ISSN: 2475-6296

Review Article

Journal of Clinical & Experimental Immunology

Therapeutic Apheresis and Human Monoclonal Antibodies in Non-Immunologic Diseases. TA, HMA in non-immunologic diseases

Rolf Bambauer[1]*, Ralf Schiel[2] and Octavio S Salgado[3]

[1]*University of Saarland; formerly: Institute for Blood Purification, Homburg, Germany*

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

[3]*School of Medicine, Universidad Católica de Cuenca, Ecuador*

***Corresponding author**

Rolf Bambauer, University of Saarland; formerly: Institute for Blood Purification, Homburg, Germany.

Submitted: 2023, July 14; **Accepted:** 2023, Aug 09; **Published:** 2023, Aug 30

Citation: Bambauer, R., Schiel, R., Salgado, O, S., (2023). Therapeutic Apheresis and Human Monoclonal Antibodies in Non-Immunologic Diseases. TA, HMA in non-immunologic diseases. *J Clin Exp Immunol,* 8(3), 603-625.

Abstract

Non-immunologic diseases such as nephrological, blood diseases, dyslipoproteinemia, cancer, infections, intoxications etc. have often a severe course or a bad prognosis. Since more than 45 years, therapeutic apheresis has led in combination with other therapies to a steady increase in survival rates. Therapeutic apheresis is indicated in the most of the non-immunologic diseases, and in all antibody-mediated diseases. Since the introduction of hollow fiber membranes, a complete separation of the corpuscular components, pathologic substances, antibodies, toxins etc. is reached. The mortality rate of severe non-immunologic diseases is reduced by therapeutic apheresis. Other new therapies are various human monoclonal antibodies alone or in combination with therapeutic apheresis. The pathological aspects, the first-line and second-lines therapies for non-immunologic such as nephrological, neurological, gastroenterological, hematological diseases, and others are shown. The guidelines of the Apheresis Applications Committee of the American Society for Apheresis are cited. Therapeutic apheresis and/or human monoclonal antibodies have shown to effectively cure severe diseases without immunologic origin.

Keywords: Therapeutic Apheresis, Human Monoclonal Antibodies, Non-Immunologic Diseases

ABBREVIATIONS

AAC: Apheresis Application Committee	AKI: acute kidney injury
ALD: adrenoleukodystrophy	ALF: acute liver failure
AMC-BAL®: Amsterdam Medical Bioartificial Liver	AMD: age-related degeneration
AP: acute pancreatitis	Apo A: apolipoprotein
Apo B: apolipoprotein B	ATP: adenosintriphosphate
ASFA: American Society for Apheresis	BLSS®: bioartificial liver support system
CAD: coronary artery disease	CKD: chronic kidney disease
CTCL: cutaneous T cell lymphoma	DALI: LDL hemoperfusion
DFPP: double filtration plasmapheresis	DIC: disseminated intravascular coagulation
ECP: extracorporeal photopheresis	ELAD®: extracorporeal liver assist system
EPP: erythropoietic protoporhyria	FH: familial hypercholesterolemia
FPSA®: Prometheus system	Gd: gadolinium
GFR: glomerular filtration rate	GTE: glyceroltrierucate
GTO: glyceroltrioleate	HD: hemodialysis
HDL: high-density lipoprotein	HELLP: elevated liver enzymes, low platelet count
HELP: heparin-induced LDL precipitation	HH: hereditary hemochromatosis
HMA: human monoclonal antibodies	HTG: Hypertriglyceridemia

HVS: hyperviscosity syndrome	IVIG: intravenous immunoglobulin
LA: Lipoprotein apheresis	LDL: low-density lipoprotein
LT: liver transplantation	MF: mycosis fungoides
Lp(a): lipoprotein (a)	FHF: fulminant hepatic failure
MARS®: molecular adsorbent recirculating system	NO: nitride oxide
MM: multiple myeloma	NID: non-immunologic diseases
NSF: nephrogenic systemic fibrosis	PA: phytanic acid
PCSK9: protein convertase subtilisin/kexin type 9	PiA: picolinic acid
PrA: pristanic acid	RBC: red blood cell
RES: reticuloendothelial system	RG: recommendation grade
SS: Sézary Syndrome	TA: therapeutic apheresis
TBV: total blood volume	TG: triglyceride
TPE: therapeutic plasma exchange	TPV: total plasma volume
VLCFA: very long chain fatty acid	VLDL: very low-density lipoprotein
WD: Wilson disease	WM: Waldenström macroglobulinemia

1. Introduction

Large numbers of technological, economic and social factors have an impact on the practice of apheresis. It is therefore important to assess the past and present status of apheresis in an effort to discover what the future impact will be [1]. Therapeutic apheresis (TA) is the generic term for different extracorporeal blood purification methods to remove inflammatory mediators, antibodies, and other toxic substances. Therapeutic apheresis is used successfully in a lot number of immunological diseases [2-7]. Disease-specific adsorbers have been developed for example, in dilated cardiomyopathy (β1-sdrenergic receptors), in systemic lupus erythematosus (C1q), and in grouping ABO group antigens, since the pathogenic relevance of autoantibodies could define in various diseases [8-11].

A complete separation of the corpuscular components from the plasma is reached and due to increase blood flow rate higher efficacy with the use of hollow fiber modules. Using centrifuges for TA has shorter treatment times such as using hollow fibers for TA shown by Hafer et al. [12]. This is no advantage, more important is to keep the blood levels with antibodies, and/or pathogenic substances on a very low level over long time during the treatment. However, the substances that should be eliminated by the hollow fibers could invade intravascular and be eliminated. Furthermore, cell damage, especially to thrombocyte, occurs less using membranes than centrifuges for all cell separation. The most selective separation of plasma components allows the adsorption technologies without the use of any substitution [11]. Membrane techniques are simple and safe to apply and can be competitive to other plasma separation and treatment technologies [13].

Therapeutic plasma exchange (TPE) using hollow fiber modules are mostly used in nephrology, as many of these membranes can be used with currently available dialysis equipment [14]. Nephrologists have an extensive training in the management of blood purification treatments including vascular access, anticoagulation, volume management and prescription for solute clearance.

However, only a few prospective controlled trials are available of treated diseases by TA that are of adequate statistical power to allow definitive conclusions to be reached regarding the therapeutic value of TA. Most of the disorders under investigations are relatively rare. Therefore, many investigators have understandably grouped heterogenous diseases together, often retrospectively, and used historical controls. The latter design in potentially hazardous, given that earlier diagnosis, recognition of milder cases, and improves general care over time be lost as benefit of TA [15]. Most history of many diseases commonly treated by TA, e.g., cryoglobulinemia, systemic lupus erythematosus, are characterized by episodes of exacerbation and remission.

The treatment protocols may vary widely between centers, rendering it difficult to compare studies. In the treatment of inflammatory renal diseases, TA is primarily used as an adjunct to conventional immunosuppressive therapy and might be expected a priori to confer only small additional benefit that require large sample size for its detection. Negative studies are inevitably less likely to be published and estimations of efficacy made based on published reports may be based in favor of TA [16].

Therapeutic apheresis in immunologic diseases is reported by many investigators over the last 45 years. The authors want to present an overview of non-immunologic diseases which are treated with TA. The most of them could be treated now with human monoclonal antibodies (HMA) or other modern drugs successfully. For the non-immunologic diseases (NID) for which the use of TA is discussed, the guidelines on the use of TA from the Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) are cited [17, 18]. The different TA methods such as TPE and various semi- or selective plasma exchange methods are discussed by Bambauer et al, [19].

Diseases without Immunologic Origin

The term of non-immunologic diseases is used for all disorders without an immunologic origin. Many NID being treated are fatal and TA is typically used when other treatments have failed. Despite all the cases of successful therapy, many of the pathophysiological processes underlying this therapy are still

not completely understood. This knowledge is necessary to be able to register and understand reactions that occur and their mutual influences. The aim of all TA methods is the elimination of pathogen substances or cells to interrupt pathological metabolism pathways. Different artificial methods are available for the temporary detoxification of the liver [20].

Acute Kidney Injury (AKI)

Acute kidney injury means reversible renal damage with oliguria or anuria. Acute kidney injury presents unique, life threatening and organ threatening therapeutic challenged that require prompt, accurate diagnosis and treatment [21]. In some cases, AKI can also take a polyuric course. Damage of the kidneys varies depending on the degree and duration of pre-renal, renal or post-renal noxae [22, 23]. Acute kidney injury is reversible only after the elimination of the noxae, in the case of structural disorders only after its repair, or it can remain irreversible.

Acute kidney injury is also defined as acute, over hours or days, developing renal function damage, which is measured by the glomerular filtration rate (GFR). Further renal functions are changed and decreased in AKI, such as the excretion of metabolic products and drugs, the reabsorption of filtrated substances, the regulation in acid base and electrolyte disorders. The incidence of AKI is 2-5 % in inpatients and up to 10-30% with intensive medical care. The mortality has essentially remained unchanged in the last four decades and of 30 to 80% is very high. Although in the last few years considerable progress has been made in dialysis technology and intensive medical care therapy. Acute kidney injury is the most frequent and expensive renal disease with the highest course of morbidity and mortality in hospitals [23, 24].

The causative noxae of AKI must be eliminated at the time of insult to the kidney and before it has been completely destroyed. They can be influenced primarily during the period in which they act on the kidneys. Thereafter, further measures against the noxae are no longer effective: all that then remains is lifelong dialysis and/or kidney transplantation [25].

A new classification of the factors in pre-renal, post-renal and renal disorders is simplistic from a therapeutic point of view. Classification is more appropriate according to factors leading to the following [25]:

1) A reduction in renal blood supply, pre-renal disorders, that is having a quantitative effect: this group comprises blood flow disorders or noxae. It covers only a part of the pre-renal disorders as commonly classified: circulatory-ischemic disorders such as reduced blood pressure or volume, which can be directly influenced therapeutically.

2) A qualitative change in renal blood supply, renal disorders, and this group includes endogenous and exogenous substances that circulate in the blood and have a damaging effect on kidney tissue. This group comprises plasma disorders or noxae, and includes, all endogenous and exogenous toxins, metabolic and decomposition products, as well as immunologically active substances that circulate in the blood and can damage the kidneys. Most of these plasma disorders can be influenced by TA. This justifies classification of these pathogenic factors of an AKI in a group of their own.

3) Post-renal disorders and damage to the parenchyma of the kidney via obstruction: this is the group of urination disorders or noxae. It comprises post-renal disorders, with the excretion of intratubular obstruction through substances originally circulating in the blood that precipitate the tubule lumen (urates, hemoglobin, and myoglobin) as a result of urine concentration. Therapies varies according to the nature of the post-renal disorder [25].

Other substances, exogenous and endogenous toxins include infective toxic substances. The epidemiologic features of the toxic agent-related AKI are associated with different culture, biodiversity of the topics, and economics status [26]. In particular, sepsis by Gram-negative cocci can easily lead to severe renal injury. The therapy in this case is primarily the application of antibiotics combined with intravenous immunoglobulin G (IVIG). In severe cases, earliest possible commencement of TA together with hemodialysis (HD) should be considered to eliminate the toxins, endotoxins and/or other larger molecular pathogenic metabolic substances [26].

The toxins and metabolic products overload the reticuloendothelial system (RES) and organs responsible for their metabolization. Early implementation of TA interrupts these pathogenic chain reactions during the damage phase, and recovery is accomplished through the elimination of toxins and other pathogenic metabolic substances. Additional to infective-toxic substances, chemicals and drugs play a part in the development of AKI [26]. Exogenous toxins that lead to AKI through tubular necrosis are mercurous chloride (sublimate) and carbon tetrachloride. Further substances such as glycol and oxalic acid, however, cause extensive cortical necrosis, usually with irreversible renal damage. Further nephrotoxins methods are heavy metals, together with organic solvents, foreign proteins and, typically those substances with a high molecular weight, and/or strong protein binding [26]. The heavy metal thallium belongs to this group. Hemodialysis and TA are also indicated in COVID 19 patients with AKI [27].

Endogenous toxins are free hemoglobin and myoglobin. Triggering factors can be transfusion reactions, which also result in hemolysis after HD, or severe operations and disseminated intravascular coagulation (DIC), burns, tissue destruction and hemolytic uremic syndrome [25]. Further toxic substances and metabolic products, which are released both trough DIC and tissue destruction, are often not detectable, however, they can have toxic effects on the tubular epithelial cells by the production of intrarenal oxidative stress or by the production of intratubular cylinders and can lead to AKI. With TA, these substances can be quickly eliminated. The cast nephropathy of plasmocytoma is a part of the endogenous toxic renal damage. The most common renal manifestations associated with cancer include AKI in the setting of multiple myeloma, tumor lysis syndrome, post-hematopoietic stem cell therapy, and AKI associated with chemotherapy [28]. In these patients, HD and TA are also indicated in an early stage of the disease to improve the outcome.

Acute kidney injury can occur due to diseases of the liver, such

as hepato-renal syndrome, decomposition products, toxic and phenols are released through the destruction of liver cells due to liver insufficiency. The pathogenesis of hepato-renal syndrome is presumably based on a reduced effective blood volume, and the increased presence of vasoactive, humoral, or neuro-humoral substances, occurring as a result of liver damage, leading to vasoconstriction of the kidney and thus insufficient blood flow [25]. The release of substances from the liver, their poor inactivation in the liver, or the bypassing of hepatic blood flow can cause the collection of vasoactive substances in the systemic circulatory system. The possibility of increased sympathetic tone has been little examined to date.

The humoral substances include false neurotransmitters. Amines and their preliminary stage, such as tyrosine and phenylalanine, can bypass the liver via portocaval collaterals and thus flood both central and peripheral nervous tissue. Noradrenalin and dopamine are displaced by these false transmitter substances. These lead to a peripheral vasoplegia in dissociation of the renal vasoconstriction. The displacement results in a reduction in vessel resistance in organs that normally have low blood flow, the blood flow then increases, the blood flow is reduced in organs that normally have high flow, such in the kidney. The tyrosine cleavage enzymes are missing, here, there is an increase in metabolic products such as keramine and octopamine in the case of liver insufficiency [25].

The activating renin-angiotensin- aldosterone, and kallikrein-kinin system probably also plays a role in the pathogenesis of hepato-renal syndrome. Studies showing conclusive results, this speculation at this point. The role of prostaglandin is also still unknown. The application of prostaglandin AI increases glomerular filtration, renal plasma flow, and natriuretic excretion in liver cirrhosis, in cases where renal insufficiency is still reversible [25]. Vasoactive intestinal peptide can be increased in liver insufficiency through inactivation and also contribute to a deterioration in renal function. The effect of all these humoral factors on the response organs such as the kidney can be eliminated simply by TA, thus justifying its indication a particularly severe case.

Acute kidney injury associated with acute pancreatitis can often be caused by DIC aggravated by dehydration. Toxic digestive enzymes released into the systemic circulation by the diseased pancreas are responsible for renal damage. The autolysis releases active enzymes, such as amylases, esterases, and nucleases, and inactive proenzymes, such as proteinase, peptidases and phospholipase A. Phospholipase A, which is activated by trypsin, releases highly toxic lysolecithin from lecithin, which can damage the organs in particular the kidneys leading to AKI [29].

Besides conservative therapy, surgical intervention must be implemented at an early stage, if necessary. Prior to surgical intervention, TA should be considered to eliminate the toxic substances and thus avert or reduce damage. The otherwise almost invariably fatal outcome of acute hemorrhage necrotizing pancreatitis can be prevented in some cases through the early implementation of TA. In addition to plasma disorders of toxic genesis, there are also these of immunological origin, which in turn can cause accompanying AKI. The results of these disorders are described elsewhere [2, 3, 11, 16].

