AUCTORES
Globalize your Research

Cardiology Research and Reports
Rolf Bambauer *

Open Access

Review Article

Therapeutic Apheresis, Immunosuppression, and/or Human Monoclonal Antibodies in Cardiology

Rolf Bambauer [1]*, Ralf Schiel [2], Octavio J Salgado [3], and Richard Straube [4]

[1] Institute for Blood Purification and University of Saarland, Germany.

[2] Clinic for Metabolic Diseases, Medigreif Inselklinik, Heringsdorf, Germany.

[3] School of Medicine, Universidad Catolica de Cuenca, Ecuador.

[4] INUSpherese®, INUS Medical Center; Cham Tagesklinikum, Germany.

***Corresponding Author:** Rolf Bambauer, Institute for Blood Purification and University of Saarland, Germany.

Received date: October 16, 2024; Accepted date: October 24, 2024; Published date: November 05, 2024

Citation: Rolf Bambauer, Ralf Schiel, Octavio J Salgado, and Richard Straube, (2024), Therapeutic Apheresis, Immunosuppression, and/or Human Monoclonal Antibodies in Cardiology, *Cardiology Research and Reports*, 6(6); **DOI:10.31579/2692-9759/145**

Abstract

Therapeutic apheresis is an essential supportive treatment for severe and refractory diseases with or without immunologic origin. The advantages of therapeutic plasma exchange with hollow fiber membranes include a complete separation of the corpuscular components from the plasma and increased efficacy due to an elevated blood flow rate. Therapeutic apheresis has been shown to significantly improve the prognosis of idiopathic dilated cardiomyopathy, coronary heart disease, acute myocardial infarction and heart transplant rejection. This therapy is indicated as first- or second-line therapy in combination with immunosuppression, and/or human monoclonal antibodies and others. The immunologic and molecular biology of the different cardiologic diseases are mentioned and discussed in relation to rationale for apheresis therapy and its place with other modern therapy. The pathogenetically backgrounds are demonstrated in these cardiologic diseases, in which they are clarified. Therapeutic apheresis using hollow fiber membranes, and/or semi-, or selective columns is a safe and highly effective method for elimination of autoantibodies, immune complexes, inflammatory moderators, paraproteins and other toxins from blood, resulting in rapid clinical improvement in cardiologic diseases. The guidelines of the American Application Committee of the American Society for Apheresis are cited for cardiologic disease, which could be treated with therapeutic apheresis, immunosuppression and human monoclonal antibodies.

Keywords: Idiopathic dilated cardiomyopathy; coronary heart disease; acute myocardial infarction; heart transplant rejection; therapeutic plasma exchange; immunoadsorption; extracorporeal photopheresis; creative reactive protein apheresis

Introduction

As an essential supportive therapy, therapeutic apheresis (TA) offers considerable benefits for patients with severe or refractory to conservative therapy. Therapeutic apheresis has shown to significantly improve the prognosis of these diseases. The utilization of hollow fiber modules enables the complete separation of cellular elements from the plasma, while concurrently reducing thrombocyte damage in comparison to the employment of centrifuges [1]. During the treatment with hollow fiber modules is important to keep the blood levels of antibodies or other pathogenic substances on a very low level over a long time during the treatment, in which the pathogenic substances that should be eliminated could enter the intravascular space and could be then removed by hollow fiber modules [2].

A multitude of technological, economic, and social factors have impact on the clinical practice of apheresis [3]. Double filtration and adsorption technologies with special columns allow a selective removal of autoantibodies, toxins, and other pathologic substances from blood without any substitution solution [4].

With more than 25 years` experience of TA in various diseases such as nephrology, hematology, neurology, dermatology diseases and others, we give an overview of the different TA methods used in cardiology [1, 2, 5, 6]. In particular, autoimmune diseases in which circulating autoantibodies play a harmful role, the removal of these immunoglobulins can have a beneficial effect on the course of the disease. With immunoadsorption (IA) by using Ig

columns, the elimination of circulating autoantibodies and immune complexes (IC) can lead to an improvement of the disease [4].

The development and maintenance of autoimmune diseases may be influenced by circulating immunoglobulins. Dilated cardiopathy (DCM) is an autoimmune disease caused by the presence of circulating autoantibodies directed against β1 adrenoceptor. Consequently, patients with DCM may be benefit from IA and immunosuppression [7, 8].

Dyslipoproteinemia plays a key role in the pathogenesis of atherosclerosis of atherosclerosis and coronary heart diseases (CHD). Elevated low-density lipoprotein cholesterol (LDL) and/or Lipoprotein (a) (Lp(a)) are well established risk factors for cardiovascular disease (CVD) [6]. There is a mutual effect between high LDL, low HDL, and hypertriglyceridemia. Despite substantial advancements in diagnostics, drug therapy, and cardiosurgical procedures, arthrosclerosis with myocardial infarction, stroke, and peripheral vascular disease still maintains its position at the top of morbidity statistics in industrialized nations [9-11]. The drug therapies include besides statins and 3.hydroxy-3-methylgluraryl-coenzyme A (HMG-CoA)-reductase inhibitors, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors), and lipoprotein apheresis (LA), which is safe and can control lipid levels [11].

C-reactive protein (CRP) is a marker of inflammation that is also elevated in acute myocardial infarction (AMI), too. It mediates tissue damage in AMI thus worsening the prognosis [12]. In addition to acute-phase proteins, CRP and other substances are deposited in the necrotic center of the infarcted myocardium [13]. This represents one of the mechanisms through which the immune system further exacerbates myocardial necrosis, mediating secondary damage to the myocardium [14]. Therefore, the demand is that the selective depletion or apheresis of these proinflammatory mediators in AMI, especially CRP, may prove beneficial in mitigating myocardial necrosis and consecutively improve outcomes. A developed specific CRP adsorbers (Pentacor GmbH; Henningsdorf, Germany), which contains a phosphocholine derivate as ligand for CRP, is capable of selectively CRP from plasma with a high efficiency [15].

In select patients with end-stage heart failure the heart transplantation is the gold standard therapeutic options. Annually, thousands of heart transplants are performed worldwide. However, successful long-term outcomes of heart transplantation can be disturbed by immune-mediated injection of the cardiac allograft, as acute cellular rejection, antibody-mediated rejection, and allograft vasculopathy [16].

In addition to immunosuppression (IS), therapeutic plasma exchange (TPE), IA, and/or human monoclonal antibodies (HMA), extracorporeal photopheresis (ECP) are indicated in acute and chronic rejection of solid organ transplantation. Extracorporeal photopheresis, a cellular immunotherapy, intails the collection and treatment of white blood cells contained in the buffy coat with a photoactive psoralen compound, followed by irradiation with ultraviolet A light [16].

