, and plasmapheresis.

Thus, we advocate consideration of plasmapheresis, even in the absence of positive immunofluorescence, in pediatric patients with late severe hemodynamic compromise. If elevated at the time of presentation, panel reactive antibody levels may be followed

to determine duration of plasmapheresis treatment, but we recommend a minimum of three treatments either daily or every other day. Ionized calcium levels should be normalized prior to starting plasmapheresis to avoid hypotension. Extracorporeal immunoadsorption may be considered as an alternative to plasmapheresis for removing circulating IgG, but experience is limited.^[97]

Heparin infusions may prevent further coronary thrombosis in patients with 'true' humoral rejection, although no controlled studies have been reported to evaluate the efficacy of heparin in this setting.^[86,88] Furthermore, there are no data in the literature regarding the use of thrombolytic agents in this setting.

2.2.3 Retransplantation

A pediatric heart transplant recipient with severe hemodynamic compromise secondary to acute rejection who has not responded to the above supportive measures may be considered for retransplantation;^[98,99] however, many such patients will have developed multi-organ system failure or infection, making them poor surgical candidates.

3. Conclusions

A major goal of medical personnel caring for pediatric heart transplant recipients is the prevention of rejection, which may lead to graft failure. Triple-drug immunosuppression strategies are initially used by most pediatric centers in the first months following transplant to prevent rejection. Preliminary data question the role of corticosteroids in the long-term management of heart transplant recipients. Induction immunotherapy holds promise to prevent acute rejection but requires further study. Allograft rejection is a leading cause of severe hemodynamic compromise in heart transplant patients. Intensive monitoring and inotropic support are necessary to maintain end organ function in such patients, while additional immunosuppressive strategies are employed to reverse allograft cellular and/or humoral rejection.

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