Up to now, there have not been enough controlled studies of TA used in the treatment of AKI: therefore, the physician who treats patients with AKI must decide for themselves whether the introduction of TA in AKI is indicated or not. It is useful to discuss the disease risk factors and therapeutic modalities which all persons involved in such case.

Nephrogenic Systemic Fibrosis (NSF)

A rare but severe systemic disorder in patients with acute or chronic kidney disease (CKD) is the nephrotic systemic fibrosis, often associated with the administration of gadolinium (Gd) [30]. It occurs in 3-7 % of patients with renal insufficiency receiving gadolinium. Most in patients with a GFR < 30ml/min/1.73 m², patients with current thrombotic or inflammation, and the use of higher dose of Gd. In patients with hepatorenal syndrome and in perioperative period following liver transplantation NSF is observed [31]. Additional factors include surgery, systemic infections, metabolic acidosis, high erythropoietin levels, and elevations calcium, iron, copper, and phosphate.

Usually, 2-4 weeks are between Gd administration and NSF onset, the range can be from 2 days to 8 years. The presentation involves the skin and shows a symmetrical erythematosus rash, non- pitting edema, paresthesia, and pruritus in the extremities. Additional symptoms could be hair loss, gastroenteritis, conjunctivitis, bilateral pulmonary infiltrates and fever. Nephrogenic systemic fibrosis results in joint contractures leading to wheelchair dependence and may extend into deeper tissue including skeletal, heart, pericardium, pleura, lungs diaphragma, esophagus, kidneys, and testes [18]. An overall mortality rate is up to 30 %. The disease progresses to death within weeks to months, in a small group and in a subgroup of patients with recovered renal function, the disease can enter remission [17]. The pathophysiology is unknown. Gadolinium may also directly fibrosis. Gadolinium administration must avoid in patients with GFR < 30 ml/min/1,73 m².

One and three full HD sessions can remove 97% and 99% of the dose, respectively. Further therapies include IVIG, alefacept, pentoxifylline imatinib, messy late, chelation therapy with sodium thiosulfate, TPE and extracorporeal photopheresis (ECP) [32-35]. In therapies with TPE or ECP, improvement of skin softening, increased range of motion, improved ambulation and improvement from wheel-chair bound to walking, decreased swelling, pain and paresthesia [36]. Treatment with TPE is 1.5 total plasma volume (TPV), the frequency ranges from daily for 5 treatments to twice per week for 10-14 treatments [17]. The ECP of 1.5 L of whole blood volume various to 2 total blood volume (TBV), and the frequency from 2 in consecutive days every 2-4 weeks up to 5 procedures every other day. The duration of ECP could be 4-16 months. The AAC of the ASFA has given the NSF the category III and the recommendation grade 2C (17, 18) (Table 1).

Apheresis Applications Committee of the ASFA 2019 (18)					
Diseases	**TA modality**	**Cate-gory**	**RG**	**Exch.volume (TPV)**	**Replace-ment**
Nephrogenic systemic fibrosis (NSF)	TPE/ECP	III	2C	1-1.5 TPV/ 1.5L blood	albumin, plasma
Familial Hypercholesterinemia (FH) - homozygotes - heterozygotes - homozygotes/heterozygotes	LA	 I II II	 1A 1A 1A	1-1.5L blood or plasma*	none
Hyperlipoproteinemia, Lipoprotein (a) (Lp(a))	LA	II	1B	1-1.5L blood or plas-ma*	none
Hypertriglyceridemic pancreatitis - severe HTG-AP - prevention of HTG-AP relapse	 TPE/LA TPE/LA	 III III	 1C 2C	1-1.5L blood or plasma*	albumin, plasma none
Acute Liver Failure (ALF) Fulminant hepatic Failure (FHF)	TPE TPE-HV BioLogic MARS FPSA	III I	2B 1A	1.5LTPV 8-12L P depends of the method	albumin, plasma albumin
Erythropoietic Protoporphyria (EPP) Liver Disease	TPE RBC exch.	III III	2C 2C	1.5LTPV exchange+	albumin, plasma
Phytanic Acid Storage Disease Refsum´s Disease	TPE/ LA	II II	2C 2C	1-1.5L TPV 3L	albumin none
Systemic Amyloidosis	TPE β_2-micro-globulin column	IV II	2C 2B	1-1.5L TPV	Albumin, Plasma none
Hereditary Hemochromatosis (HH)	Erythrocyt-apheresis	I	1B	up to 800 ml RBCs	-1/2 of re-moved RBC
Hyperviscosity in Hypergamma-globulinemia (HVS) - symptomatic - prophylaxis for rituximab	 TPE TPE	 I I	 1B 1C	 1-1.5L TPV	 albumin, plasma
Age related macular Degeneration, dry (AMD)	Rheo-phersis	II	2B	0.8-1.5L TPV	none
Wilson Disease, fulminant	TPE	I	1C	1-1.5L TPV	albumin, plasma
Cutaneous T Cell Lymphoma(CTCL) Mycosis fungoides, Sézary Syndrome	ECP ECP	I III	1B 2C	1.5L blood	none
Infections (Septicemia) - Malaria	 RBC exchange	III	2B	1-2 total RBC vol.	RBCs
Overdose, Envenomation, Poisoning - mushroom poisoning - envenomation - Drug overdose/poisoning	 TPE TPR TPE	 II III III	 2C 2C 2C	 1-2 TVP	 albumin, plasma

TA. Therapeutic apheresis, RG: recommendation grade, Exch. Volume: exchange volume, TPV: total plasma volume, TPE: therapeutic plasma exchange, ECP: extracorporeal photopheresis, LA: Lipoprotein apheresis, TPE-HV: high-volume TPE, P: plasma, BioLogic: Hemoadsorption with pushpull sorbent-based pheresis, MARS: molecular adsorbent recirculating system, FPSA: Prometheus system, RBC: red blood cell,

*Whole blood or plasma volumes depend from the used device. +The amount of RBCs based on the desired post-procedure-HCT

Table 1: Therapeutic apheresis in non-immunologic diseases (Category 1: is 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; Category IV: not accepted for TA, IMB approval is desirable if TA is undertaken (17, 18))

Dyslipoproteinemia

Familial hypercholesterolemia (FH) is an autosomal dominant disorder associated with well characterized mutations of hepatocyte apolipoprotein B (apo-B) receptors usually called low density lipoprotein (LDL) receptor. A decreased LDL removal by the liver is following. Homozygote patients may have cholesterol in blood in the range of 600 – 1,000 mg/dL, xanthomas by the age of 4 years, and death from coronary heart disease by the age of 20, and heterozygote patients may have cholesterol in the range of 250 – 550 mg/dL, xanthoma by the age of 20 years, and atherosclerosis by the age of 30, both without therapy [17].

Worldwide, there are more than 10,000,000 people with FH, mainly heterozygote. Familial hypercholesterolemia is one of the most common inherited disorders. Mutations along the entire gene that encode for LDL receptor protein are the most common FH cause [37]. However, mutations in apo B and protein convertase subtilisin/kexin type 9 gene produce this phenotype have also described, A very low-density lipoprotein (VLDL) and a decrease in high density lipoprotein (HDL) follows a high concentration LDL in FH. The consequence of this situation is the development of atherosclerosis and, in particular, of coronary artery disease (CAD). Heterozygous FH has a frequency of 1: 500 may be closer to 1: 250 and the homozygous form a frequency of 1: 1,000,000 [20]. The most patients with dyslipoproteinemia have a complex genetic etiology consisting of multiple variants, Genetic assessment can help to identify patients at risk for developing dyslipoproteinemia and for treatment based on "risk allele" profiles [38].

Atherosclerosis with myocardial infarction, stroke, and peripheral vascular disease still remains it position at the top of morbidity and mortality statistics in industrial countries [39]. Risk factors which are widely accepted, are besides familial disposition, smoking, arterial hypertension, diabetes mellitus, and central obesity stress, reduced HDL, increased Lp(a), and fibrinogen.

A strong correlation between dyslipoproteinemia and atherosclerosis was found [40-43]. The vascular endothelium is the largest endocrine, paracrine, and autocrine participant in the regulation of numerous homeostatic vascular functions. Vasoactive substances released by blood cells are sensed by endothelial cells which are formed by changes in hemodynamic forces such as pressure and shear stress. These endothelial cells synthetize and release biological active substances such as nitride oxide (NO), prostacyclin, endothelium-derived hyperpolarization factor, endothelin, prostaglandin H2, thromboxane A2, heparin sulfate, transforming growth factor, vascular endothelial growth factor, basic fibroblast activator, plasminogen activator inhibitor-1, oxygen free radicals, and others [41-44]. These substances together form the vascular tone through their relaxing and contracting actions as well as vascular structure through production of growth promoting and growth-inhibiting substances.

Intravenous reconstituted HDL infusion in dyslipoproteinemia patients rapidly normalizes endothelium-dependent vasodilatation by increasing NO bioavailability. High-density lipoprotein has perhaps a protective effect on CAD and a therapeutic benefit of increasing HDL in patients at risk of atherosclerosis [45]. The endothelium regulates hemostasis and thrombus through its antiplatelet, anticoagulant, and fibrinolytic function as well as inflammation through the expression of chemo tactic and adhesion molecules. The endothelium is in a location between the blood and vascular smooth muscle and this is a primary target for injury from mechanical forces and processes related to cardiovascular risk factors [46]. The development of atherosclerotic plaques especially in CAD results from high lipid concentration in the blood which leads to their accumulation in the intima. The changes in vessel tone and endothelium regulation seem to be accompanied by these alterations.

High triglycerides (TG) are often accompanied by low HDL cholesterol blood levels. Increased triglycerides represent a useful marker for risk of CAD, when HDL levels are low [46]. The strong association between the ratio of TG/HDL and the risk of CAD suggests a metabolic interaction between the TG and cholesterol ester-rich lipoproteins in increasing risk of CAD [47, 48]. A cumulative insult to the vasculature resulting in more severe disease which occurs at an earlier age in large and small vessels as well as capillaries is caused in dyslipoproteinemia in combination with diabetes mellitus.

The LDL/HDL ratio is a strong predictor of premature CAD events. A ratio of > 5 in patients with high triglyceride concentrations is four times higher than in those with normal triglycerides [49]. Acute pancreatitis is one of the most severe complications of severe hypertriglyceridemia [29]. The primary goal in these patients is a rapid lowering of the excessively elevated triglycerides, activated enzymes, released cytokines and other inflammatory substances.

An acquired lpiprotein (a) (Lp(a)) excess in patients with renal disease is a marker for cardiovascular risk [50]. High Lp(a) blood concentration and gene types were associated with increased risk of aortic valve stenosis, with concentration > 90 mg/dL predicting a threefold increased risk and independent predictor for stroke [51, 52]. Further investigations and research projects must clarify the role of Lp(a) in stroke [53].

N-acetylcysteine has been shown to induce a dose-dependent reduction in Lp(a) levels about seven percent by causing dissociation of the Apo A by cleavage of disulfide bonds [54]. Very high levels of Lp(a) can only be normalized by lipoprotein-apheresis (LA), and/or with the therapy of the proprotein convertase subtilisin/kexin type 9 (PCSK9) with evolocumab as a fully HMA which is directed against human PCSK9 [55, 56]. Evolocumab up regulates LDL receptors causing increased catabolism of LDL and the reduction of LDL and is higher than of Lp(a) blood concentrations [57]. Evolocumab could reduce LDL of 53 - 75% and Lp(a) 24 – 39% in monotherapy or in combination therapies, and is associated with minor side effects [37, 58]. The inhibition of PCSK9 with HMA is as effective as the regularly weekly or every two-week LA. Both method the lipoprotein apheresis and HMA are comparable in the higher decreases for pretreatment concentrations over time and could combine in the most severe cases [37].

In the industrial nations, CAD remains one of the main causes of death in the mortality statistics despite considerable progress in diagnostics, development of new medications, such as

HMG-CoA-reductase inhibitors as well as cardiosurgical measures. Cholesterol concentrations of over 200 mg/dL in the blood show an increased coronary risk "This risk is double at cholesterol values between 200-250 mg/dL and fourfold at values of 250-300 mg/dL!" [59].

In severe forms of hypercholesterolemia, a relative or absolute reduction of LDL receptors in the liver results in a decreased plasma clearance of lipids. A reduction intake of dietary fats is advised in all these patients. Various medications are available, such as colestyramin, colestipol, ß-fibrates, fenofibrate, ß-pyridylcarbinol, probucol, and D-thyroxine depending on the type of condition [37]. With HMG-CoA-reductase inhibitors, which could be combined with other lipid-lowering substances, LDL reduction up to 50 % of the original concentration can be achieved. In most cases this appears to be sufficient. Numerous side effects like diarrhea, obstipation, other gastrointestinal diseases, myositis, rhabdomyolysis, and others where observed [37]. However, the introduction of lipoprotein apheresis (LA) and HMA all forms of previous therapy-resistant dyslipoproteinemia can now effectively treat [37, 60, 61].

Homozygous, severe heterozygous forms of FH or other forms of severe dyslipoproteinemia with cholesterol values between 250 to 600 mg/dL, are indicated for LA. First require these forms maximum diet and medicational therapy, for example with 24-32 g ion exchange (e.g., cholestyramine) in combination with 40-80mg statins (HMG-CoA reductase inhibitors). If, this maximum therapy or due to therapy intolerance, LDL cannot be constantly held below 150mg/dL LA and/or HMA are indicated. In patient with isolated Lp(a) higher than 60 mg/dL, normal LDL cholesterol and a progressed cardiovascular disease the LA and/or HMA are indicated, too. The patient should be a non-smoker and be placed under cardiologic, observation [37].

The quotient relevant for cost-effective assessment: (cost of treatment-costs saved): (improvement in life quality) cannot exactly calculated at present. To calculate it, detailed information is required about the expenses saved through illness avoided (heart attack, angina pectoris, and premature coronary death) [47]. Up to now cascade filtration, immunoadsorption, heparin-induced LDL precipitation, LDL adsorption through dextran sulfate, the LDL hemoperfusion systems have been of clinical relevance. The acute reduction rates of LDL cholesterol and Lp(a) depend on the treatment volume achieved with each LA method [37, 57]. The various methods for extracorporeal LDL reduction are assessed differently in the literature. The most used are HELP, dextran sulfate apheresis, DALI. Lipid filtration, and Liposorber D (Table 2) [73-77].

Authors	Methods / drugs	Advantage	Disadvantage
De Gennes et al. (46), 1967	Therapeutic plasma exchange	Quick and well-tolerated elimination of pathologic substances	Unselectively of infection, bleeding, risks of human albumin
Agishi et al. (61), 1980	Cascade filtration	Semi-selectivity	Expensive technology
Stoffel et al. (62), 1981	Immunoadsorption	Selectivity, effectiveness, regeneration, reusable	Expensive technology
Seidel et al. (63), 1982	Heparin-induced LDL precipitation (HELP)	Selectivity, effectiveness	Expensive technology
Nosé et al. (64), 1985	Thermo-filtration	Selectivity, effectiveness	Expensive technology, not available
Mabuchi et al. (65), 1987	Dextran sulfate LDL adsorption	Selectivity, effectiveness	Expensive technology
Pokrovski et al. (66), 1991	Lp(a) immunoadsorption	Selectivity, effectiveness	Expensive technology
Bosch et al. (67), 1993	LDL hemoperfusion (DALI)	Selectivity, effectiveness	Technology not expensive
Klingel et al. (68), 2002	Lipid filtration	Semi-selectivity	Expensive technology
Otto et al. (69), 2003	LDL hemoperfusion (Liposorber D)	Selectivity, effectiveness	Expensive technology
Kreuzer et al. (70), 2010	Lipoprotein filtration	Semi-selectivity	Expensive technology
Grossmann et al. (71), 1995	Lomitapide, Mipormersan	Low effectiveness	Unknown, not available
Raal et al. (57), 2014	Evolocumab	Selectivity, effectiveness	Unknown
Gaudet et al. (72), 2014	Alirocumab	Selectivity, effectiveness	Unknown

Table 2: Extracorporeal methods, human monoclonal antibodies and other new drugs for elimination of LDL and Lp(a) (modified after 46)

The reduction of cholesterol blood concentration is to prevent the development and progression of atherosclerosis. It is known that the decrease and slower progression of atherosclerosis changes in coronary vessels and carotids after patients have been treated for one or more years with LA. Lipoprotein apheresis represents a decisive breakthrough in the treatment of high-risk patients with FH, whose treatment has, up to now, been inadequate, despite strict diets and lipid-reducing medication [37]. During

pregnancy, LDL cholesterol levels in individuals affected by FH can rise to extreme levels that can compromise uteroplacental perfusion. The use of lipoprotein apheresis in these patients allows for successful completion of pregnancy [18].