All these mentioned heart diseases require TA, IS with steroids and/or cytotoxic agents, and/or HMA. The therapy is most individually tailored to the specific needs of the patients in the greatest possible degree [17, 18]. The TA methods, which are used in cardiology are TPE, IA, LA, ECP, and CRP apheresis. In the present review, the authors sought to provide an overview of the pathogens aspects indicating that TA, IS and/or HMA may serve as be a supportive therapy in these severe cardiologic diseases. The Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) is cited for these disorders in which TA, IS and/or HMA are indicated. (Table 1).

Idiopathic Dilated Cardiomyopathy (IDCM)

Idiopathic dilated cardiomyopathy is a disease consisting of left ventricular dilation and contractile dysfunction accompanied by impairment of multiple β-adrenergic receptor function [19, 20]. The disturbed β-adrenergic receptors function may be based on an elevated sympathetic tone observed in patients with dilated cardiomyopathy. The tissue concentration of norepinephrine is decreased and plasma concentration of this transmitter is elevated providing evidence of sympathetic activation. Such an increased sympathetic tone results in down-regulation of the β-adrenoceptor-mediated signal transduction cascade, the induction of fetal proteins, and markers of hypertrophy [21]. Another possibility is that such prolonged adrenergic stimulation induces metabolic and electrophysiologic disturbances in the myocardium and is responsible for tachyarrhythmia and sudden death [22].

The blood of patients with IDCM contains circulating antibodies directed against β1 adrenoceptor [23]. The number of β1-adrenoceptors and the β-adrenergic responsiveness are decreased in patients with IDCM. The fact that the anti-β1-adrenoceptor antibodies could play a role in the pathogenesis of IDCM has been demonstrated in patients with end-stage ICDM who were supported by a ventricular assist device [19].

The incidence of IDCM varies between 5 to 8 patients per 100,000 of the population, and in the United States on average 36 patients per 200,000 of the population [24]. The prognosis is worst for patients with the lowest ejection fractions of severe diastolic dysfunction [20]. The treatment of ICDM comprises medications to improve survival and reduce hospitalization, such as angiotensin converting enzyme inhibitors and β-blockers. Other therapies include enrolment in a multidisciplinary heart failure service, and device therapy for arrhythmia management and sudden death prevention [17]. Patients who are refractory to medical therapy may benefit from an implantable defibrillator and/or heart transplantation [20, 25].

In animal and receptor studies, autoantibodies have been identified that contribute to the progressive deterioration of cardiac function in a subset of patients with IDCM [26]. These antibodies, initially detected in patients with Chagas´ disease, were present in 80 percent of patients with end-stage IDCM and all patients required mechanical cardiac support [27]. Cardiac function recovered to near-normal values concomitant with gradual disappearance of β1-autoantibodies in 20 percent of the mechanically supported patients [27].

The hypothesis postulates that cardiac antibodies play an important role for the induction, maintenance, and progression of IDCM and that their elimination through IgA IA should improve or at least stabilize the function of the heart in a analogous manner to other autoimmune diseases. This was shown in short-time effects with IgA IA treatments in 7 patients with IDCM by Wallukat et al. [28]. The β1-autoantibodies, a part of the IgG fraction, were used as a marker for autoantibody presence to identify patients who might benefit from IA.

The echocardiographic evaluation of left ventricular ejection fraction (LVEF) and internal diameters were chosen to determine cardiac performance, and the New York Heart Association (NYHA) functional class was correspondingly assessed. Immunoadsorption offers an effective and low-risk treatment that has the potential to postpone or even avoid heart transplantation, which otherwise would be the midterm perspective for patients with IDCM. The removal of β1-autoantibodies has been proposed as a potential mechanism for the improvement of the LVEF in ICDM [27].

Patients with IDCM were treated with adsorber against immunoglobulins (Miltenyi Biotec, Germany), the Corafin column (Affina, Germany), the protein-A IA (Fresenius, Germany), or special columns containing a combination of synthetic peptides which are binding antibodies which inhibits the β1-adrenergic receptors of the heart muscle. The IA treatments were conducted on 5 – 9 consecutive days with or without IgG substitution

over 4 weeks (1 cycle; in total 4 cycles). Several authors, who treated patients with IDCM with different IA systems and IS, found improvement in short-term hemodynamics as well as long-term follow-up with severe IDCM [29-36].

Therapeutic apheresis, immunosuppressive therapy and intravenous immunoglobulins (IVIG) have been demonstrated to improve both cardiac function and daily activities in patients with IDCM and arrhythmias resulting from myocarditis, and may be an effective treatment. Immunoadsorption represents viable alternative to the use of immunosuppressive medication or the reduction of high doses of it, and is a safe method (33, 34). The AAC of the ASFA has given the IDCM the category III with recommendation grade (RG) 2B and 2C respectively for TPE and IA (17, 18) (Table 1).

Table 1: Therapeutic Apheresis in Cardiology (17, 18)

	Category	Recommen-dation grade	TA-modality	Treatment volume (TPV)	Replacement solution	Frequency
Idiopathic dilated cardiomyo-pathy (IDCM)	III III	2B 2C	TPE IA-Protein-A	1-1.5 1-1.5	5% HA ---	daily or every other day
Coronary heart disease and dysliproteinemia (CHD)	II	1A	TPE, selective separation methods	1-1.5 ---	5% HA ---	daily or every other day
Acute myocardial infarction (AMI)	---	---	---	---	---	---
Heart transplant rejection	II (desensitization) III (AMR)	1C	TPE	1-1.5	5% HA	daily or every other day
		2C	TPE	1-1.5	5% HA	
	II (cellular/recurrent rejection)	1B	ECP	1-1.5 L Blood	---	weekly or every 2-8 weeks for several months
	II (rejection prophylaxis)	2A	ECP	1-1.5 l blood	---	

(**Category I:** accepted for TA as first-line therapy; **Category II:** accepted for TA as second-line therapy; **Category III:** not accepted for TA, decision should be individualized)

TPE: therapeutic plasma exchange, IA: immunoadsorption, ECP: extracorporeal photopheresis, 5%HA: human albumin electrolyte solution

Coronary Heart Disease (CHD) and Dyslipoproteinemia

Dyslipoproteinemia plays a key role in the pathogenesis of atherosclerosis and CHD. Elevated LDL, reduced HDL, and hypertriglyceridemia affect each other. Despite progress in diagnostics, drug therapy, and cardiosurgical procedures, atherosclerosis with myocardial infarction, stroke, and peripheral vascular disease continues to present a significant burden in industrialized nations, as evidenced by its prominence in morbidity statistics [37, 38]. Widely accepted established risk factors are smoking, arterial hypertension, diabetes mellitus, central obesity, hyperlipidemia for atherosclerosis [39].