Proprotein convertase subtilisin/kexin type 9 is a serein protease involved in cholesterol metabolism that is enzymatically inactive following secretion. It is a proprotein convertase belonging to the subtilase subfamily [78]. In healthy humans, plasma PCSK9 concentration decrease with fasting and increase following meals [79]. The PCSK9 with a gain-of-function mutation PCSK9 is associated with FH [78]. Loss-of-function mutations in PCSK9 are associated with reduced LDL concentration and that these lifetime reductions confer substantial protection against CAD [80]. The PCSK9 gene expression is regulated by nuclear transcription factor sterol regulatory element-binding protein-2. Concentration of sterol regulatory element-binding protein-2 are increased by statin therapy, which thus also increases PCSK9-conccntration [37]. The PCSK9 is expressed predominantly the liver, and to a lesser extent in the intestine and kidney in adults. The only known physiologically relevant function of circulating PCSK9 is to regulate receptor in the liver [81]. Human monoclonal antibodies are target-specific antibodies created through recombinant DNA technology. These proteins have the characteristic Y-shaped protein structure of B-cell-derived antibodies and are designed to bind to single therapeutic target with high specificity [82].

Human monoclonal antibodies exert their therapeutic action through a variety of mechanisms, including direct effects associated with the binding of the antibody to the target and indirect effects involving depletion of cells targeted by the monoclonal antibody [81]. The elimination occurs not through the liver or kidneys, but primarily through antigen-specific target-mediated disposition and nonspecific pathway of the reticuloendothelial system [81]. The monoclonal antibody inhibition of PCSK9 have demonstrated reduction in LDL and Lp(a) blood concentration. The PCSK9 inhibition with HMA offers substantial LDL lowering in patients with dyslipoproteinemia and those with clinical atherosclerotic cardiovascular disease who are on maximally tolerated statins. Evolocumab and Alirocumab are generally well tolerated and the prolonged dosing schedules may offer the benefit of high patient adherence [83-85].

The possible development of neutralizing antibodies that can reduce the therapeutic efficacy of monoclonal antibodies is of particular concern [86]. Further development initially resulted in chimeric antibodies, which consisted of human antibody with murine variable regions [37]. Evolocumab and Alirocumab are fully human anti-PCSK9 monoclonal antibodies, and administered as monotherapy or in combination with statins and or ezetimibe in patients with dyslipoproteinemia [81, 87-90]. A meta-analysis of 16,721 patients from 33 randomized clinical trials with 10,532 patients who received PCSK9 inhibitors and 6,189 controls showed that PCSK9 inhibitors improve lipid profiles and lower all-cause mortality in patients with FH (ODYSSEY ESCAPE) [84]. The FOURIER study randomized controlled study Evolocumab versus placebo included 27,564 patients with atherosclerotic diseases showed a significantly reduced cardiovascular risk in these patients [85]. Further studies are necessary to show that the inhibition of PSCK9 with HMA is as effective as the regularly weekly or two weekly LA. Of interest for both therapeutic methods such as LA and HMA are the higher decreases of the pre-treatment concentration over the time in older patients with initial higher Lp(a) concentration than in younger patients with lower Lp(a) and lower risk [57, 91- 93].

Inclisran is a long-acting TNA interference that inhibits the synthesis of PCSK9. In subcutaneous injection study group, a single-ascending-dose or a multiple-dose brought a reduction of the PCSK9 blood concentrations of up to 80% and of the LDL cholesterol concentrations of up to 60%, without no side effects [94].

Lomitapide and mipomersen are no HMA. The gene therapy is still until today no real alternative to regular lipoprotein-apheresis treatment [95]. The gene therapy in FH is the expression on the LDL receptor by insertion of receptor-encoding transgene with the help of a suitable vector. In some patient in a pilot study with isolated, cultured, and then infected hepatocytes with one of the LDL receptor gene-encoding retroviruses, LDL was lowered by 2-25 percent [96]. Further studies are necessary.

The effect of Alirocumab on frequency of standard LA (weekly or every 2 weeks) in dyslipoproteinemia was investigated by Moriarty et al. [84]. Guideline recommended threshold values may be achievable in individual patients through treatment with Alirocumab alone or in combination with LA. Not clear is the question if in long-term application with HMA an antibody expression against the HMA would be possible and what can be done than – LA again? The antibody expression against HMA was observed in the cancer therapy by mutation of the oncogenes, then new HMA are necessary [37]. The AAC of the ASFA has given the lipoprotein (a) hyperlipoproteinemia the category II and the RG 1B. The FH has for the homozygotes the category I and the RG 1A, for the heterozygotes the category II and the RG II and the RG 1A (Table 1) [17, 18].

In conclusion all LA methods are safe and effective [97-101]. Lipoprotein apheresis is the gold standard for patients with homozygous FH [101, 102]. The treatment with PCSK9 inhibitors is safe and effective, too [103]. Evolocumab or Evinacumab have excellent reduction of LDL and Lp(a) [104, 105].

A reduction in costs is a valid demand in view of the scare resources available in the healthcare system. Physicians are committed to help all patients entrusted to them to the best of their knowledge, and this means that medical treatment – and particularly the apheresis methods – must become affordable [37].

Hyperlipidemic Pancreatitis

Acute pancreatitis (AP) is a clinical entity that can develop into multiple organ failure, and still has a poor prognosis. Humoral mediators such as proinflammatory cytokines play important roles in the pathogenesis of organ failure in patients with AP [106]. Alcohol abuse, cholelithiasis, hyperlipidemia and other specific factors are the important causes of AP [18, 107]. The morbidity has been increased in recent years with number of patients with AP. Acute pancreatitis occurred in 12-38 % of patients with hypertriglyceridemia (HTG) [108].

The autolysis of the pancreatitis releases active enzymes such as lipase, amylase, esterase, and nuclease, as well as inactive-pro-enzymes such as proteinase, peptidase, phospholipase A, trypsin, and others [29]. Phospholipase A, which is activated by trypsin, releases highly toxic lysolecithin from lecithin. The local changes in the pancreas, such as proteolysis, bleeding, and necrosis of fatty tissue, and the systemic effects such as shock, adult respiratory distress syndrome, and coagulopathy are a result of the combined effect of this enzyme activity. Oxygen radicals such as oxy-reductase, which is toxic for tissue, also play an important role in the pathogenesis. Acute pancreatitis can be connected to AKI [29].

Acute pancreatitis is a well-known complication of severe hypertriglyceridemia. Patients with triglyceride levels of ≥ 500-1,000 mg/dL are at high risk for AP [109, 110]. The combining capacity of albumin-binding of albumin surpassed by over production of free fatty acid would cause tissue toxicity is the leading mechanism to severe AP, and pancreatitis acinar and micro-vessels were injured [111]. Elevations in the lipoproteins for triglyceride transport result in HTG. Primary causes include mutations in gene such as that encoding lipoprotein lipase and its activator C-II. Secondary causes include diabetes mellitus, hypothyroidism, pregnancy, and medications [29].

Complications occur when triglyceride levels are ≥ 500-1,000 mg/dL [18]. These include AP, chronic abdominal pain, hepatosplenomegaly, eruptive xanthomas, lipemia retinalis, peripheral neuropathy, memory loss, dementia irritation by fatty acids and lysolecithin is felt to cause pancreatitis while hyperviscosity and tissue deposition produce the other complications [112].

Hypertriglyceridemia induced pancreatitis is disturbance of pancreatitic microcirculation by very large TG-rich lipoproteins, with resulting ischemia, and subsequent hydrolytic release of free fatty acids that are toxic to the pancreatic endothelium and acinar cells. The elimination with LA of large lipoproteins is hypothesized to stop further organ damage [18]. Lipoprotein apheresis can significantly decrease TG, levels, reduce inflammatory cytokines and potentially toxic substances. Reductions in TG levels of 49-97% following a single LA treatment are reported. However, the LA effect is transient; adequate lipid lowering treatment is essential to achieve a persistent effect (Table 1). Besides the LA procedures, double filtration plasmapheresis (DFPP) can use to avoid the need of substituting human plasma products with their potential adverse-affects. Other special LA procedures are Heparin LDL precipitation (HELP, Braun, Germany), Liposorber LA (Kaneka, Japan), directed adsorption of lipoproteins (DALI, Fresenius, Germany) [18, 29].

Acute Liver Failure (ALF)

Acute liver failure is the result of extremely severe insult to the liver resulting in organ failure and typically results in death of the patient. The etiologies of acute ALF can be endogenous or exogenous causes [113]. Endogenous liver failure coma results from liver decomposition, liver dystrophy, or more rarely, from a hepatocellular metabolic disorder without liver decomposition, Reye´s syndrome, acute pregnancy-induced fatty liver, while exogenous liver failure coma is caused by a hepatofugal collateral circulation, as in liver cirrhosis. The main cause of hepatitis C is the viral hepatitis, approximately 70 percent, the most frequent, followed by hepatitis B, and to a much lesser extent hepatitis A [114]. Further causes include toadstool poisoning, paracetamol intoxications, fructose intolerance, hemolysis, elevated liver enzymes, low platelets, HELLP syndrome. The most cause of ALF is viral hepatitis in the United States, and acetaminophen toxicity in Great Britain [18].

With a loss of 70-80 percent of total liver parenchyma, the liver still functions adequately, and its considerable regenerative capacity almost fully restores liver functions such as synthesis, regulation, and detoxification [113]. Both coma forms end most in death, due to the ineffectiveness of conservative therapy. However, the critical phase of liver failure can be successfully bridged with artificial detoxification, even acute morphological and functional damage can be repaired, due to the regenerative capacity of the liver. The critical liver cell mass necessary for survival is a hepatocyte volume fraction of 40 – 45 percent.

The mortality rate in ALF is 50 – 90 percent due to acute metabolic disturbance hepatic encephalopathy, and severe coagulopathy; however, following transplantation, the survival rate is > 60 percent [18]. Spontaneous recovery from ALF depends from the high recovery rates, which are observed in fatty liver pregnancy, acetaminophen ingestion, and hepatitis A. Hepatitis B has an intermediate prognosis; other drugs and unknown etiologies have less than 20 percent recovery rate; and patients with ALF due to Wilson´s disease rarely recover spontaneously. Acute-on-chronic liver failure is an acute deterioration of liver function in patients with cirrhosis, which is usually associated with a precipitation event and results in the failure of one or more organs and high short-term mortality [114]. Without spontaneous recovery, the standard treatment of ALF is supportive care as a bridge to liver transplantation. Transplantation is performed for acute or acute-on-chronic failure due to a variety of causes. About 30 percent of liver transplantation recipients have ALF [18].

The detoxification processes described more frequently in recent years, such as exchange transfusion, and extracorporeal liver perfusion over baboon or human liver are complicated and harbor many side effects [115]. Lepore et al. first reported of plasmapheresis in the treatment of liver coma [116]. Many researchers have studied the effect of TPE in this disease, particularly on membrane plasma separation since this [113]. More and more combinations of different detoxification methods such as BioLogic-DTPP system, Molecular adsorbent Recirculating system (MARS), Prometheus system (FPSA), and the cell-based liver support devices (Table 3) [113, 117-120].

	Non-cell-based liver support devices			Cell-based liver support devices				
Company	Hemo-Cleans, Lafayette, NI, US	Gambro, Sweden	Fresenius Medical Care, Germany	Arbios, USA	Vital 3Therapy USA	Charité Clinic, Berlin, Germany	Excop. Medical, USA	Amsterdam Medical Center, Netherl.
Name	BioLogic DTPP Hemo-di-asorption With push-pull sor-bent-based pheresis	Molecular Adsorbent Recircu-lating System MARS®	Prome-theus® (FPSA)	Hepat Assist®	Extra-corporeal liver assist device ELAD®	Molecular extracor-poreal liver support system Mels®	Bioarti-ficial liver support system BLSS®	Amster-dam Medical Bioarti-ficial Liver AMC-BAL®
Cells	none	none	none	7 billion porcine hepato-cytes	C3A human hepato-blastoma cells	fresh primary porcine hepato-cyte	100 g of primary porcine hepato-cyte	100 g of primary porcine hepa-to-cyte

Table 3: Artificial and bioartificial liver support devices (modified after 113)

The pathogenetic mechanisms for triggering the clinical manifestation of hepatic coma are extremely diverse and not entirely understood. Besides a whole range of toxic substances, a reduced synthesis performance of the liver are the factors of ALF. The limited functioning of Kupffer cells can enable bacterial endotoxins to enter the synthetic circulation, thus contributing to the triggering of coma hepaticum [113].

The hepatic encephalopathy is an intoxication of the central nervous system with substances that can no longer be sufficiently eliminated due to impaired function of the liver, and the most of these substances, such as bile acids, biogenic amines like tryptophan, and tyrosine originate are from bacterial flora of the intestinal tract [113]. Through their accumulation in the central nervous system, noradrenalin and dopamine are competitively inhibited.

Intracranial hypertension is a major cause of morbidity and mortality of patients with ALF. The mechanism of brain edema and intracranial hypertension in ALF is not entirely understood. Three primary hypotheses are [113]:

• **The accumulation of glutamine within astrocytes of the cerebral cortex.** Brain edema in ALF is most localized to the cerebral cortex. The main feature is the swelling of astrocytes. Astrocytes have several critical metabolic functions involved in the maintenance and regulation of the extracellular glutamine via the amidation of glutamine by an astrocyte enzyme, glutamine synthetase. Glutamine leaves the astrocytes by passing diffusion into the extracellular space where it is taken up by neurons covered to glutamine [120]. The osmotic effects of intracellular glutamine may be more prominent due to an impairment in the extrusion of glutamine from cells [113].

• **Products arising from the necrotic liver.** Total hepatectomy as a last-ditch effort in critical ill patients with ALF has shown improvement in hemodynamic instability, allowing time to be gained prior to transplant, and indicates improvement in the control of brain edema. This therapeutic procedure restricts its use to a few centers and to desperate situations [113].

• **Abnormalities of the cerebral circulation.** Brain edema has been postulated to arise from dilated cerebral vascular. A failure of cerebrovascular autoregulation and evidence of luxury perfusion may be factors that increase water transfer into brain tissue [113].

In hepatic encephalopathy, increased pressure in the brain is often the result of the dilation of the brain arteries as a result of increased blood supply. Histamine or similar substances also play a role. The administration of ranitidine and theophylline can reduce the brain pressure. Ammonia as a key toxin in the genesis of brain edema can removed by dialysis. Other products arising from the necrotic liver must eliminated using TPE or artificial or bioartificial liver support systems.

Fulminant Hepatic Failure (FHF)

Therapeutic apheresis can remove in FHF albumin bound toxins and unbound toxins, including aromatic amino acid, ammonia, endotoxins, indols, mercaptans, phenols and other factors which may be responsible for hepatic coma, hyperkinetic syndrome, and decreased systemic vascular resistance and cerebral blood flow [18]. Therapeutic apheresis treatments show improvement in cerebral blood flow, mean arterial pressure, cerebral perfusion pressure, cerebral metabolic rate, increased hepatic flow, and improvement in other laboratory parameters.

Therapeutic apheresis and liver support systems can partly replace not only the detoxification function, but also the regular function of the liver. Through elimination of toxic substances, the disturbed relationship between various amino acids and lipids is partly restored. The synthesis function of the liver can also be substituted by fresh frozen plasma [113].

The survival rate in ALF is with conservative therapy alone

under 20 percent. Therefore, attempts are increasingly being undertaken to combine hemodialysis, hemoperfusion, TA, and artificial liver support systems and to make use of new enzyme systems such as bioartificial liver support systems (Table 3). Liver transplantation is the effective therapy that improves survival, but because of donor organ shortage and urgency, an artificial or bioartificial liver system could act as an effective bridge to liver transplantation in patients with FHF [121].

Some resulting guidelines for the treatment of ALF and FHF are [113]:

• Sufficient intake of fluids and high-calorie parenteral nutrition is necessary, as well as administration of amino acids that are either not being produced at all or are reduced due to hepatic failure.
• Therapeutic apheresis and/or artificial or bioartificial liver support systems must be implemented very early, if possible, in the beginning of the coma, to achieve a rapid detoxification.
• Treatment must at least six to nine hours per day or longer. This time allows to implement the artificial or bioartificial liver support systems.
• Adequate substitution of fresh frozen plasma, coagulation and other factors are necessary to prevent increased bleeding and to replace liver synthesis, at least in part.
• Through the elimination of toxic substances, the disturbed relationship between various amino acids and lipids is re-established.
• Sufficient substitution of immunoglobulins is necessary to keep the risk of infection as low as possible.

In the guideline on the use of TA of the AAC of the ASFA, the ALF has the category III with the recommendation grade (RG) 2B, and the FHF the category I and the RG 1A (Table 1) [17, 18]. In the last years, TPE may be most employed as a bridge to liver transplantation in patients with acute -on-chronic liver failure [121]. The introduction of high-volume TPE (8-12 L/per day) with the substitution solution of fresh frozen Plasma (FFP) and albumin-electrolyte solution is successfully report in the treatment of ALF [122, 123]. TPE or IA are indicated in antibody-mediated rejection with immunosuppression. In the guidelines on the use of TA of the AAC of the ASFA, the liver transplant rejection is the same as ABO-incompatible solid organ transplantation and has the category I and the RG 1C for TPE, and the category III with RG 2C for TPE for desensitization deceased donor, and humoral rejection [18].

Erythropoietic Protoporphyria (EPP), Liver Disease

Erythropoietic protoporhyria is a rare autosomal recessive disease, which is characterized by reduced activity of mitochondrial ferro chelatase, the final enzyme in the heme biosynthetic pathway [18]. Ferro chelatase catalyzes insertion of ferrous iron into protoporphyrin to form heme. The deficiency of this enzyme results in the accumulation of metal-free protoporphyrin in bone marrow reticulocytes, which can appear in the plasma and is taken up in the liver and is excreted in bile and feces. The diagnosis is found in an increased level of erythrocyte total population and especially metal-free protoporphyrin. Erythropoietic protoporphyria presents with skin photosensitivity with pain, redness and itching which minutes of sunlight exposure in childhood. Protoporphyrin is lipophilic and poorly water soluble. The damage of the liver occurs in > 5% of patients [18].

The treatment of the photosensitivity is avoiding light exposure. Besides the conservative therapy with ursodiol to enhance protoporphyrin solubility in bile, cholestyramine to interrupt the enterohepatic circulation of protoporphyrin, and oral oxidants such as Vit. A, E, N-Acetal Cysteine, green tea in combination with TPE to decrease the protoporphyrin levels in the blood to prevent further deposition in the liver. Therapeutic plasma exchange or RBC exchange alone or in combination with transfusions, hemin, ursodiol and Vit. E is unlikely to reverse advanced-stage disease. This therapy has potential benefits to bridge patients to liver transplantation or hematopoietic stem cell transplantation [18, 124, 125]. For TPE, the frequency is every 1 – 3 days and for red blood cell exchange 3x/week. The replacement fluid for TPE can be albumin-electrolyte solution and/or fresh frozen plasma (Table 1) [18, 126].

Phytanic Acid Storage Disease (Refsum´s Disease)

Refsum´s disease, also called heredopathia atactica polyneuritiformis, is a rare recessive autosomal inherited metabolic disease, based on an isolated lack of the enzyme, which results in phytanic acid (PA) being stored in the body and causing corresponding symptoms [127, 128]. The clinical symptoms include retinitis pigmentosa, anosmia, deafness, chronic sensory-motor neuropathy, ataxia and the accumulation of PA in blood and body tissues [129]. The elimination of PA by TPE and a phytanic acid-reduced diet can achieve a significant improvement in the disease [130]. Diet is the first and important therapy step in Refsum´s disease. The average intake of PA is 50-100 mg/day, and ideally, this should be reduced to 10-20 mg/day. Phytanic acid is almost exclusively of exogenous origin and levels of PA > 800 µmol/L is not uncommon. Poorly metabolized PA, pristanic acid (PrA), and picolenic acid (PiA) accumulate in fatty issues, myelitis sheaths, heart, kidneys and retina, leading to retinitis pigmentosa, peripheral dissociative polyneuropathy, cerebral ataxia, "sailors walk", renal, cardiac and liver impairment 65 percent of plasma PA and PrA is localized within VLDL, LDL, HDL lipoprotein particles. The diet of PA is mostly not sufficient to prevent acute attacks and stabilize the progressive course [130]. Clinical improvement is given achieved when the PA is reduced to below 500 mg/L by TPE. Experience with black cumin oil (nigella sativa) in a dose of 3g/day shows a support and regression of some malnutrition effects in PA restricted dietary and a supportive effect to membrane differential filtration [131].

In the guidelines of the AAC of the ASFA, the Refsum´s disease has the category II with the RG 2C (18) (Table 1). Therapeutic plasma exchange can eliminate the elevated plasma levels of PA. The elimination of PA can avoid acute attacks or exacerbation of the disease as well as for maintenance therapy. The normal plasma PA level in humans is < 33 µmol/L, and symptomatic levels of Refsum´s disease range from 700 to 800 µmol/L. Phytanic acid is also bound to plasma lipoproteins and triglycerides; therefore, LA has been used successfully [18]. A typical course of TA in Refsum´s disease consists of 1-2 TPE per week for several weeks to months. In some cases, maintenance TPE continue with decreasing frequency over subsequent weeks or months. Therapeutic strategy is ultimately determined by monitoring the

patient´s PA level, clinical signs and symptoms, and the need to control or prevent exacerbations of the disease [132]. To date, no cure exists for Refsum´s disease, but phytanate levels in patients can be reduced by TPE and a strict diet [132, 133].

Systemic Amyloidosis

Amyloidosis belongs to a heterogenous group of genetic and acquired disorders characterized by pathological extracellular deposition of insoluble polymeric fibrils consisting of misfolded proteins or protein precursors, leading to progressive organ damage [18]. Amyloidosis is composed of highly organized proteinaceous fibrils, insoluble and degradation-resistant. This results in progressive tissue amyloid accumulation, and 36 different proteins have been identified as amyloidogenic. At least 17 of them can cause systemic diseases, in which the amyloidogenic protein is produced in one site (e.g., bone marrow, liver) and is deposited at distant sites, e.g., heart, kidneys [134].

The most common acquired diseases involve deposition of monoclonal immunoglobulin light chain, serum amyloid a protein or β_2-microglobulin, dialysis-related amyloidosis, but several other types of amyloidosis have been described [18]. Amyloidosis is associated with multiple myeloma, Waldenström´s macroglobulinemia, non-Hodgkin lymphoma, and primary plasma cell dyscrasia. Amyloidosis is a relatively rare disorder with estimated incidence of 3-12 per million patients per year.

The treatment goal in amyloidosis is the elimination of the production of the amyloidogenic light chain by the plasma cells clone and achieving the lowest level of the involved light chain in serum, as this will halt further amyloid deposition and will allow better chances for organ recovery [134]. Due to concurrent immunosuppressive therapies, limited information on TPE procedures performed, and failure to establish improvement in symptoms is due to reduction in amyloid, the relative benefit of TPE is not clearly discernible. Intensive TPE with immunosuppressive therapy has been used to manage rapidly progressive glomerulonephritis with amyloidosis [18] (Table 1). A survey of 138 institutions revealed that attending physicians considered β_2-microglobulin adsorption column treatment to be at least partially effective in greater than 70% of patients (n=345) [135]. Lipoprotein apheresis has been demonstrated mechanistically to acutely lower some amyloid related proteins. However, further clinical studies are necessary. In the last years studies with new therapies have been published have been published. Daratumumab combined with bortezomib emerged as a new standard of care [136, 137].

Adrenoleukodystrophy (ALD)

Adrenoleukodystrophy is an x-linked disorder of metabolism of very long chain fatty acids (VLCFAs) with an estimated frequency of up to 1:20,000 in male subjects in male subjects (138). Adrenoleukodystrophy is caused by a defective gene located within the xq28 region of the X-chromosome [139], probably resulting in a defect of lignoceroyl-CoA lipase, an adenosine triphosphate (ATP) binding transporter [140], in peroxisomal fatty acid β-oxidation. Apparently, this defect is associated with an impairment of the degradation of saturated VLCFAs C24: 0 [141, 142]. The fatty acids accumulate in the cholesterol ester and ganglioside fraction of the patient's white matter and adrenal cortexes as well as in plasma and red blood cells [140]. Adrenoleukodystrophy shows an extreme variability in the level of expression and symptoms. In childhood, it usually begins with a period of unspecific symptoms such as disturbances of concentration and behavior. Neurological deterioration develops. Progressive ataxia, loss of visual and auditory functions, and cerebral convulsions are followed. Virtually 50% of the patients die within 2 years after the onset of symptoms [143].

Different therapeutic approaches have been used in attempts to modify the inexorable evolution of ALD. Therapeutic studies have been carried out to lower the concentrations of VLCFAs by restriction of the dietary intake or by combinations of VLCFA-restricted diet with glyeroltrioleate (GTO), and these therapies have been shown to be effective in fibroblast culture. However, both therapeutic strategies were only of limited success. Recently some studies have been published showing good effects of a therapy combing a VLCFA-restricted diet with the application of GTO and glyceroltrierucate, (GTE) [139, 144- 150].

A further experimental strategy for reduction of elevated blood VLCFA levels is the treatment with TPE and diet [151]. The concentration of C223:0, C245:0, and C236:0 were reduced on average by 56.2%. 54.5%, and 51.8% per treatment ($p = 0.0001$) respectively by TPE. The C24:/C22:0 and the C26:0/C22:0 ratios remained with means of 1.58 ± 0.18 (range: 1.1-1.85, $n = 13$) and 0.0071 ± 0.016 (range: 0.05-0. 105.n = 13) stable but elevated, normal values are from literature [152]. With TPE a significant reduction of C24:0, C126:0, and C22:0 levels but no normalization of the C24:/C22:0 and C26:0/C22:0 was reached. The patient reported a in clinical performance and general well-being. There was no further progression of neurological disorders, but rather a regression of physiological disorders [151]. The present results, even though limited to a single patient, support the need for further evaluation of TPE therapy in a patient refractory to other therapeutic regiments or suffering from severe side effects from these regimen [151, 152].

However, in the last years, studies have shown, bone marrow transplantation and hematopoietic stem cell gene therapy are only effective when performed at an early stage of onsets in ALD [153, 154]. Nonetheless, current research and development of novel therapies are hampered by a lack of in-depth understanding disease pathophysiology and a lack of reliable ALD models [154].

Hereditary Hemochromatosis (HH)

Hereditary hemochromatosis includes several inherited disorders, which show iron deposition in the liver heart, pancreas and other organs [18]. The genetic mutation, accounting for > 90 % of patients is homozygosity for a single missense mutation of HFE on chromosome 6p21 that results in substitution of cysteine with tyrosine at amino acid 282 (C282Y), known as type I HH [18]. In HH, iron accumulation can ultimately result in liver failure such as cirrhosis, hepatocellular carcinoma, diabetes, hypogonadism, hypopituitarism, arthropathy, and cardiomyopathy and skin pigmentation. Diagnosis is suggested by a persistent serum transferrin saturation of ≥ 45% and/or unexplained serum ferritin of ≥ 200 ng/ml in premenopausal woman. The clinical penetrance of disease is variable [18, 155].

The treatment must be in HH, with iron overload, the removal of iron by therapeutic phlebotomy. The mainstay of treatment both to remove iron and to increase erythropoiesis is to mobilize store iron [18]. Two to four phlebotomies per year are needed to maintain the ferritin ≤ 50 ng/ml. Malaise, weakness, fatigability and liver transaminase elevations often improve during the first several weeks of treatment. Other complications and side effects could be improved or not, such as cardiomyopathy or insulin dependent diabetes mellitus. If phlebotomy is contraindicated, iron chelation can be used as an alternative treatment, although it is costly and has side effects [18].

Erythrocytapheresis of 350-800 ml of RBCs over several weeks is comparable with phlebotomy in adverse events and treatment costs [156, 157]. The reduction in the number of required procedures per year to maintain a goal ferritin level may give a cost benefit of erythrocytapheresis over phlebotomy [158]. Erythrocytapheresis is a modality which has proven to reduce treatment duration of patients with iron overload from HH [159]. The AAC of the ASFA has given the HH for erythrocytapheresis the category I and the RG 1B (Table 1) [18].

Hyperviscosity in Hypergammaglobulinemia

Hyperviscosity syndrome (HVS) varies as a function of hematocrit, RBC aggregation, plasma proteins, and interaction between the blood and the blood vessel wall [18]. Hyperviscosity syndrome refers to the clinical sequelae caused by the altered physiology related to plasma hyperviscous states, most typically seen in Waldenström´s macroglobulinemia (WM) associated with monoclonal IgM or, less frequently, with multiple myeloma (MM) associated with monoclonal IgA or IgG3. The signs and symptoms include headache. Dizziness, nystagmus, hearing loss, visual impairment, somnolence, coma, and seizures. Other manifestations include congestive heart failure, respiratory compromise, coagulation, abnormalities, anemia, fatigue, peripheral polyneuropathy, and anorexia. Serum viscosity measurement does not consistently correlate with clinical symptoms among individual patients. Most patients will be symptomatic at levels of 6-7 cp, cp: relative to water: normal ranges, 1.4-1.8 cp [18].
The treatment of HVS is the removal of the paraproteins by TPE [160, 161]. Therapeutic plasma exchange should be carried as soon as the diagnosis is made [162]. The underlying disease process, as chemotherapy or immunotherapy, should be initiated soon after TPE as serum IgM levels will return to baseline in 4-5 weeks. A combination of bendamustine and rituximab has been recommended as first line therapy for bulky disease. Dexamethasone-rituximab-cyclophosphamide has been suggested as an alternative, especially in the setting of non-bulky disease. Other therapy regiments include protease inhibitors, nucleoside analogs, and ibrutinib. IgM is 80% intravascular and serum viscosity rises steeply with increasing IgM levels. TPE reduces viscosity per treatment of 20-30% [18]. A transient increase in IgM levels after rituximab therapy, has been reported in 30-70% of patients, Therefore TPE should be considered before giving rituximab [163, 164]. Therapeutic plasma exchange is safe and effective and reduced all biochemical markers related to HVS, which making a significant contribution to clinical improvement (Table 1) [165, 166].