The vascular endothelium is the largest endocrine, paracrine and autocrine participants in the regulation of numerous homeostatic vascular functions [40]. Endothelial cells are capable of sensing alterations in hemodynamic forces such as pressure and shear stress, as well as circulating and locally formed vasoactive substances released by blood cells. From these stimuli, endothelial cells synthesize and release biologically active substances such as nitride oxide (NO), prostacyclin (PGI2), endothelium-derived hyperpolarizing factor (ED-HF), endothelin's, prostaglandin H2 (PGH2), thromboxane A2, heparin sulfate, transforming growth factor, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), tissue plasminogen-activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), oxygen free radicals, and others [40]. These substances modulate vascular tone through their relaxing and contracting actions, as well as vascular structure through production of growth-promoting and growth-inhibiting factors. In the development of endothelial dysfunction in dyslipoproteinemia is important a decrease in the synthesis of endothelial NO and an increase in its active radicals, causing modification of low-density lipoprotein and their deposition in the vascular endothelium [41]. The endothelium also regulates hemostasis and thrombosis through the expression of chemotactic and adhesion molecules [42].

Elevated lipid concentration in the blood lead to their accumulation in the intima of arteries, resulting in the development of atherogenic plaques, which are accompanied by changes in vessel tone and endothelium regulation [43, 44]. High levels of LDL increase the risk of the development and progression of CHD [38].

Lipoprotein (a), as an atherogenic substance is very similar to LDL, and Lp(a) contains Apo(a), which is very similar to plasminogen, enabling Lp(a) to bind fibrin clots. The binding of plasminogen is prevented and fibrinolysis obstructed, and has 6 different Lp(a) phenotypes S4, S3, S2, S1, B, and F. [45, 46]. The isoforms S2; S1, B, and F are linked to CHD, and patients with premature CHD showed the highest the highest Lp(a) levels as well as the isoforms S2, S1, B, and F [47]. A number of mechanisms have been postulated, as blocking of plasminogen, a binding site on fibrin clots, interaction with other coagulation proteins, and hepatic growth factor [38, 48]. In summary, potentially modifiable CHD risk factors are systemic inflammation, diabetes mellitus, low-density lipoprotein, high triglycerides, remnant lipoproteins, Lp(a), and vascular dysfunction [49,50].

A further risk factor for accelerated atherosclerosis is the widespread high level of homocysteine, which are particularly prevalent in dialysis patients [51]. Homocysteine is a independent risk factor, and is a sulfur amino acid and produced int the metabolism of methionine [52]. Vitamins are important cofactors for the enzymes in the methionine metabolism such as folic acid, vitamin B 12 for remethylation pathway, and vitamin B 6, or pyridoxine for

the transculturation pathway. The kidneys are responsible for the removal of up to 70 percent of plasma homocysteine. The therapy with Vitamins B 6 and B 12 are sufficient in most dialysis patients [53].

Table 2 illustrate the pharmacological treatments for dyslipoproteinemia in CHD, which is the main causes of death in the mortality statistics of the industrial nations. All HMG-CoA-reductase inhibitors, which can be combined with other lipid reducers, were found to cause a variety of adverse effects liked diarrhea, obstipation, other gastrointestinal diseases, myositis, rhabdomyolysis, and others were observed [54]. Ezetimibe is another cholesterol absorption inhibitor that prevents the absorption of cholesterol by inhibiting the passage of cholesterol of dietary and biliary origin across the intestinal wall. It is well tolerated and can be combined with HMG-CoA reductase inhibitors, and has been demonstrated to be highly efficacious [55, 56].

Drugs	**Cholesterol (%)**	**LDL (%)**	**HDL (%)**	**Triglycerides (%)**
Ion exchanger	-10 - -30	-10 - -30	+0 - +10	+0 - -20
Fibrates	-10 - -25	-5 - 25	+5 - +25	-25 – 260
Nicotinic acid	-10 - -25	-5 - -25	+5 - +25	-40 - -60
Probenol	-5 - -5	-5 - -25	+5 - +15	-40 - -60
HMG-CoA reductase inhibitor	-20 - -40	-25 - -40	+0 - +15	-10 - -20
Ezetimibe	-15 - -20	-15 - -25	+2.5 - +5	-6 - -14

Table 2: The effects of maximum dosage of different lipid reducers [38, 57, 58]

Nevertheless, the combination HMG-CoA-reductase inhibitor, with ezetimibe or other lipid reducers, a LDL reduction of up to 50 percent of the original concentration can be achieved. In a considerable number of patients, this appears to be a quite effective approach (Table 2).

With the semi-selective and selective extracorporeal TA techniques all severe forms or therapy-resistant forms can be effectively treated [59]. In Table 3 are summarized the semi-selective and selective LDL-methods with their effectiveness of different substances.

	Cascade filtration 2500-3000 ml plasma **(%)**	**Immuno-adsorption** 4000-5000 ml plasma **(%)**	**Heparin-induced LDL preci-pitation (HELP)** 2500-3000 ml plasma **(%)**	**LDL adsorption, Liposorber** 2500-3000 ml plasma **(%)**	**LDL-hemoper-fusion (DALI)** 1.6 blood volume **(%)**	**LDL-hemoper-fusion (Lipo-sorber D)** 1.5 blood Volume **(%)**
Cholesterol	35 50	30	50	45	60	55
LDL	30 - 45	35	45	33 - 40	60 - 75	60 - 75
HDL	35 - 50	20	10 - 20	---	16 - 29	5 - 13
Lp(a)	60 - 70	60	46	60	60 - 75	60 - 75
Triglycerides	60	60	60	70	ca 40	ca 66
Fibrinogen	50	10 - 20	50	30	16	20 - 40
IgM	35	10 - 20	---	---	21	14
IgA	55	10 - 20	---	---	---	---
Factor VIII	---	10 - 20	10 - 20	20	---	---
C 3	---	---	50	---	---	---
C 4	---	---	50	---	---	---
Plasminogen	---	---	50	---	---	---

Table 3: Effectiveness of the different LA methods (reduction in percent of original concentration in blood (38, 59, 60).

All the methods mentioned above are effective, safe, and well tolerated. The average LDL cholesterol concentration can be reduced to approximately 50-60 percent of the original values, with weekly or biweekly treatments. The cholesterol concentration increases after each apheresis session, but does not return to the original concentration. Following a few sessions, the levels return to equilibrium. The increase after apheresis treatment must be slowed down with a combination of TA and HMG-CoA-reductase inhibitor and ezetimibe, or others [60]. The primary aim in reducing cholesterol concentration is to prevent the development and progression of atherosclerosis. The lowering of cholesterol from 400 mg/dL to 200 mg treatment could almost double a patient´s life expectance [61]. The TA treatment in indicated in homozygous and severe heterozygous or other forms of hypercholesterolemia which failed by conservative therapy life-long or until other therapy technologies such as HMAs or gene therapy are available for everyone. The AAC of the ASFA has given the CHD the category II and the RG 1A for TPE, respectively selective separation methods [17, 18] (Table 1)

Proprotein convertase subtilisin/kexin type 9 is involved in cholesterol metabolism that is enzymatically inactive following secretion. Plasma PCSK9 concentration decreases with fasting and increases following meals in healthy humans [62]. The PCSK9 has an important regulator of cholesterol metabolisms. The PCSK9-inhibitors showed favourable outcomes in terms of lipid lowering, with a 50 to 60 percent improvement in original LDL-levels [63,64]. With evolocumab and alirocumab, two PCSK9-inhibitors, and other statins, and/or LA, all severe hypercholesterolemia with cardiovascular disease are treatable.