Age-Related Macular Degeneration (AMD), Dry

Age-related macular degeneration is the leading cause of severe visual loss and legal blindness in people aged 50 years or older in developed countries. The most common disease is the dry AMD and is characterized by the accumulation of debris (drusen) which disrupt the functional complex of the rertina and may progress to geographic atrophy [18]. About 80% patients have dry AMD, wet AMD which is responsible for nearly 90% of severe vision loss. The most severe, the wer AMD, is characterized by abnormal neovascularization. AMD can be classified into early, intermediate, and late stage. Clinical manifestations appear as drusen, atrophy of the retinal pigment epithelium and choriocapillaris, retinal pigment epithelium detachment, and choroidal neovascularization [167]. Geographic atrophy of the fovea and neovascular maculopathy are always late stage. Smoking is the modifiable risk factor [18]. Genetic risk factors include mutations in complement factor H, cholesterol, collagen matrix and angiopathways. The pathogenesis of AMD is not completely known.

The conservative medical management for dry AMD is limited to oral supplements high doses of antioxidant vitamins, zinc, and copper. Further therapies for dry AMD are in development [18]. Intravenous anti-vascular endothelial growth factor injection has become first-line therapy for wet AMD. Photodynamic therapy and laser photocoagulation are used as second-line therapy.

Rheopheresis is a TA-methods, which removes rheologically active, high-molecular weight molecules, such as fibrinogen, LDL, α2-macroglobulin, fibronectin, von Willebrand factor. These substances may impair the retinal microcirculation or contribute to a chronic inflammatory state. Rheopheresis results in a reduction in blood plasma viscosity, platelet and red cell aggregation, which may improve the perfusion and function (Table 1) [18]. In different studies, the treatment groups showed significantly best-corrected visual acuity [168-170].

Criticism of current evidence supporting the use of rheopheresis for treatment of dry AMD include the hypothetical mechanism of action by which the apheresis procedure improves the retinal pigment endothelium function, uncertainty surrounding the clinical relevance of reported visual improvements, and the natural history of the disease which may have a stable course without deterioration for long periods of time [18, 171, 172]. Further studies are required to assess the clinical benefit of rheopheresis in the treatment of AMD before this therapy could be recommended for clinical routine.

Wilson Disease (WD), Fulminant

Wilson disease is an autosomal recessive genetic disorder and results from a mutation in the ATP7B gene, which encodes a copper transporting ATPase protein, leading to impaired biliary cooper excretion. The consequence is the accumulation of copper in the liver, brain, cornea, and kidney [18]. Copper´s incorporation into ceruloplasmin is also impaired. Birth incidence rates are 1/30,000-40,000.

The spectrum of liver disease includes asymptomatic liver function test abnormalities, hepatitis, cirrhosis, and ALF. Neurological symptoms include Parkinsonism, dystonia, cerebellar and

pyramidal symptoms [173]. The appearance of Kayser-Fleischer rings, copper deposits in the outer rim of the cornea, and direct antiglobulin test negative hemolytic anemia are relatively common. The hemolysis appears to be primarily due to copper-induced oxidant stress to RBC enzyme pathways and membrane damage. Acute liver failure is accompanied by hemolytic crisis and multiorgan failure with rapid clinical deterioration and is nearly always fatal without LT. The laboratory includes low serum ceruloplasmin, increased 24-hour urinary copper excretion, and elevated serum copper. Most important for diagnosis is a liver biopsy showing elevated copper content and/or a genetic test for ATP7B gene mutation [18].

Low-copper diets and copper reduction therapy must be lifelong. Zinc acetate is non-toxic and stimulates metallothionin, which reduces dietary and enterohepatic adsorption of copper [17]. This is the therapy of choice for asymptomatic patients or patients with hepatitis or cirrhosis, but without evidence. Chelation therapy increases urinary copper excretion. Other therapies for reducing copper include hemofiltration, albumin dialysis and the molecular adsorbents recirculating system [174]. Tetrathiomolybdate is emerging as the drug of choice because of its rapid action preservation of neurologic function, and low toxicity. Liver transplantation is potentially curative and is the main stay of therapy for patients with ALF [175].

The massive amounts of copper in the circulation can be beneficial and rapidly remove significant amounts from the circulation by TPE [176, 177]. The AAC of the ASFA has given the Wilson disease for TPE the category I and the RG 1C (Table 1) [17, 18]. Decreased serum copper may decrease hemolysis, prevent progression of renal failure and provide clinical stabilization. Therapeutic plasma exchange can also remove large molecular weight toxins such as aromatic amino acids, ammonia, endotoxins and other factors, which may be responsible for hepatic coma. In most patients, TPE can be used as a bridge to LT. Reports showed that TPE combined with chelating agents improved ALF and eliminated the need for LT. High volume TPE acts not only as a bridging therapy to LT, but may also improve proportion of the cases with transplant free survival [178]. New copper chelating agents were covalently immobilized onto macroporous microspheres to prepare copper specific adsorbents, which demonstrate good adsorption capacity of 63.44 and 58.48 mg/g, respectively, for Cu^{2+} ion [179].

Cutaneous T Cell Lymphoma (CTCL); Mycosis Fungoides: Sézary Syndrome Mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), account for 55% and 5% of CTCL cases respectively [18]. Both involve clonal (malignant) epidermotropic CD3+/CD4+ T cells. Diagnosis includes clinical, histopathologic, molecular and immunopathologic results. Disease staging evaluates skin, lymph node, visceral and blood involvement using TNMB criteria [180]. Early-stage MF can be challenging to diagnose. In the stage I, the disease is limited to the skin, with patches, papules or plaques. The stage II indicates low grade lymph node involvement, or skin tumors. Erythrodermic MF is characterized by generalized erythroderma alone or in the presence or a low burden of clonal CD4+ T cells (Sézary cells) in the peripheral blood. Diseases with high grade lymph node or visceral involvement is associated with very poor prognosis [18].

The treatment of MF/SS is first palliative with therapy aimed at alleviating symptoms, improving skin manifestations, controlling extracutaneous complications and minimizing immunosuppression. The treatment of the skin includes topical corticosteroids, topical mechlorethamine, topical bexarotene, ultraviolet phototherapy, local radiotherapy and total skin electron beam therapy [181]. Systemic therapies are retinoids, interferon-alpha, and chemotherapy with methotrexate, liposomal doxorubicin, and gemcitabine, targeted immunotherapy, such as alemtuzumab, brentuximab, ECP, histone deacetylase inhibitors and allogenic stem cell transplantation [182]. ECP is currently recommended as first line treatment, alone or in combination with other skin directed or systemic therapy [18].

Extracorporeal photopheresis, ex vivo treatment with 8-methoxypsoralen and UVA light, and subsequent reinfusion of the treated cells. Treatment induces apoptosis of malignant cells, which are phagocytosed by antigens presenting cells following reinfusion, and stimulates monocyte differentiation to myeloid dendritic cells with a Th1 phenotype that launch a cytotoxic response against malignant clone [183]. The response rate of CTCL to ECP is approximately 60 % with complete response rates of 14-26 %. Extracorporeal photopheresis can be combined with systemic therapy such as retinoids and interferons for better response. The National Comprehensive Cancer Network Guidelines lists ECP as a treatment option for refractory early stage disease (Table 1) [18]. Advantages of ECP include the relative lack of immune suppression and lower risk of infections compared to systemic therapy [184, 185].

Infections (Septicemia)

Most human pathogenic bacteria produce endotoxins, which damage the plasma membranes of the target organs. One main mechanism for the damage is the formation of trans-membrane pores [20]. The antibiotic therapy alone may be inadequate to successfully treat overwhelming sepsis with multiorgan organ system failure. The effect of bacterial toxins and sepsis mediators leading to multiorgan failure must be effectively arrested. In sepsis, the clarification of the pathophysiology of the toxins and its role as mediator of organ damage is of decisive critical importance. In addition to focal surgery and an effective antibiotic therapy, additional therapy is indicated must also be sought to effectively neutralize or eliminate these toxins and sepsis mediators. Important is also to consider those to clarify the influence variables related to the therapy, dose and timing, and the precipitating infection, severity, site and type [20].

As an example, malaria is shown. Malaria is vector-borne protozoal infection caused by Plasmodium vivax, P. malaria or P. falciparum [17]. Until today, malaria still causes >400,000 deaths annually worldwide. Infections with P. falciparum has the highest mortality in Africa in pregnant women, nonimmune travelers, patients with HIV and children < 5 years. The life circle of the intraerythrocytic stage of the Plasmodium is responsible for the disease manifestation. The clinical signs of malaria are RBC rigidity and aggregation, microvascular obstruction, hemolysis

and activation of inflammatory cells and cytokines. The most severe malaria cases are Plasmodium falciparum with high-grade, > 5%, parasitemia with single or multi-system dysfunction. The symptoms are consciousness, seizures, pulmonary edema, acute respiratory distress syndrome, shock, DIC, AKI, hemoglobinuria, jaundice, which can be poor prognostic features.

Malaria tropical is particularly lethal. Cerebral involvement is associated with a significant very unfavorable prognosis [20]. It often leads to death after a course of altered mental status, parses and seizures, spasms paresis, and a state of confusion. The consumption coagulopathy is another lethal complication, the pathogenesis of which includes is still unclear among other factors, probably, hemolysis and intravascular coagulation exercise a mutual influence here.

Severe malaria should be treated promptly with intravenous quinidine gluconate and transition to oral quinine combination when stable [18]. Intensive care is also often necessary. The early implementation of TPE or erythrocytapheresis can potentially interrupt the pathogenetic chain reaction before irreversible damage occurs and promote recovery by eliminating circulating immune complexes, antigens, and other toxins [20, 186]. The AAC of the ASFA has given severe malaria the category III and the recommendation grade 2B for TPE or erythrocytapheresis (Table 1) [18].

For infection diseases can be concluded [20]:
- The aim of primary therapy in cases of severe infections with septicemia must be the rapid elimination of the basic disease, e.g., through surgical debridement, antibiotic therapy, and administration of immunoglobulins.
- Therapeutic apheresis can be beneficial in only appears justified in very severe cases when impending with further complications, such as AKI, DIC, pulmonal insufficiency, and multiorgan system failure are impending, to prevent worse consequences or to weaken the course of the disease. In addition, after TA immunoglobulins should generously substituted.
- At present it is not possible to draw up a general approach to TA therapy in infectious diseases

Intoxications, Exogenous and Endogenous

Exogenous intoxication, whether accidental, intentional, or iatrogenic, results from excessive exposure to an agent capable of producing tissue injury and/or or dysfunction, ingestion, inhalation and injection are common routes of exposure [18]. The agents potentially toxic to human are enormous and divers. To quantify the morbidity and mortality attributable to these problems is difficult. Most poisoning incidents are accidental and occur at home. Fortunately, serious injury, is the exception, not the rule [18, 20]. The mechanism of tissue damage varies with the nature of the offending substance and the mode of entrance into the body. Agents may be directly toxic to human tissue or may require enzymatic conversion to an active, injurious metabolite. Local effects at the site of the entry into the body may accompany systemic effects, and the onset of symptoms may be rapid or delayed. Initial treatment focuses on supportive care and the removal of the toxic agent [18].

Evaluation and stabilization of the airway, breathing, circulation, and neurologic status are primary concerns. Toxin-specific antidotes, when available are promptly administered [18, 20]. Induced emesis, gastric lavage, and oral administration of activated charcoal may be used to minimize gastrointestinal absorption of ingested toxins. Gastro-intestinal decontamination, is particularly useful for removing poorly absorbed agents that are not absorbed to charcoal. Forced acid or alkaline diuresis is used to promote the elimination of ionized agents that are not strongly bound to proteins. Hemodialysis is an effective technique for removing drugs that are not rightly bound to plasma and that readily diffuse through a semipermeable membrane. Hemoperfusion, a procedure in which blood is passed directly over sorbent particles, can be more effective than dialysis for protein-bound drugs and large molecule [18, 20].

Therapeutic apheresis has also been successfully implemented in the treatment of exogenous and endogenous intoxications. Therapeutic plasma exchange is often useful in the treatment of toxins or drug overdose involving protein bound substances that are not removable with dialysis. Especially in case of intoxication with exogenous substances with a high protein-binding capacity and low organ affinity, is TPE indicated [20, 187]. Therapeutic plasma exchange can achieve a rapid decrease in toxin concentration and thus acceleration on after flow from tissue, even in poisoning intoxications with substances with high organ affinity. Hemoperfusion has been increasingly applied again in the cases of poisoning, such as with Amanita phalloides, paraquat, methaqualone, carbamarepine, sotalol, phenytoin, and other drugs. A combination of hemoperfusion and TPE, described as plasma-perfusion, is also successful in the treatment of poisoning [188-190].

Therapeutic plasma exchange is an alternative technique for the removal of protein-bound toxins that are not readily removed with dialysis or hemoperfusion [20]. It is effective in removing highly protein-bound toxins from the blood but not from other fluid compartments. Efficiency is limited by the unique characteristics of the toxic substance. Agents that are most amenable to removal by TPE are not lipid soluble or bound to tissue, and do not have large volume of distribution outside the bloodstream. The clinical benefit can be achieved only if toxin levels can be reduced to concentrations below the threshold for tissue damage. Reports of the successful use of TA in the treatment of various drug overdose and poisonings are generally anecdotal. There are no correlations between protein-binding and a volume of distribution among substances which were successfully treated with TPE. This may indicate that other factors played more important role in patient´s recovery. There are also case reports of the failure of plasma exchange to remove substances bound to protein and lipids such as barbiturates, chlordecone, aluminium, tricyclic antidepressants, benzodiazepine, quinine, phenytoin, and others (Table 4). Agents with highly protein bound or those with delayed metabolic effects are the best for removal by TPE. Indications for TA include progressive deterioration, coma, and comprised excretory functions [18, 20].

In the guidelines on the use of TA of the AAC of the ASFA, the overdose, poisonings, and mushroom poisoning for TPE has the category II with the RG 2C and the category III with the RG 2C and the other compound (Table 1) [17, 18]. The treated volume

is 2-4 TPV, replacement fluid is an albumin-electrolyte solution and/or fresh frozen plasma and the frequency daily, depending of the clinical symptoms. However, as most substances can be equally well eliminated with plasmaperfusion or hemoperfusion, indication for TPE, plasmaperfusion or hemoperfusion should depend on the expected benefits and side-effects in each individual case [20].

Advisable in:	Cytostatic, immunosuppressives, ethylchlorvenol*, glutethimide* Acetaminophen, paraquat, parathion (E 605), amanithin, natrium chlorate, and other substances, which can cause hemolysis
More or less advisable in:	Aluminium*, tricyclic antidepressants, amanita phaloides, diazepam*, digitoxin, chinidin
No advantage over other detoxification methods in:	Barbiturates, salicylates, and various other poisons
Not advisable in:	Digitoxin

• Not mentioned as a possible TA indication in the Poison Index, 4th edition (191).

Table 4: Indications for TA in exogenous intoxication (modified after 191)

Accidental or intentional poisoning and drug overdose are a significant source of morbidity, mortality and health care expenditure worldwide. Extracorporeal removal treatments have been used to treat poisoning for decades and different modalities are available, including hemodialysis, hemofiltration, hemoperfusion, continuous replacement therapy and TA. A comprehensive understanding of their purpose is key to choose the right modality for each clinical scenario [192].