However, after a long period of diet and maximum lipid lowering drugs therapy, or refractory to drug therapy, LA is indicated. The prospective utilization of HMA, including evolocumab or alirocumab, may be expedited by the identification of techniques to augment antibody expression [65]. Nevertheless, the number of patients with extremely elevated Lp(a) who need the extracorporeal therapy or the HMA- or gene therapy will increase. Therefore, larger studies must be showing which methods the LA or the PCSK9 inhibition in combination or alone would be preferred [66, 67].

Acute Myocardial Infarction (AMI)

C-reactive protein is marker of inflammation. It is less documented, however, that CRP mediates secondary damage of the myocardium after AMI [12]. C-reactive protein is an acute-phase mediator which activates the classical complement pathway, resulting in the elimination of pathogens or reversible damaged or dead body cells [68]. The presence of inflammatory markers, such as CRP, can serve as an indicator for the potential development of acute coronary syndrome (ACS) development. Inflammation is a physiological reaction in which fibrosis is induced to facilitate the healing of tissue, an excessive inflammatory response in this process intensifies the necrosis of infarcted myocardium and inhibits healing processes, such as angiogenesis and the replacement of collagens fibers [69]. In patients with AMI, circulating levels of CRP increase beginning six hours after the onset of ischemia, reaching their peak levels between 24 and 72 hours later. The magnitude of CRP rise is a prognostic marker of one-year outcomes post myocardial infarction [70].

As a result of trauma, inflammation, or infection, CRP is synthetized and secreted into the blood by hepatic cells [66]. Proinflammatory cytokines, interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor α (TNF-α) induce CRP expression in these ways [71]. The elevated CRP initiates the phagocytosis via the activation of the classical pathway, up to C4 [68, 72]. In the necrotic center of the infarcted myocardium, acute-phase proteins, CRP and secretory phospholipase A2 type IIa are deposited [73]. In this way, the immune system exacerbates myocardial necrosis, mediating secondary damage to the myocardium (68, 70). The hypothesis that can be derived from these observations is that a selective depletion or selective apheresis of these proinflammatory mediators in AMI may help mitigate myocardial necrosis and consecutive improve.

C-reactive protein is the prototype of human acute-phase proteins and a marker of inflammation, it has also been demonstrated to mediate tissue damage in various conditions including ischemic tissue injury, autoimmune disease, etc. [68] C-reactive protein is not only a marker of inflammation but also an active pro-inflammatory protein. In patients presenting with a ST-elevation myocardial infarction, CRP levels are associated with larger infarct size, transmural extent, and poor function of left ventricle, and independently predict 30-day mortality [74]. The elimination of CRP from plasma may potentially be a broadly applicable therapeutic strategy.

In recent years, a specific CRP adsorber has been developed which allows efficient lowering of CRP levels and may ultimately lead to improve survival outcomes [12]. The CRP adsorber, an agarose-based resin, which contains a phosphocholine-derivate as ligand for CRP and is capable of selectively depleting CRP from plasma with an efficiency of up to 94 percent [15, 68]. The CRP adsorber is introduced in a primary plasma separation method. The CRP adsorber can be used up to a maximum cumulative treatment time of 24 h, and regenerable and is stored in sodium acid at 2-8° C. 6,000 ml plasma are usually treated in 12 cycles over 4-5 h. Vascular access is obtained across a central venous catheter in the internal jugular vein or canula insertion into antecubital veins. Two to ten treatments on the following days can performed. The therapy is safe with no serious side effects, which was shown in case reports [75-77]. The increase of CRP concentration during the acute response after AMI correlated significantly with the infarct size in control patients [15]. Patients under CRP apheresis showed smaller infarct sizes and improved left ventricular function and wall motion compared to patients without CRP apheresis [78].

The use of CRP apheresis seems efficient for selective CRP depletion from human plasma. Nevertheless, further investigation is required through larger, multicentric studies to elucidate the role of CRP apheresis in the treatment of AMI.

Heart Transplant Rejection

Thousands of heart transplantations are performed worldwide each year. The outcomes have gradually improved since the first successful heart transplantation since 1967. Nevertheless, long-term survival is still threatened by infection, neoplasia, allograft rejection, or vasculopathy [79]. The most common form of rejection is the cellular rejection mediated by T cells, which is diagnosed through histo-pathologically analysis. Humoral rejection is less frequent but associated with increased graft loss, mortality, and vasculopathy [80]. Allograft vasculopathy is an accelerated of atherosclerosis that occurs in up to 60 percent of transplant recipients within 5 years post-transplantation [79]. Alloreactive immune response begins immediately after blood circulation is re-initiated and the contact with donor organ occurs. During this early phase, the strongest immune response must be expected [81]. In thoracic transplantation, the antibody-mediated rejection (AMR) remains a severe problem. The AMR typically does not respond to conventional therapies, and there are no standard therapy strategies [82, 83]. Immunosuppressants generally affect only cellular signal transfer and are associated with various drug-adverse effects. The introduction of novel immunosuppressive medications reduced the rate of acute allograft rejection but did not improve significantly the long-term graft survival [84]. Important for the antitumoral therapy is the TA such as TPE or IA because with TA performed non-HLA and HLA-ab can be quickly and effectively removed [85].

In the year following after heart transplantation, a significant number of patients develop cardiac allograft vasculopathy (CAV) [86]. The pathogenesis of CAV can attribute to initial endothelial injury followed by intima hyperplasia and proliferation of vascular smooth muscle cells. Cardiac allograft vasculopathy is defined as intimal proliferation of 0.5 mm or more [87]. A characteristic of CAV is a diffuse concentric stenosis of allograft coronary arteries due to intimal expansion, or the CAV is defined by the presence of a coronary stenosis of 40 percent or more and/or distal pruning of secondary side branches. The CAV can be diagnosed either by angiography or by intravascular ultrasound, and is induced by immunologic or non-immunologic factors [88, 89]. Vascular endothelial growth factor, a leukocyte mitogen produced by activated endothelial cells and leukocytes, may play a specific role not only in leukocyte trafficking, but also in the augmentation of acute cellular rejection and development of CAV [90].

For prevention and treatment of rejection, the therapy includes cyclosporine, azathioprine or mycophenolate mofetil, corticosteroids with or without antilymphocyte antibodies, HMAs and TA [17, 91, 92]. There are many therapy protocols to prevent acute allograft rejection, which include early TPE or IA, bortezomib, a proteasome inhibitor, basiliximab and thymoglobulin, and others [93-95]. All clinically successful AMR treatment protocols include TPE or IA [38 96]. Therapeutic apheresis in heart transplantation rejection is well tolerated, and besides its anti-rejection effects, it also affects has beneficial effects on other systems including oxidized particles, coagulation, CRP, adhesion molecules, plasma viscosity, monocytes, inflammatory HDL particles [86].

Extracorporeal photopheresis is also used to manage the heart transplant rejection. The precise mechanism of action of ECP remains unclear. Two explanations are discussed: The first is stimulation of the immune system to destroy clone-specific T cells causing allograft rejection. The second mechanism of action is the induction of antigen-specific immunotolerance via expansion of regulatory T cells [97]. Extracorporeal photopheresis is generally well tolerated with few adverse effects and low infection risk [98]. The European ECP study showed in heart transplantation that ECP can effectively be used to treat different rejection types and to prevent rejection in the modern era of immunosuppression [99]. Extracorporeal photopheresis is an immunomodulatory therapy currently recommended as an adjunctive

treatment for the prevention and management of organ rejection in heart transplantation [100].

In the guidelines on the use of TA of the AAC of the ASFA has the heart transplant rejection for TPE the category II with RG 1C for desensitization, category III with 2C for AMR, and for ECP the category II with RG 2A for prophylaxis or rejection and the category II with RG 1B for treatment of cellular or recurrent rejection [17, 18](Table 1). The extracorporeal methods are qualified for rescue therapy of acute or hyper-acute rejection (81). Nevertheless, future research is required to ascertain the extent to which TA contributes to the survival of heart transplantation. The present discussion does not address other cardiologic diseases, as they are treated by different modalities

Closing Remark

It can be concluded that all mentioned cardiologic disease must be treated with TA, Immunosuppression, and/or HMAs. This demand presents a great challenge to physicians, politicians, health organizations, and especially manufactures [101]. The medical supply companies constantly justifying the high costs by pointing to the expensive research and development that is required. All those involved in the healthcare system must strengthen their cooperation in the respect.

Idiopathic dilated cardiomyopathy is an example of antibody-mediated immune disease. Patients with severe symptoms of IDCM who have failed high doses of conventional therapy and/or have an aggressive and rapidly progressive course of the disorders, must be treated with TPE or IA with immunosuppression and/or HMAs. Coronary heart disease by dyslipoproteinemia still maintains its position at the top morbidity statistics in industrialized nations, if diet and lipid lowering drugs failed, LA and/or PCSK9-inhibitors, and HMA are indicated. Acute myocardial infarction with the acute phase mediator CRP can be treated with CRP apheresis, which is an efficient and selective CRP removal from plasma with improvement of the left ventricular function. In rejection prophylaxis, desensitization, AMR, and cellular or recurrent heart rejection, especially in acute or hyper-acute rejection, TPE, IA or ECP are indicated besides the immunosuppression and/or HMAs. The various TA methods are an immunomodulatory therapy, and recommended as a adjunctive treatment for prevention and management of heart transplant rejection [38].

Well trained and experienced physicians and staff can overcome technically difficulties to complete the procedure without complications [102]. In order to assess the cost-effectiveness of the aforementioned diseases, it is essential to calculate the quotient relevant for cost-effectiveness assessment, defined as the cost of treatment minus the cost saved divided by the improvement in life quality. This must be discussed and calculated precisely by all involved parties [103]. Every effort should be made to delay the progression of acute and chronic disease. Therapeutic apheresis is clearly an important tool in the treatment of many complex conditions both currently and in future [104]. In diseases the treatment with TA must be combined with immunosuppression, IVIG, and/or HMAs, or others.

The medical progress is advancing and will not be stopped. Since the introduction of hollow fiber membranes, exceptional efforts in research and development have been undertaken in the apheresis sector alone, enabling, for example, the introduction of semi- and selective separation techniques into clinical practice [4]. This is reflected in the numerous national and international specialist congresses, which take place every year.

Conclusion

Besides conservative therapy, immunosuppression, and/or HMAs, some cardiologic diseases could be treated successfully with TA. All TA techniques described here are all effective and safe. With daily or other day treatment a rapid improvement could be reached. Immunoadsorption with special adsorbers which are binding antibodies that inhibit the β1-adrenergic receptors of the heart muscle and conservative therapy improved severe IDCM. In severe CHD and dyslipoproteinemia LA and lipid lowering such as HMG-CoA-reductase inhibitors and ezetimibe are indicated. In AMI with elevated CRP specific CRP adsorbers remove efficiently CRP and lead to improve survival outcomes. For prevention and treatment of heart transplant rejection, besides immunosuppression, HMAs, TPE, IA, and/or ECP are indicated, and is well tolerated and safe. Well trained and experienced physicians and staff can overcome technically difficulties and complications. However, the costs of TA, especially the hollow fibers and adsorbers, must be decreased, and further multicenter studies must be taken to clarify the TA in the treatment of various cardiologic disease.

Abbreviations

AAC: Apheresis Application Committee, ASFA: American Society for Apheresis, ACS: Acute coronary syndrome, AMI: acute myocardial infarction, AMR: antibody-mediated rejection, bFGF: basic fibroblast growth factor, CAV: Cardiac allograft vasculopathy, CHD: coronary heart disease, CRP: C-reactive protein, CVD: cardiovascular disease, DCM: dilated cardiomyopathy, ECP: extracorporeal photopheresis, ED-HF: HDL: high-density lipoprotein, HLA: human leukocyte antigen, HMA: human monoclonal antibody, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A, IA: Immunoadsorption, IC: immune complexes, IDCM: Idiopathic dilated cardiomyopathy, IS: immunosuppression, IVIG: intravenous immunoglobulin, LA: lipid apheresis, LDL. Low-density lipoprotein, Il-1: interleukin 1, IL-6: interleukin 6, Lp(a): lipoprotein (a), LVEF: left ventricular election fraction, NO. nitride oxide, NYHA: New York Heart Association, PAI-1: plasminogen activator inhibitor-1, PCSK9-inhibitor: proprotein convertase subtilisin/kexin type 9 inhibitor, PDGF: platelet derived growth factor, PGI2: prostacyclin, PGH2: prostaglandin H2 RG: recommendation grade, TA: therapeutic apheresis, TNF: tumor necrosis factor, t-PA: tissue plasminogen activator, TPE: therapeutic plasma exchange, VEGF: vascular endothelial growth factor,