2. Conclusion

Many different non-immunological diseases are treated with various apheresis methods. Up today, only few prospective controlled trials are available. Therefore, no definitive conclusions could be allowed. After the new classification of AKI, the renal disorders could be treated most with TA, especially the diseases with immunological origin, however, all with endogenous and exogenous metabolics and decomposition disorders or noxae [25]. Besides conservative therapies, NSF could be treated successfully with TPE and/or ECP. The various dyslipoproteinemia diseases are treated successful with TA, too, However, HMA, PCSK9 inhibitors and others, which are introduced as therapy alone or in combination with TA, are successfully in removing LDL and/or Lp(a) and other substances [37]. For the treatment of ALF, FHF, EEP besides the TA methods are artificial and bioartificial liver support devices are available and all have improved the bad prognosis. Other non-immunologic diseases such as Refsum´s disease, systemic Amyloidosis, ALD, HH, HVS, AMD and Wilson disease could be treated with TA. The malignant MF and SS are treated with ECP and chemotherapy successful. In infectious diseases, TA can be beneficial in very severe cases with further complications such as AKI, DIC pulmonal insufficiency and multiorgan system failure. The indications for TA in exogenous and endogenous intoxifications include progressive deterioration, coma, and comprised excretory functions.

However, all mentioned TA, artificial, bioartificial liver support systems, are still technically complicated and such as HMA very expensive [193]. A great reduction in costs is a valid demand in view of the scare reduces available in the healthcare system. Physicians are committed to helping all patients entrusted to them to the best of their knowledge. This means that medical treatment and TA methods must become affordable. To all physicians, politicians, health organizations and above all to the manufacturers, this demand represents a great challenge. The industry justifies the high costs with the expensive research and development required. All those involved in the health-care system must intensify their cooperation in this respect [194].

Nevertheless, medical research and development are advancing and will not be stopped. With the introduction of hollow fiber membranes, exceptional efforts in research and development have been undertaken in the apheresis sector alone, enabling, the introduction of selective separation technics or artificial or bioartificial support systems.

However, for all mentioned diseases the quotient relevant for cost-effectiveness assessment (cost of treatment – cost saved): improvement in life quality must be discussed and calculated exactly by all involved persons. Every effort should be made to delay the progression of acute or chronic disorders [195].

References

1. Malchesky, P. S., Bambauer, R., Horiuchi, T., Kaplan, D., Sakurada, Y., & Samuelsson, G. (1995). Apheresis technologies: an international perspective. Artificial organs, 19(4), 315-323.
2. Jayne, D. R., Gaskin, G., Rasmussen, N., Abramowicz, D., Ferrario, F., Guillevin, L., & European Vasculitis Study Group. (2007). Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. Journal of the American Society of Nephrology, 18(7), 2180-2188.
3. Cascian AL, Jayne DRW, Role of plasma exchange in the treatment of primary vasculitis. Int J Clin Rheu-matol. 2010; 5: 339-344.
4. Yamada, Y., Harada, M., Hara, Y., Iwabuchi, R., Hashimoto, K., Yamamoto, S., & Kamijo, Y. (2021). Efficacy of plasma exchange for antineutrophil cytoplasmic antibody-associated systemic vasculitis: a systematic review and meta-analysis. Arthritis Research & Therapy, 23(1), 1-11.
5. Bambauer, R., Latza, R., Bambauer, C., Burgard, D., & Schiel, R. (2013). Therapeutic apheresis in autoimmune diseases. Open Access Rheumatology: Research and Reviews, 93-103.

6. Bambauer R, Schiel R. Therapeutic Apheresis and Immunosuppression in Immunologic Diseases. A Re-view and Own Observation. Clin Immunol Res. 2021; 5(2): 1-36.
7. Bambauer R. Therapeutic Apheresis in Renal Diseases with Immunologic Origin. Ann Immunol Immuno-ther. 2020; 2: 000114.
8. Wallukat G, Reinke P, Dörffel WW, et al. Removal of autobodies in dilated cardiopathy by immunoad-sorption. Int J Cardiol.1996; 54: 191. PMID: https://www.ncbi.nlm.nih.gov/pubmed/8803685.
9. Hiepe, F., Pfüller, B., Wolbart, K., Bruns, A., Leinenbach, H. P., Hepper, M., ... & Otto, V. (1999). C1q: a multifunctional ligand for a new immunoadsorption treatment. Therapeutic Apheresis, 3(3), 246-251.
10. epl
11. Kumlien G, Ullsröm L, Losvall A et al. Clinical experience with a new apheresis filter has specifically de-tes ABO blood group antibodies. Transfusion 2006; 46: 1568-1575. PMID: https://www.ncbi.nlm.nib.gov/pubmed/16965585.
12. Bambauer R, Latza R, Burgard D, Schiel R. Therapeutic Apheresis in Hematologic, Autoimmune and Der-matologic Diseases with Immunologic Origin. Ther Apher Dial. 2016; 20(5): 433-452. Doi 10.1111/1744-9987.12474.
13. Hafer, C., Golla, P., Gericke, M., Eden, G., Beutel, G., Schmidt, J. J., & Kielstein, J. T. (2016). Membrane versus centrifuge-based therapeutic plasma exchange: a randomized prospective crossover study. International urology and nephrology, 48, 133-138.
14. Malchesky PS. Membrane processes for plasma separation and plasma fractionation. Guideline Princi-ples for clinical use. Ther Apher.2001; 5: 270-282.
15. Kaplan, A. A. (2009). Why nephrologists should perform therapeutic plasma exchange. Dialysis & Transplantation, 38(2), 65-70.
16. Madore, F., Lazarus, J. M., & Brady, H. R. (1996). Therapeutic plasma exchange in renal diseases. Journal of the American Society of Nephrology, 7(3), 367-386.
17. Bambauer, R., Bambauer, C., Latza, R., & Schiel, R. (2014). Therapeutic apheresis in nephrology. Clinical Nephrology and Urology Science, 1.
18. Schwartz J, Winters JL, Padmanabhan A et al. T Guidelines on the Use of Therapeutic Apheresis in Clini-cal Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apher-esis: The Sixth Special Issue. J Clin Apher. 2013; 28: 145-284 .
19. Padmanabhan, A., Connelly-Smith, L., Aqui, N., Balogun, R. A., Klingel, R., Meyer, E., ... & Schwartz, G. E. J. (2019). Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the Writing Committee of the American Society for Apheresis: the eighth special issue. Journal of clinical apheresis, 34(3), 171-354.
20. Bambauer, R., Schiel, R., Lehmann, B., & Bambauer, C. (2012). Therapeutic apheresis, technical overview. ARPN J Sci Technol, 2(5), 399-421.
21. Bambauer, R., Latzo, R., & Schiel, R. (2013). THERAPEUTIC PLASMA EXCHANGE AND SELECTIVE PLASMA SEPARATION METHODS. PABST-SCIENCE PUB.
22. Webb, S., & Dobb, G. (2007). ARF, ATN or AKI? It's now acute kidney injury. Anaesthesia and intensive care, 35(6), 843-844.
23. Jörres, A., & Frei, U. (2001). Akutes Nierenversagen. Der Internist, 42, 379-403.
24. Kribben A. Pathogenese des akuten Nierenversagens. Mitt Klin Nephrologie. 2004; XXXIII: 33-34.
25. Thurau, K., & JW, B. (1976). Acute renal success. The unexpected logic of oliguria in acute renal failure.
26. Bambauer, R. (2009). New approaches in the treatment of acute kidney injury. Therapeutic Apheresis and Dialysis, 13(4), 248-253.
27. Albuerque P, Meneses G. Toxin-related Acute Kidney Injury. In. Silva Junior GB, Ferreiro Fuentes A, Nan-gaku M, Remuzzi G, Ronco C (eds.). Nephrology and Public Health Worldwide. Contrib Nephrol. Basel Karger, 2021; 199: 131-142.
28. https://doi.org/10.1159/000517699.
29. Nalesso, F., Stefanelli, F. L., Di Vico, V., Cattarin, L., Cirella, I., Scaparrotta, G., ... & Calò, L. A. (2022). The Supporting Role of Combined and Sequential Extracorporeal Blood Purification Therapies in COVID-19 Patients in Intensive Care Unit. Biomedicines, 10(8), 2017.
30. Rosner, M. H., & Perazella, M. A. (2019). Acute kidney injury in the patient with cancer. Kidney Research and Clinical Practice, 38(3), 295.
31. Bambauer R, Schiel R. Therapeutic Apheresis in Acute Pancreatitis due to Hypertriglyeridemia. Ann Cardiol Cardiovascul Dis. 2017; 2(1): 1014- 1022.
32. Bardin, T., & Richette, P. (2010). Nephrogenic systemic fibrosis. Current opinion in rheumatology, 22(1), 54-58.
33. Baron, P. W., Cantos, K., Hillebrand, D. J., Hu, K. Q., Ojogho, O. N., Nehlsen-Cannarella, S., & Concepcion, W. (2003). Nephrogenic fibrosing dermopathy after liver transplantation successfully treated with plasmapheresis. The American journal of dermatopathology, 25(3), 204-209.
34. Hofmann, J. C., Reynolds, S. L., & Kiprov, D. D. (2005). Nephrogenic fibrosing dermopathy: response to plasma exchange. J Clin Apher, 20, 12-13.
35. Gillier M, Cozzio A, Burg G, Nestle FO: Successful treatment of these cases of nephrogenic fibrosing der-mopathy with extracorporeal photopheresis. Br. J Dermatol. 2005; 152: 531-536.
36. Poisson, J. L., Low, A., & Park, Y. A. (2013). The treatment of nephrogenic systemic fibrosis with therapeutic plasma exchange. Journal of clinical apheresis, 28(4), 317-320.
37. Mathur, K., Morris, S., Deighan, C., Green, R., & Douglas, K. W. (2008). Extracorporeal photopheresis improves nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis: three case reports and review of literature. Journal of Clinical Apheresis: The Official Journal of the American Society for Apheresis, 23(4), 144-150.
38. Zhang, R., & Rose, W. N. (2017). Photopheresis provides significant long-lasting benefit in nephrogenic systemic fibrosis. Case Reports in Dermatological Medicine, 2017.
39. Bambauer R, Schiel R. Dyslipoproteinemia therapy with lipoprotein-apheresis and/or human mono-clonal antibodies. Trends in Medicine. 2019; 19: 1-10.
40. Ramasamy I. Update on the molecular biology of dyslidemias. Clin Chim Acta. 2016; 454: 143-185.
41. Bambauer, R., Schiel, R., & Latza, R. (2003). Low-density

lipoprotein apheresis: an overview. Therapeutic Apheresis and Dialysis, 7(4), 382-390.
42. Stampfer, M. J., Krauss, R. M., Ma, J., Blanche, P. J., Holl, L. G., Sacks, F. M., & Hennekens, C. H. (1996). A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. Jama, 276(11), 882-888.
43. Schiel, R., Bambauer, R., & Miiller, U. (1996). Low–Density Lipoprotein Apheresis Versus Lipid Lowering Drugs in the Treatment of Severe Hypercholesterolemia: Four Years' Experience. Artificial organs, 20(4), 318-323.
44. Bambauer, R., Schiel, R., Latza, R., & Klinkmann, J. (1996). Treatment of Severe Hyperlipidemia: Six Years' Experience with Low–Density Lipoprotein Apheresis. Artificial organs, 20(4), 336-339.
45. Bambauer, R. (2002). Low-density lipoprotein apheresis: clinical results with different methods. Artificial organs, 26(2), 133-139.
46. Lahere V, Navaaro-Cid J, Ruilope LM. Endothelial dysfunction. Dyslipidemia and atherosclerosis: patho-physiologic and therapeutic implications. Cardio Risk Fact. 1997; 7: 59
47. Spieker LE, Sudano I, Hurliman D, et al. High-density lipoprotein restores endothelial function in hyper-cholesterolemic men. Circulation. 2002; 105: 1399-1402.
48. Bambauer, R., Bambauer, C., Lehmann, B., Latza, R., & Schiel, R. (2012). LDL-apheresis: technical and clinical aspects. The Scientific World Journal, 2012.
49. Assmann, G., Schulte, H., & von Eckadstein, A. (1995). Epidemiological and clinical relevance of triglycerides and high density lipoprotein cholesterol. Cardiovascular Risk Factors, 5, 4.
50. Soma, M. R., & Paoletti, R. (1996). The future of cardiovascular disease prevention and the role of lipid regulation. Cardiovascular Risk Factors, 6(5), 262-268.
51. Van BuurenF, Kreikmann S, Horskotte D, et al. HELP apheresis in hypercholesterolemia and cardiovascu-lar disease: efficacy and adverse events after 8,500 procedures. Clin Res Cardiol. (Supplements) 2012; 7: 24-30.
52. Ducas J, Siversides C, Dembinski TC. Apoprotein (a) phenotype and lipoprotein (a) level predict eritoneal dialysis patient mortality. Periton Dial Int. 2002; 22:492-499.
53. Ariyo AA, Thach C, Tracy R. Cardiovascular Health Study Investigators. Lp(a) lipoprotein, vascular dise-ase, and mortality in the elderly. N Engl J Med. 2003; 349: 2108-2115.
54. Kamstrup, P. R, Tybjærg-Hansen, A., & Nordestgaard, B. G. (2014). Elevated lipoprotein (a) and risk of aortic valve stenosis in the general population. Journal of the American College of Cardiology, 63(5), 470-477.
55. Mazhar, Z., Hughes, A., & Garelnabi, M. (2017). Targeting the role of lipoprotein (a) in stroke. Cardiovascular & Haematological Disorders-Drug Targets (Formerly Current Drug Targets-Cardiovascular & Hematological Disorders), 17(1), 64-72.
56. Kroon, A. A., Demacker, P. N. M., & Stalenhoef, A. F. H. (1991). N-acetylcysteine and serum concentrations of lipoprotein (a). Journal of internal medicine, 230(6), 519-526.
57. Hopewell, J. C., Seedorf, U., Farrall, M., Parish, S., Kyriakou, T., Goel, A. & PROCARDIS Consortium. (2014). Impact of lipoprotein (a) levels and apolipoprotein (a) isoform size on risk of coronary heart disease. Journal of internal medicine, 276(3), 260-268.
58. Roeseler, E. Julius, U. Heigl, F. Spitthoever, R. Heutling, D., Breitenberger, P. & Klingel, R. (2016). Lipoprotein apheresis for lipoprotein (a)-associated cardiovascular disease: prospective 5 years of follow-up and apolipoprotein (a) characterization. Arteriosclerosis, thrombosis, and vascular biology, 36(9), 2019-2027.
59. Raal, F. J. Giugliano, R. P. Sabatine, M. S. Koren, M. J. Langslet, G., Bays, H. & Stein, E. A. (2014). Reduction in lipoprotein (a) with PCSK9 monoclonal antibody evolocumab (AMG 145) a pooled analysis of more than 1,300 patients in 4 phase II trials. Journal of the American College of Cardiology, 63(13), 1278-1288.
60. Henry CA, Lyon RA, Ling H. Clinical efficacy and safety of Evolocumab for low-density lipoprotein chole-sterol reduction. Vascul Health Risk Manag. 2016; 12:163-169.
61. European Atherosclerosis Society (Study group). Strategies for prevention of coronary heart disease: ma policy statement of the European Atherosclerosis Society. European Heart J. 1990; 8: 77-88.
62. Yamamoto, A., Kawaguchi, A., Harada-Shiba, M., Tsushima, M., & Kojima, S. I. (1997). Apheresis technology for prevention and regression of atherosclerosis: an overview. Therapeutic Apheresis, 1(3), 233-241.
63. Agishi, T. Kaneko, J. Hasuo, Y. Hayasaka, Y. Sanaka, T. Ota, K. & Sugino, N. (1980). Double filtration plasmapheresis with no or minimal amount of blood derivative for substitution. Plasma exchange, 53.
64. Stoffel, W. Borberg, H. & Greve, V. (1981). Application of specific extracorporeal removal of low density lipoprotein in familial hypercholesterolaemia. The Lancet, 318(8254), 1005-1007.
65. Seidel, D., & Wieland, H. (1982). Ein neues Verfahren zur selektiven Messung und extrakorporalen Elimination von low density Lipoproteinen. J Clin Chem Clin Biochem, 20, 684-685.
66. Nosé, Y., Usami, M., Malchesky, P. S., Emura, M., Horiuchi, T. Sakamoto, H., & Smith, J. W. (1985). Clinical thermofiltration: initial application. Artificial organs, 9(4), 425-427.
67. Mabuchi H, Michishita J, Mitsuaki T, et al. A new low-density lipoprotein apheresis system using two dextran sulfate cellulose columns in an automated column regenerating unit (LDL continuous apher-esis). Atherosclerosis 1987; 68: 19-25.
68. Pokrovsky, S. N. Adamova, I. Y. & Afanasieva, O. Y. (1991). Immunosorbent for selective removal of lipoprotein (a) from human plasma: in vitro study. Artificial Organs, 15(2), 136-140.
69. Bosch, T. Schmidt, B. Blumenstein, M., & Gurland, H. J. (1993). Lipid apheresis by hemoperfusion: in vitro efficacy and ex vivo biocompatibility of a new low-density lipoprotein adsorber compatible with human whole blood. Artificial Organs, 17(7), 640-652.
70. Klingel, R. Göhlen, B. & Fassbender, C. (2002). Fortschritte der Lipidapherese am Beispiel der Membran-Differential-Filtration. Lipidreport, 11, 12.
71. Otto, C. Kern, P. Bambauer, R. Kallert, S., Schwandt, P., &