References

1. Bambauer R, Latza R, Burgard D, Schiel R. (2016). Therapeutic Aphersis in Hematologic, Autoimmune and Dermatologic Diseases with Immunologic origins. Ther Apher Dial. 20:433-452.
2. Bambauer R, Schiel R, (2023). Therapeutic Apheresis, Immunosuppression, and Human Monoclonal Antibodies in Hematologic Diseases. Med Res Arch. 11(7):
3. Malchesky PS, Bambauer R, Horiuchi T, Kaplan A, et al. (1995). Apheresis Technologies: An International Perspective. Artif Org. 19/4):315-323.
4. Bambauer R, Schiel R, Lehmann B, Bambauer C. (2012). Therapeutic Apheresis, Technical Overview. ARPN *J Sci Technol.* 2:399-422.
5. Bambauer R, Latza R, Burgard D, Schiel R. (2017). Therapeutic Apheresis in Immunologie Renal and Neurological Disease. Ther Apher Dial. 21(1):6-21.
6. Bambauer R, Burgard D, Latza R, Schiel R. (2017). LDL- and Lipoprotein (a) – Apheresis in Hypercholesterolemia and Coronary Artery Diseases. In: Coronary Artery Disease:Research and Practice. iConcept Press, pp 1-27.
7. Magnusson Y, Marullo S, Höyer S, et al. (1990). mapping of a functional autoimmune epitope on the β1-adrenergic receptor in patients with idiopathic dilated cardiomyopathy. *J. Clin Onvest.* 86:1658-1663.

8. Wallukat G. (2002). The β-Adrenereggic Receptors. Herz. 27:683-690.
9. Carlson L, Pernow A (eds.). (1982). Metabolic risk factors in ischemic cardiovascular disease. Raven Press, New York,
10. Stamper MJ, Krauss RM, Ma J, et al. (1996). A prosp3ective study of triglyceride level low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 276; 882-888.
11. Raina R, Young C, Krishnappa V, et al. (2019). Role of Lipoprotein Apheresis in Cardiovascular Disease Risk Reduction. Blood Purif. 47(4):301-316.
12. Ries W, Torzewski J, Heigel F, et al. (2021). C-Reactive Protein Apheresis as Anti-inflammatory Therapy in Acute Myocardial Infarction: Results of the CAM-1 Study. *Front Cardiovasc Med.* 8:
13. Milosevic M, Balint B, Ilic I, et al. (2023). C-reactive Protein Apheresis in Acute myocardial Infarctio. Curr Pharmaned Des. DOI:10.2174/13816/2829666230310090601.
14. Sheriff A, Schindler R, Vogt B, et al. (2015). Selective apheresis of C-reactive protein: A new therapeutic option in myocardial infarction? *J Clin Apher.* 30(1):15-21.
15. Kayser S, Brunner P, Althaus K, et al. (2020). Selective Apheresis of C-Reactive protein for Treatment of Indications with Elevated CRP Concentrations. *J Clin Med.* 9:2947: doi:10.3390/jcm9092947.
16. https://onlinelibrary.wiley.com/doi/abs/10.1111/ctr.14333
17. Padmanabhan A, Conelly SL, Aqui N, et al. (2019). Guidelines on the use of Therapeutic Apheresis in Clincal Practice Evidence – Based Approach from the Writing Committee of the American Society for Apheresis. *J Clin Apher.* 34:171-354.
18. Connelly SL, Alquist CR, Aqui NA, et al. (2023). Guidelines on the use of Therapeutic Apheresis in Clincal Practice Evidence – Based Approach from the Writing Committee of the American Society for Apheresis. *J Clin Apher.* 38:77-278.
19. Wallukat G, Müller S, Podlowski, et al. (1999). Agonist-like beta-adrenocepter antibodies in heart failure. *Am J Cardiol.* 83: Macdonald 75H.
20. Weintraub RG, Semsarian C, P. (2017). Dilated cardiomyopathy. Lancet 390:400-414.
21. Bristov MR, Ginsburg R, Umas V, et al. (1986). β1- and β2-adrenergic receptor-subtypes in nonfailing and failing ventricular myocardium: coupling of regulation in heart failure. Circ Res. 59:297-309
22. Haft J. (1974). Cardiovascular injury induced by sympathetic catecholamines. Prog Cardiovasc. 17:73.
23. Magnusson Y, Marullo S, Höyer S, et al. (1990). Mapping functional autoimmune epitope on the β1-adrenergic receptor in patients with idiopathic dilated cardiomyopathy. J Clin Invest. 86:1658-1663.
24. Dec GW, Fuster V. (1994). Idiopathic Dilated Cardiomyopathy. *N Engl J Med.* 1564-1575
25. Tamburro P, Wilber D. (1992). Sudden death in idiopathic dilated cardiomyopathy. Am *Heart J.* 124:1035-1045.
26. Podlowski S, Luther HP, Morwinski, et al. (1998). Agonistic anti-β1-adrenergic receptor autoantibodies from cardiomyopathy patients reduce the β1-adrenergic receptor expression in neonatal rat cardiomyiotes. *Circulation.* 98:2470-2476.
27. Müller J, Wallukat G, Wenig YG, et al. (2000). Weaning from mechanical cardiac support patients with idiopathic dilated cardiomyopathy. Circulation. 101:385.102
28. Wallukat G, Reinke P, Dörfler WV, et al. (1996). Removal of autoantibodies in dilated cardiomyopathy by immunoadsorption. *Int. J Cardiol* 54:191-195.
29. Mobini R, Staudt A, Felix DSB. (2003). Hemodynamic improvement and removal of autoantibodies against β1 adrenergic receptor by immunoadsorption therapy in dilated cardiomyopathy. Autoimmunity. 20:345-350.
30. Dörffel WV, Wallukat G, Dörffel Y, et al. (2004). Immunoadsorption in idiopathic dilated cardiomyopathy, a 3-year follow-up. Am Heart Surg. 97:529-534.
31. Burgstaler E, Cooper LT, Winters JF, et al. (2007). Treatment of chronic cardiomyopathy with immunoadsorption using the Staphylococcal A-agarose column: A comparison of immunoglobulin reduction using two different techniques. *J. Clin Apher.* 22:224-232.
32. Doesch AO, Konstatin M, Celik S, et al. (2009). Effects of protein-A immunoadsorption in patients with advanced chronic dilated cardiomyopathy. *J Clin Apher.* 24:141-149.
33. Staudt A, Herda LR, Trimpert C, et al. (2010). Fcγ-receptor IIa polymorphism and the role of immunoadsorption in cardiac dysfunction in patients with dilated cardiomyopathy. *Clin Pharmacol Ther.* 87:452-458.
34. Herda LR, Trimpert C, Nauke U, et al. (2010). Effects of immunoadsorption and subsequent immunoglobulin G substitution on cardiopulmonary excise in patients with dilated cardiomyopathy. *Am Heart Surg* 159:809-816.
35. Staudt A. (2001). Immunohistological changes in dilated cardiomyopathy induced by immunoadsorption therapy and subsequent immunoglobulin substitution. Circulation. 103:2681-2686.
36. Kulikova VA, Nedostup AV, Blagova OV, et al. (2019). Therapeutic Plasma exchange with inflammatory dilated cardiomyopathy. Clin Experiment Surg. 7(1):6-16. Doi:10.24411/13308-1198-2019-1101.
37. (1991). Heart Study. Central findings and clinical implications. Ann Med. 23:155-159.
38. Bambauer R, Latza R, Schiel R. (2013). Therapeutic Plasma Exchange and Selective Plasma Separations Methods, Fundamental Technologies, Pathophysiology and Clinical Results. Fourth Edition. Pabst Science Publishers, Lengerich, Germany.
39. Schiel R, Bambauer R, Müller U. (1996). Low-density lipoprotein apheresis versus lipid lowering drugs in the treatment of severe hypercholesterolemia: Four years' experience. Art Org: 20:318-323.
40. Lahere V, Navaaro-Cid J, Ruilope LM, et al. (1997). Endothelial dysfunction. Dyslipidemia and atherosclerosis: Pathophysiology and therapeutic implications. *Cardiovasc Risk Fact.* 7:59.
41. Baykulov AK. (2023).Vascular endothelial dysfunctions with hyperlipoproteinemia. Golden Brain. 7(1):4-11.
42. Moncada S, Palmer RMJ, (1991). Higgs EA: Nitric oxide: Pathology, pathophysiology, and pharmacology. *Pharmacol Rev.* 43:109-142.
43. Schwandt P, Richter WO,(1995). (eds.) Handbuch der Stoffwechselstörungen. Pathophysiologie, Diagnostik, Therapie

und Prävention der Dyslipoproteinämien. Schattauer-Verlag, New York.
44. Shepherd J, Cobbe SM, Ford I, et al. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 333:1301-1308.
45. Futterman G. (1993). The mysteries of lipoprotein(a). Science. 246:904.
46. Lau FD, Giugliano RP. (2022). Lipoprotein(a) and its Significans in Cardiovascular Disease. JAMA Cardiol. 7(7):760-769.
47. Jauhianen M, Koskinen P, Ehnholm P, et al. (1991). Lipoprotein (a) and coronary heart disease risk: A nested case-control study of the Helsinki Heart Study participants. Atherosclerosis. 89:59-67.
48. White AL, Lanford RE. (1994). Cell surface assembly of lipoprotein (a) in primary cultures of baboon hepatocytes. Biol Chem. 269:28716 -28723.
49. Shaya GE, Leucker TM, Jones SR, et al. (2022). Coronary heart disease risk: Low-density lipoprotein and beyond. Trends Cardiovasc Med. 32:181-194.
50. (2024). Lipoprotein(a) and cardiovascular disease: sifting the evidence to guide future research. *Eur J Prev Cardiol.* 31(7):903-914.
51. Rosenthal AF, Ginsburg J, Crawford F. (1998). Homocysteine and heart disease in dialysis patients. Dial Transplant. 27:627-629.
52. Biasoli S, Shiavon R. (2000). Homocysteine as a cardiovascular risk factor. Blood Purif. 18:177-182.
53. Lilien M, Duran M, van Hoek K, et al. (1999). Hyper-homocysteine in children with chronic renal failure. Nephrol Dial Transplant. 14:366-368.
54. Duell FB, Connor WE, Illingworth DR. (1998). Rhabdomyolysis after taking artorvastatin with gemfibrozil. Exerp Med. 81(3):368-369.
55. Knopp RH, Gitter H, Truitt T, et al. (2002). Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 24:729-741.
56. Darkes MJM, Poole EM, Goa KL. (2012). Ezetimibe. Am *J Cardiovasc.* 3:67-76.
57. Rizzo M, Rini GB, Spinas GA, et al. (2009). The effects of ezetimibe on LDL-cholesterol: Quantitative changes?. *Atherosclerosis.* 204(2):330-333.
58. Nutescu EA, Shapiro NL. (2012). Ezetimibe: A Selective Cholesterol Absorption Inhibitor. *J Hum Pharmacol Drug* Ther. 23(11):1463-1474.
59. Yamamoto A, Kawaguci A, Harada-Shiba M, et al. (1997). Apheresis technologies for prevention and regression of atherosclerosis. An Overview: Ther Apher. 1:233-241.
60. Bambauer R, Bambauer C, Lehmann B, Latza R, Schiel R. (2012). LDL-Apheresis: Technical and Clinical Aspect. Sci World J. Article ID 314283, 19 pages.
61. Bambauer R, Schiel R. (2023). LDL Apheresis and/or Human Monoclonal Antibodies in Severe Dyslipoproteinemia. Appl Cell Biol. 11(1):55-59.
62. Browning JD, Horton JD. (2012). Fasting reduces plasma protein convertase subtilisin/kexin type 9 and cholesterol biosynthesis in humans. Lip Res. 0;5: 3359-3363.
63. Vally M, Khan R, Orchard A. (2020). Is LDL apheresis a thing of the past? A *Afr Gen Practit.* 4(1).
64. Pasta A, Cremonini AL, Pisciotta L, et al. (2020). PCSK) inhibitors for treating hypercholesterolemia. Exp Opin Pharmacoth. 21(3):353-363.
65. Ahamad S, Bhat SA. (2022). Recent Update on the Development of PCSK) Inhibitors for Hypercholesterolemia Trreatment. J Med Chem. 65,23:15513-15539.
66. Bambauer R, Schiel R. (2021). Therapeutic Apheresis and Immunosuppression in Immunologic Diseases: A review and Own Observations. *Clin Immunol Res.* 5(2):1-36.
67. Julius J, Tselmin S. (2023). Lipoprotein Apheresis for Reduction of Lipoprotein (a). Cham: Springer International Publishing. 377-407
68. Milosevic M, Balint B, Ilic I, et al. (2023). A-reactive Protein Apheresis in Acute Infarction. Cur *Pharmaceut Des.*
69. Anzai T. (2018). Inflammatory mechanisms of cardiovascular remodeling. Circ J. 82(3):629-635.
70. Sheriff A, Schindler R, Vogt B, et al. (2015). Selective apheresis of C-reactive protein: A new therapeutic option in myocardial infarction? *J Clin Apher*. 30(1):15-21.
71. Kayser S, Brunner P, Althaus K, et al. (2020). Selective ap apheresis of C-reactive protein for treatment of indications with elevated CRP concentration. *J Clin Med.* 9(9):2947.
72. Buerke M, Sheriff A,Garlichs CD.(2022). CRP apheresis in acute myocardial infarction or COVID-19. Med Klin Intensivmed Notf Med. 117(3):191-199.
73. Nijmeijer R, Willemsen, Meijer CJLM, et al. (2023). Type II secretory phospholipase A2 binds to ischemic flip-flopped cardiomyocytes and subsequently induces cell death. Am *J Physiol Heat Circ* Physiol. 285(5):H2218-H2224.
74. Boljevic D, Nikolic A, Rosovic S, et al. (2020). A Promising Innovative Treatment for ST-Elevation Myocardial Infarction: The Use of C-Reactive Protein Selective Apheresis: Case Report. Blood Purif. 49(6):753-757.
75. Ries W, Heigel F, Garlichs, et al. (2019). Selective C-Reactive Protein—Apheresis in Patients. Ther Apher Dial 23:570-574.
76. Torzewski J Heigl F, Zimmermann O, et al. (2020). Case Report of Selective C-Reactive Protein Apheresis in a Patient with SARS-CoV-2 Infection. Am *J Case Rep*. 21: e925020.
77. Schäfer A, König T, Bauersachs J, et al. (2022). Novel Therapeutic Strategies to Reduce Reperfusion Injury After Acute Myocardial Infarction. Cur *Probl Cardiol.* 47(12):101398.
78. Mattecka SM, Brunner P, Hähnel B, et al. (2019). PetraSorb C-Reactive Protein: Characterization of the Selective C-Reactive Protein Adsorber Resin. Ther Apher Dial. 23(5):474-481.
79. Szczepiorkowski M, Banderenko N, Kim HC, et al. (2007). Guidelines on the use of therapeutic in clinical practice-evidence-based approach from the Apheresis Application Committee of the American Society for Apheresis. *J Clin Apher.* 22:96-167.
80. Velez M, Johnson MR. (2009). Management of allosensitized cardiac transplant candidates. Transplant Trev, Orlando. 23:235-247.
81. Rummler S, Breuer M, Maier K, et al. (2010). Extracorporeal immune modulation of sensitized recipients of thoracic organ transplant. Transplantationsmed. 22:369-378.
82. Jhang J, Middlesworth W, Shaw R, et al. (2007). Therapeutic plasma exchange performed in parallel with extra corporeal