Parhofer, K. G. (2003). Efficacy and safety of a new whole-blood low-density lipoprotein apheresis system (Liposorber D) in severe hypercholesterolemia. Artificial organs, 27(12), 1116-1122.
72. Kreuzer, J. & Tiefenbacher, C. (2003). Atherosklerose: Taschenatlas spezial. Georg Thieme Verlag.
73. Grossman, M. Rader, D. J. Muller, D. W. Kolansky, D. M. Kozarsky, K., Clark III, B. J. & Wilson, J. M. (1995). A pilot study of ex vivo gene therapy for homozygous familial hypercholesterolaemia. Nature medicine, 1(11), 1148-1154.
74. Gaudet D, Keriakes DJ, McKenney JM, et al. Effect of Alicocumab, a monoclonal protein convertase sub-tilisin/Kexin 9 antibody, on lipoprotein(a) concentration (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). Am J Cardiol. 2014; 114: 711-715.
75. Bambauer, R. Schiel, R. & Latza, R. (2001). Current topics on low-density lipoprotein apheresis. Therapeutic Apheresis, 5(4), 293-300.
76. Jaeger, B. R. & Seidel, D. (2001). Hyperlioproteinämie und LDL-ApheresеKlinische Erfahrungen mit dem HELP-System: Klinische Erfahrungen mit dem HELP-System. Herz, 26, 531-544.
77. Bambauer, R. Olbricht, C. J. & Schoeppe, E. (1997). Low-density lipoprotein apheresis for prevention and regression of atherosclerosis: clinical results. Therapeutic Apheresis, 1(3), 242-248.
78. Bosch T, Lennertz A, Schmidt B, et al. Dali apheresis in hyperlipidemic patients: biocompatibility, effi-cacy, and selectivity of direct adsorption of lipoprotein from whole blood. Art Organs. 2000; 24: 81-90.
79. Moriarty, P. Sosland, R. Gibson, C., & Belmont, J. (2010). Comparison of different low density lipoprotein apheresis machines on brain natriuretic peptide levels in patients with familial hypercholesterolemia. Therapeutic Apheresis and Dialysis, 14(1), 74-78.
80. Abifadel M, Varet M, Rabes JP, et al. Mutations in PCSK9 causes autosomal dominant hypercholester-olemia. Nat Genet. 2003; 34: 154-156.
81. Browning JD, Horton JD. Fasting reduces plasma protein convertase subtilisin/kexin type 9 and choles-terol biosynthesis in human. J Lip Res. 2010; 5: 3359-3363.
82. Lopez, D. (2008). PCSK9: an enigmatic protease. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1781(4), 184-191.
83. Blom, D. J. Dent, R. Castro, R. C. & Toth, P. P. (2016). PCSK9 inhibition in the management of hyperlipidemia: focus on evolocumab. Vascular Health and Risk Management, 185-197.
84. Murphy, K. Travers, P. & Walport, M. (2008). Janeways Immuno Biology 7th ed. Garland Pub. Inc. New York and London, 599-654.
85. Lobo, E. D. Hansen, R. J. & Balthasar, J. P. (2004). Antibody pharmacokinetics and pharmacodynamics. Journal of pharmaceutical sciences, 93(11), 2645-2668.
86. Moriatry PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hyper-cholesterolemia undergoing lipoprotein apheresis: ODYSEY ESCAPE trial. Eur Heart J. 201^6; 37: 3588-3595.
87. Sabatine, M. S. Leiter, L. A. Wiviott, S. D. Giugliano, R. P. Deedwania, P. De Ferrari, G. M. & Pedersen, T. R. (2017). Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. The lancet Diabetes & endocrinology, 5(12), 941-950.
88. Henry CA, Lyon RA, Ling H. Clinical efficacy and safety of Evolocumab for low-density lipoprotein choles-terol reduction. Vascul Health Risk Manag. 2016; 12.: 163-169.
89. Hwang, W. Y. K. & Foote, J. (2005). Immunogenicity of engineered antibodies. Methods, 36(1), 3-10.
90. Lonberg, N. (2005). Human antibodies from transgenic animals. Nature biotechnology, 23(9), 1117-1125.
91. Lonberg, N. (2008). Fully human antibodies from transgenic mouse and phage display platforms. Current opinion in immunology, 20(4), 450-459.
92. Stoekebroek RM, Hartgens ML, Rute R, et al. PCSK9 inhibitors in clinical practice: Delivering on the pro-mise? Atherosclerosis. 2018; 270: 205-210.
93. Karatasakis A, Danek B, Karacsonyi J. The effect of proprotein convertase subtilisin-kexin Type 9 inhibi-tors on clinical outcomes in patient with hypercholesterolemia: A meta-analysis of 16,721 patients from 33 randomized clinical trials. J Am Col Cardiol. 2017; 69:
94. Raal, F. J. Stein, E. A. & Dufour, R. (2015). PCSK9 Inhibition With Evolocumab (AMG 145) in Heterozygous Familial Hypercholesterolemia (RUTHERFORD-2): A Randomised, Double-Blind, Placebo-Controlled Trial. Journal of Vascular Surgery, 62(5), 1368.
95. Groß, E. Hohenstein, B. & Julius, U. (2015). Effects of Lipoprotein apheresis on the Lipoprotein (a) levels in the long run. Atherosclerosis Supplements, 18, 226-232.
96. Fitzgerald, K. White, S. Borodovsky, A. Bettencourt, B. R., Strahs, A. Clausen, V. & Simon, A. (2017). A highly durable RNAi therapeutic inhibitor of PCSK9. New England Journal of Medicine, 376(1), 41-51.
97. Rader, D. J. & Kastelein, J. J. (2014). Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Circulation, 129(9), 1022-1032.
98. Grossman, M. Rader, D. J. Muller, D. W. Kolansky, D. M., Kozarsky, K. Clark III, B. J. & Wilson, J. M. (1995). A pilot study of ex vivo gene therapy for homozygous familial hypercholesterolaemia. Nature medicine, 1(11), 1148-1154.
99. Bambauer R, Schiel R, Keller, HE, Latza R. LDL-apheresis in two patients with extremely elevated lipo-protein (a) levels. Int J Artif Organs. 1995; 18(5): 286-290.
100. Bambauer, R., Schiel, R., & Latza, R. (2001). Current topics on low-density lipoprotein apheresis. Therapeutic Apheresis, 5(4), 293-300.
101. Bambauer, R. (2002). Low-density lipoprotein apheresis: clinical results with different methods. Artificial organs, 26(2), 133-139.
102. Wang. A, Richhariya. A, Gandra. S. R, Calimlim. B, Kim. L (2016). Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. Journal of the American Heart Association, 5(7), e003294.
103. Thompson. G, & Parhofer, K. G. (2019). Current role of lipoprotein apheresis. Current atherosclerosis reports, 21,

1-8.
104. Safarova, M. S., Nugent, A. K., Gorby, L., Dutton, J. A., Thompson, W. J., & Moriarty, P. M. (2022). Effect of lipoprotein apheresis on progression of carotid intima-media thickness in patients with severe hypercholesterolemia. The American Journal of Cardiology, 177, 22-27.
105. Jatem E, Lima J, Monmtoro B, et al. Efficacy and Safety of PCSK9 Inhibitors in Hypercholesterolemia Ass-ociated with Refractory Nephrotic Syndrome. Kid Int Rep. 2021; 6(1): 101-109.
106. Torres E, Goicoechea M, Hernández A, et al. Efficacy of Evoloocumab vs low-density lipoprotein choles-terol apheresis in patients with familial hypercholesterolemia and high cardiovascular risk (EVOLAFER01). J Clin Apher. 2021; 35(1): 9-17.
107. Raal, F. J., Rosenson, R. S., Reeskamp, L. F., Hovingh, G. K., Kastelein, J. J., Rubba, P., ... & Gaudet, D. (2020). Evinacumab for homozygous familial hypercholesterolemia. New England Journal of Medicine, 383(8), 711-720.
108. Saotome, T., Endo, Y., Sasaki, T., Tabata. (2005). A Case of Severe Acute Pancreatitis Treated With CTR-001 Direct Hemoperfusion for Cytokine Apheresis. Therapeutic Apheresis and Dialysis, 9(4), 367-371.
109. Mao, E. Q., Tang, Y. Q., & Zhang, S. D. (2003). Formalized therapeutic guideline for hyperlipidemic severe acute pancreatitis. World Journal of Gastroenterology, 9(11), 2622.
110. Gubensek J, Buturovic-Ponikvar J, Romozi K, et al. factors affecting outcome in acute hypertriglycerid-emic pancreatitis treated with plasma exchange: an observational cohort study. PloS One. 2014; 9: e102748.
111. Stefanutti C. Therapeutic Plasmapheresis. A gate to an Effective Treatment of Severe pathological Cond-itions. Adv Biosc Clin Med. 2014; 2: 1-3.
112. Campos A, Santos J, Freitas C, et al. Plasmapheresis in the management of Acute Pancreatitis due to Se-vere Hypertriglyceridemia-Reporting New Cases. J Renal hepatitis Dis. 2017; 1: 29-34.
113. Nasa, P., Alexander, G., Kulkarni, A. (2015). Early plasmapheresis in patients with severe hypertriglyceridemia induced acute pancreatitis. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine, 19(8), 487.
114. Bambauer R, Marquart U. Therapeutic Plasma Exchange in the Treatment of Acute hepatic Failure. In: Agishi T et al. (Eds.), Therapeutic Plasmapheresis (XII), VSP.1993, pp. 197-200.
115. Bambauer R, Bambauer C, Burgard D, Schiel Ralf. Therapeutic Apheresis and other Artificial Liver Sup-port Systems in Liver Diseases: Technical and Clinical Aspects. In: Konstandin K (Ed.), Apheresis. Nova Science Publishers. 2014.
116. Jalan, R., Gines, P., Olson, J. C., Mookerjee, R. (2012). Acute-on chronic liver failure. Journal of hepatology, 57(6), 1336-1348.
117. Lie TS. Treatment of acute hepatic failure by extracorporeal perfusion over baboon or human liver. In: Chang TMS (ed.), Artificial Kidney, artificial liver, artificial cells. Plenum Press, New York, 1978, pp: 105-114.
118. Lepore, M. J., & Martel, A. J. (1970). Plasmapheresis with plasma exchange in hepatic coma: methods and results in five patients with acute fulminant hepatic necrosis. Annals of internal medicine, 72(2), 165-174.
119. Ash, S. R., Steczko, J., Knab, W. R. (2000). Push-pull sorbent-based pheresis and hemodiabsorption in the treatment of hepatic failure: preliminary results of a clinical trial with the BioLogic-DTPF System. Therapeutic Apheresis, 4(3), 218-228.
120. Falkenhagen, D., Strobl, W., Vogt, G. (1999). Fractionated plasma separation and adsorption system: a novel system for blood purification to remove albumin bound substances. Artificial organs, 23(1), 81-86.
121. Stange, Mitzner, Risler, Erley. (1999). Molecular adsorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. Artificial organs, 23(4), 319-330.
122. Detry, O., De Roover, A., Honoré, P., & Meurisse, M. (2006). Brain edema and intracranial hypertension in fulminant hepatic failure: pathophysiology and management. World journal of gastroenterology: WJG, 12(46), 7405.
123. Nosé Y. Artificial Liver for a bridge to liver transplantation. Artif Organs. 1989; 13: 415.
124. Chris-Olaiya, A., Kapoor, A., Ricci, K. S., & Lindenmeyer, C. C. (2021). Therapeutic plasma exchange in liver failure. World Journal of Hepatology, 13(8), 904.
125. Kim, J. E., Chun, S., Sinn, D. H., Kim, N. J. (2021). Initial experience with high-volume plasma exchange in patients with acute liver failure. Journal of Clinical Apheresis, 36(3), 379-389.
126. Pagano, M. B., Hobbs, W., Linenberger, M., & Delaney, M. (2012). Plasma and red cell exchange transfusions for erythropoietic protoporphyria: a case report and review of the literature. Journal of clinical apheresis, 27(6), 336-341.
127. Pham HP, Schwartz J, Tanhehco Y. Therapeutic plasma exchange in a patient with erytrpoietic protopor-phyria status post orthotopic liver transplantation as a bridge to hematopoietic stem cell transplantation. J Clin Apher. 2014; 29:341-342.
128. Spiva DA, Lewis CE. Erythropoietic protoporphyria: therapeutic response to combined erythrocyte ex-change and plasmapheresis. Photodermatol 1984; 1: 211-220.
129. Frankovich J, Swedo SE, Murphy TK, et al. Clinical Management of Pediatric Acute-onset Neuropsy-chiatric Syndrome: Part II-Use of Immunodulatory Therapies. J Child Adolesc Psychopharma. 2017; 27(7): 1-16.
130. Hagerman, R. J., Hall, D. A., Coffey, S., Leehey, M., Bourgeois, J. (2008). Treatment of fragile X-associated tremor ataxia syndrome (FXTAS) and related neurological problems. Clinical interventions in aging, 3(2), 251-262.
131. Verny, C., Prundean, A., Nicolas, G.,. (2006). Refsum's disease may mimic familial Guillain Barre syndrome. Neuromuscular Disorders, 16(11), 805-808.
132. Wills, A. J., Manning, N. J., & Reilly, M. M. (2001). Refsum's disease. Qjm, 94(8), 403-406.
133. Straube, R., Gäckler, D., Thiele, A., Muselmann, L., & Klingel, R. (2003). Membrane differential filtration is safe and effective for the long-term treatment of Refsum syndrome—an update of treatment modalities and pathophysiological cognition. Transfusion and apheresis science,