membrane oxygenation for antibody mediated rejection after heart transplantation. *J Clin Apher.* 22:333-338.

83. Kaczmarek I, Deutsch MA, Sadoni S, et al. (2007). Successful management of antibody-mediated cardiac allograft rejection with combined immunoadsorption and anti-CD20 monoclonal antibody treatment: Case report and literature. *J Heart Lung Transplant.* 26:511-515.
84. D´Addio F, Margonato D, Pensato U, et al. (2015). Novel therapeutic and diagnostic management of heart transplant patients. Heart Lang Vessel. 7(3):198-207.
85. Luch SH, Lopez- Cepero M, LeFor WM, et al. (2006). Management of the sensitized cardiac-recipient: the use of plasmapheresis and intravenous immunoglobulin. *Clin Transplant.* 20:476-484.
86. Julius U, Tselmin S, Fischer S, et al. (2010). Lipid apheresis after heart transplantation – the Dresden experience: Transplantationsmedizin. 22:355-2362.
87. Lazaro DIJ, Bonet AL, Lopez MJ, et al. (2008). Influence of traditional cardiovascular risk factors in the recipient on the development of cardiac allograft vasculopathy after heart transplantation. Transplant Proc. 40:3056-3057.
88. Pflugfelder PW, Boughner DR, Rudas L, et al. (1993). Enhanced detection of cardiac allograft arterial disease with intracoronary ultrasonographic imaging. *Am Heart J.* 125:1583-1591.
89. Raichlin E, Edwards BS, Kremers WK, et al. (2009). Acute cellular rejection and the subsequent development of allograft vasculopathy after cardiac transplantation. *J Heart Transplant.* 28:320-327.
90. Bayliss J, Bailey M, Lee A, et al. (2008). Late onset antibody-mediated rejection and endothelial localization of vascular endothelial growth factor are associated with development of acute allograft vasculopathy. Transplantation. 86:991-997.
91. Söderlund C, Rädegran G. (2015). Immunosuppressive therapies after heart transplantation – The balance between under – and over – immunosuppression. Transplant Rev. 29(3):181-189.
92. Thrush PT, Pahl E, Naftel DC, et al. (2016). A multi-institutional evaluation of antibody-mediated rejection utilizing the Pediatric Heart Transplant Study database: Incidence, therapies and outcomes. *J Heart Lung Transplant.* 35(12):1496-1504.
93. Davies E, Khan S, Mo YD, et al. (2023). Modifications to therapeutic plasma exchange to achieve rapid exchange on cardiopulmonary bypass prior to pediatric cardiac transplant. *J Clin Apher.* 38(5):514-521.
94. Dhillon M, Kobashigawa JA, Kittzleson M, et al. (2023). Does bortezomib influence pre-transplant therapy or benefit post-transplant outcome for highly sensitized patients?. Clin Transplant. 38(1): e15165.
95. Fortan F, Guyatt G, Stehlik J, et al. (2024). Use of induction therapy post-heart transplantation: Clinical practice recommendations based on systematic review and network meta-analysis of evidence. Clin Transplant. 38(3). e15270.
96. Elfrefaei M, Narula T, Alvarez F, et al. (2024). Clinical Utilityof 1:16 Dilution as a Predictor of Response to Therapeutic Plasma Exchange for HLA Antibody-Mediated Rejection Treatment in Lung Transplant Recipients. A Two Center Study. 45(4): Suppl.S333-334.
97. Siomovich S, Kevin J, Clerkin KJ, et al. (2021). Extracorporeal photopheresis and its role in heart transplant rejection: prophylaxis and treatment. Clin Transplant. 35(7): e14333.
98. Patel J, Klapper E, Shafti H, et al. (2015). Extracorporeal photopheresis in heart transplant rejection. Transfus Apher Sci. 52(2):167-170.
99. Barten MJ, Sax B, Schopka S, et al. (2023). European multicenter study on the real-world use and clinical impact of extracorporeal photopheresis after heart transplantation. J Heart Lung Transplant. 42(8):1131-1139.
100. Barten MJ, Fisher AJ, Hertig A. (2024). The use of extracorporeal photopheresis in solid organ transplantation – current status and future directions. Am *J Transplant.*
101. Bambauer R, Schiel R, Salgado OJ, Straube R. (2024). Therapeutic, Immunosuppression, and Human Monoclonal Antibodies in Dermatologic Diseases. Adv *Res Dermatol Cosmetica.* 3:1017-1026.
102. Steffanuti C, Lanmfi A, Di Giacomo M, et al. (2004). Therapeutic apheresis in low weight patients: technical feasibility, tolerance, compliance, and risk. Transfus Apher. 31(1):3-10.
103. Bambauer R, Latza R, Burgard D, Schiel R. (2004). Therapeutic apheresis in Immunologic Renal and Neurological Disease. Ther Apher Dial. 3(1):3-10.
104. Malchesky PS. (2015). Therapeutic Apheresis Why? 19(5):417-426.

DOI:10.31579/2692-9759/145