29(1), 85-91.
134. Wegrzyn, A. B., Herzog, K., Gerding, A. & Bakker, B. M. (2020). Fibroblast-specific genome-scale modelling predicts an imbalance in amino acid metabolism in Refsum disease. The FEBS Journal, 287(23), 5096-5113.
135. Stepien, K. M., Wierzbicki, A. S., Poll-The, B. T., Waterham, H. R., & Hendriksz, C. J. (2017). The Challenges of a Successful Pregnancy in a Patient with Adult Refsum's Disease due to Phytanoyl-CoA Hydroxylase Deficiency. JIMD Reports, Volume 33, 49-53.
136. Muchtat E, Dispenzierl H, Magen M, et al. Systemic amyloidosis from A (AA) to T (ATTR): a review. J In-tern Med. 2020; 289(3): 268-292.
137. Gejyo, F., Amano, I., Ando, T., Ishida, M., Obayashi, S., Ogawa, H., & Ono, T. (2013). Society of β2-microglobulin adsorption therapy. Survey of the effects of a column for adsorption of β2-microglobulin in patients with dialysis-related amyloidosis in Japan. Ther Apher Dial, 17, 40-47.
138. Kastritis E, Leleu X, Arnulf B, et al. Bortezomib, melphalan and dexamethasone for light chain amyloid-dosis. J Clin Oncol. 2020; 38(28): 3252-3260.
139. Kastritis, E., Palladini, G., Minnema, M., Wechalekar, A., Jaccard, A., Lee, H., & Venner, C. (2020). Subcutaneous daratumumab+ cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients with newly diagnosed light chain (AL) amyloidosis: primary results from the phase 3 ANDROMEDA study. EHA library, 303396, LB2604.
140. Moser HW, Lorenz´s oil. Lancet1993; 341-344.
141. Watkins, P. A., Naidu, S., & Moser, H. W. (1987). Adrenoleukodystrophy: biochemical procedures in diagnosis, prevention and treatment. Journal of Inherited Metabolic Disease, 10, 46-53.
142. Mosser, J., Douar, A. M., Sarde, C. O., Kioschis, P., Feil, R., Moser, H., & Aubourg, P. (1993). Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. Nature, 361(6414), 726-730.
143. Lazo, O., Contreras, M., Hashmi, M., Stanley, W., Irazu, C., & Singh, I. (1988). Peroxisomal lignoceroyl-CoA ligase deficiency in childhood adrenoleukodystrophy and adrenomyeloneuropathy. Proceedings of the National Academy of Sciences, 85(20), 7647-7651.
144. Wanders, R. J. A., Van Roermund, C. W. T., Van Wijland, M. J. A., Schutgens, R. B. H., Schram, A. W., Tager, J. M., & Schalkwijk, C. (1988). X-linked adrenoleukodystrophy: identification of the primary defect at the level of a deficient peroxisomal very long chain fatty acyl-CoA synthetase using a newly developed method for the isolation of peroxisomes from skin fibroblasts. Studies in Inherited Metabolic Disease: Lipoproteins Ethical Issues, 173-177.
145. Moser, H. W., Moser, A. B., Smith, K. D., Bergin, A., Borel, J., Shankroff, J., & Shapiro, E. (1992). Adrenoleukodystrophy: phenotypic variability and implications for therapy. Journal of inherited metabolic disease, 15(4), 645-664.
146. Moser Ab, Borel J, Odone A, et al. A new dietary therapy for adrenoleukodystrophy; Biochemical and pre-liminary clinical results in 36 patients. Ann Neiurol. 1987: 21: 240-249.
147. Rizzo, W. B., Phillips, M. W., Dammann, A. L., Leshner, R. T., & Proud, V. K. (1987). Adrenoleukodystrophy: dietary oleic acid lowers hexacosanoate levels. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 21(3), 232-239.
148. Rizzo, W. B., Leshner, R. T., Odone, A., Dammann, A. L., Craft, D. A., Jensen, M. E., & Sgro, J. A. (1989). Dietary erucic acid therapy for X-linked adrenoleukodystrophy. Neurology, 39(11), 1415-1415.
149. Aubourg, P., Adamsbaum, C., Lavallard-Rousseau, M. C., Rocchiccioli, F., & Bougneres, P. F. (1993). A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. New England Journal of Medicine, 329(11), 745-752.
150. Kaplan, P. W., Tusa, R. J., Shankroff, J., Heller, J., & Moser, H. W. (1993). Visual evoked potentials in adrenolukodystrophy: A trial with glycerol trioleate and Lorenzo oil. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 34(2), 169-174.
151. Maeda K, Suzuki Y, Yajima S, et al. Imptovement of clinical and MRI findings in a boy with adrenoleuko-dystrophy by dietary erucic acid therapy. Brain Dev. 1992; 14: 409-412.
152. Korenke, G. C., Hunneman, D. H., Konler, J., Stöckler, S., Landmark, K., & Hanefeld, F. (1995). Glyceroltrioleate/glyceroltrierucate therapy in 16 patients with X-chromosomal adrenoleukodystrophy/adrenomyeloneuropathy: effect on clinical, biochemical and neurophysiological parameters. European journal of pediatrics, 154, 64-70.
153. Bambauer, R., Schiel, R., Cordes, H., Latza, R., Klinkmann, J., & Schneidewind, J. M. (1997). Plasmapheresis in treatment of adrenoleukodystrophy. Therapeutic Apheresis, 1(2), 152-154.
154. Moser, H. W., Moser, A. B., Frayer, K. K., Chen, W., Schulman, J. D., O'Neill, B. P., & Kishimoto, Y. (1981). Adrenoleukodystrophy: increased plasma content of saturated very long chain fatty acids. Neurology, 31(10), 1241-1241.
155. Ma CY, Li C, Zhou X, et al. Management of adrenoleukodystrophy: From pre-clincal studies to the deve-lopment of new therapies. Biome Pharmacother. 2021: 112214.
156. Engelen M, van Ballegoij WJC, Mallavck EJ, et al. International Revcommendations fort the Diagnosis and management of Patients With Adrenoleukodystrophy: A Consensus-Based Approach. Neurology, Cont-emo Issues Pract Educat Res. 2022. Doi: https://doi.org/10.1212/WNL.0000000000201374.
157. Buzzenti E, Kalafatelli M, Thorburn D, et al. Interventions for hereditary haemochromatosis: an attempt-ted network meta-analysis. Cochrane Database syst Rev. 2017: (3): CDOI 1647.
158. Fernandez-Mosteirin, N., Salvador-Osuna, C., Perez-Lungmus, G., & Giralt, M. (2006). Comparison between phlebotomy and erythrocytapheresis of iron overload in patients with HFE gene mutations. Medicina Clinica, 127(11), 409-412.
159. Rombout-Sestrienkova, E., Winkens, B., Noord, P. A., & Koek, G. H. (2016). Erythrocytapheresis versus phlebotomy in the maintenance treatment of HFE hemochromatosis patients: results from a randomized crossover trial. Transfusion, 56(1), 261-270.
160. Sundic, T., Hervig, T., Hannisdal, S., Assmus, J., & Ulvik, R. J., (2014). Erythrocytapheresis compared with whole

blood phlebotomy for the treatment of hereditary haemochromatosis. Blood Transfusion, 12(Suppl 1), s84.
161. Rombout-Sestrienkova, E., Brandts, L., Koek, G. H., & van Deursen, C. T. B. M. (2022). Patients with hereditary hemochromatosis reach safe range of transferrin saturation sooner with erythrocytaphereses than with phlebotomies. Journal of Clinical Apheresis, 37(1), 100-105.
162. Miyamoto Y, Hamasaki Y, Matsumoto A, et al. Prediction of immunoglobulin M reduction via simple dose of therapeutic plasma exchange and double filtration plasmapheresis using membrane separation in pa-tients with hyperviscosity syndrome caused by Waldenström macroglobulin. J Clin Apher. 2018; 33:611-615.
163. Datta SS, Mukherjee S, Talukder B, et al. Immunoglobulin M "flare" seen in a case of Waldensröm macro-globulinemia successfully managed by therapeutic plasma exchange. Indian J Hematol Blood Transfus. 2016; 32: 208-210.
164. Merz T, Marchesoni I, Caminit G, et al. Efficacy of plasmapheresis as treatment for bilateral hypervisco-sity syndrome related retinopathy in multiple myeloma. Eur J Ophthalmol. 2022: 32(4): NP48-NP51. Doi:10.1177/1120672121997069.
165. Dimopoulos MAI, Gracia-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldensröm macrogol-bulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood; 122: 3276-3378.
166. Kastritis, E., Kyrtsonis, M. C., Morel, P., Gavriatopoulou, M., Hatjiharissi, E., Symeonidis, A. S., & Dimopoulos, M. A. (2015). Competing risk survival analysis in patients with symptomatic Waldenström macroglobulinemia: the impact of disease unrelated mortality and of rituximab-based primary therapy. Haematologica, 100(11), e446.
167. Lokhandwala, P. M., Shabihkhani, M., Ness, P. M., & Bloch, E. M. (2018). Therapeutic plasma exchange for hyperviscosity syndrome secondary to high rheumatoid factor. Transfusion and Apheresis Science, 57(2), 225-227.
168. Kalpakci Y, Hacibekiroglu T, Darcin T, et al. Efficacy and safety of plasmapheresis in symptomatic hyper-viscosity and cast nephropathy: A Multicenter Experience in Turkey. Transfus Apher Sci. 2021; 60(5):103244.
169. Lim, L. S., Mitchell, P., Seddon, J. M., Holz, F. G., & Wong, T. Y. (2012). Age-related macular degeneration. The Lancet, 379(9827), 1728-1738.
170. Pulido JS, Winters JL, Boyer D. Preliominary analysis of the final multicenter investigation of rheopher-esis for age related macular degeneration (AMD) trial (MIRA-1) results. Trans Am Opth6thalmol Soc. 2006; 104: 221-231.
171. Klingel, R., Fassbender, C., Heibges, A., Koch, F., & Erdtracht, B. (2010). RheoNet registry analysis of rheopheresis for microcirculatory disorders with a focus on age-related macular degeneration. Therapeutic Apheresis and Dialysis, 14(3), 276-286.
172. Blaha M, Renova E, Langrova H, et al. Rheohaemapheresis in the treatment of nonvascular macular de-generation. Atheroschler Suppl. 2013; 14: 179-184.
173. Finger, R. P., Krohne, T. U., Issa, P. C., & Fleckenstein, M., (2009). Plasmapheresis for dry age-related macular degeneration—evidence based?. Retina, 29(5), 569-572.
174. Waugh N, Loveman E, Colquit J, et al. Treatments for dry age-related macular degeneration and Star-gardt disease: a systemic review: Southampton (UK): NIHR Journals Library; 2018 May, (Health Technology Assessment, No. 22.27), 2022.
175. Bandmann, O., Weiss, K. H., & Kaler, S. G. (2015). Wilson's disease and other neurological copper disorders. The Lancet Neurology, 14(1), 103-113.
176. Chiu, A., Tsoi, N. S., & Fan, S. T. (2008). Use of the molecular adsorbents recirculating system as a treatment for acute decompensated Wilson disease. Liver Transplantation, 14(10), 1512-1516.
177. Weiss, K. H., Askari, F. K., Czlonkowska, A., Ferenci, P., & Schilsky, M. L. (2017). Bis-choline tetrathiomolybdate in patients with Wilson's disease: an open-label, multicentre, phase 2 study. The Lancet Gastroenterology & Hepatology, 2(12), 869-876.
178. Akyldz, B. N., Yldrm, S., Kondolot, M., & Arslan, D. (2011). Is plasma exchange effective in prevention of hepatic transplantation in fulminant Wilson disease with hepatic failure?. Journal of pediatric gastroenterology and nutrition, 52(6), 778-780.
179. Asfaha, S., Almansori, M., Qarni, U., & Gutfreund, K. S. (2007). Plasmapheresis for hemolytic crisis and impending acute liver failure in Wilson disease. Journal of Clinical Apheresis: The Official Journal of the American Society for Apheresis, 22(5), 295-298.
180. Pawaria A, Sood V, Bihari B, et al. Ninety days transplant free survival with high volume plasma exchan-ge in Wilson disease presenting as acute liver failure. J Clin Apher. 2020; 36(1): 109-117.
181. Yu, Z., Wu, R. A., Wu, M., Zhao, L., Li, R., & Zou, H. (2010). Preparation of polyamine-functionalized copper specific adsorbents for selective adsorption of copper. Colloids and Surfaces B: Biointerfaces, 78(2), 222-228.
182. Foss, F. M., & Girardi, M. (2017). Mycosis fungoides and Sezary syndrome. Hematology/Oncology Clinics, 31(2), 297-315.
183. Wilcox RA. Cutaneous T-cell lymphoma: 201^6 update on diagnostic, risk-stratification, and manage-ment. Am J Hematol. 2016; 91: 151-165.
184. Trautinger, F., Eder, J., Assaf, C., Cozzio, A., & Dummer, R. (2017). European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome–Update 2017. European journal of cancer, 77, 57-74.
185. Alfred A, Taylor PC, Dignan F, et al. The role of extracorporeal photopheresis in the management of cuta-neous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement up-date from the UK Photopheresis Society. Br J Hematol. 2017; 177: 287-310.
186. Atilla, E., Atilla, P. A., Bozdag, S. C., Yuksel, M. K., & Toprak, S. K. 2017). Extracorporeal photochemotherapy in mycosis fungoides. Transfusion clinique et biologique, 24(4), 454-457.
187. Sanyal S, Child F, Alfred A, et al. UK national of extracorporeal photopheresis in cutaneous T-cell lymp-homa. Br J Dermatol. 2018; 178: 569-570.
188. Siegenthaler, N., Giraud, R., & Bendjelid, K. (2010). Erythrocytapheresis and sublingual micro-vascular flow in severe malaria. Clinical hemorheology and microcirculation,

46(4), 299-304.
189. Schutt, R. C., Ronco, C., & Rosner, M. H. (2012, March). The role of therapeutic plasma exchange in poisonings and intoxications. In Seminars in dialysis (Vol. 25, No. 2, pp. 201-206). Oxford, UK: Blackwell Publishing Ltd.
190. Dişel, N. R., Akpınar, A. A., Sebe, A., & Matyar, S. (2015). Therapeutic plasma exchange in poisoning: 8 years' experience of a university hospital. The American Journal of Emergency Medicine, 33(10), 1391-1395.
191. Geith, S., Renner, B., Rabe, C., Stenzel, J., & Eyer, F. (2017). Ibuprofen plasma concentration profile in deliberate ibuprofen overdose with circulatory depression treated with therapeutic plasma exchange: a case report. BMC Pharmacology and Toxicology, 18, 1-5.
192. Ibrahim, R. B., & Balogun, R. A. (2012, March). Medications in patients treated with therapeutic plasma exchange: prescription dosage, timing, and drug overdose. In Seminars in dialysis (Vol. 25, No. 2, pp. 176-189). Oxford, UK: Blackwell Publishing Ltd.
193. Seyffart, G. (1997). Poison index: the treatment of acute intoxication. Pabst Science Publishers.
194. Cardoso C, Coelho S. Extracorporeal Treatment for Poisoning. Port Nephrol Hypert. 2022; 36(3): 148-155.
195. Bambauer, R., & Schiel, R. (2021). Therapeutic Apheresis and Immunosuppression in Immuno-logic Diseases. A Review and Own Observa-tions. Clin Immunol Res, 5(2), 1-36.
196. Bambauer R, Schiel R, Salgado OJ. Therapeutic Apheresis, Immunosuppression and Human Monoclonal Antibodies in Hematologic diseases most with immunologic origin. Medical Research Archives (online) 2022; 10(10. https://doi.ora/10.18103/mro.v1Oil0.3147.
197. Malchesky PS. Therapeutic Apheresis: Why? Ther Apher Dial. 2015; 19: 417-426.

Copyright: *©2023 Rolf Bambauer, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.*