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

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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

<table>
<thead>
<tr>
<th>AAC</th>
<th>Apheresis Application Committee</th>
<th>AKI</th>
<th>acute kidney injury</th>
</tr>
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<tbody>
<tr>
<td>ALD</td>
<td>adrenoleukodystrophy</td>
<td>ALF</td>
<td>acute liver failure</td>
</tr>
<tr>
<td>AMC-BAL®</td>
<td>Amsterdam Medical Bioartificial Liver</td>
<td>AMD</td>
<td>age-related degeneration</td>
</tr>
<tr>
<td>AP</td>
<td>acute pancreatitis</td>
<td>Apo A</td>
<td>apolipoprotein</td>
</tr>
<tr>
<td>Apo B</td>
<td>apolipoprotein B</td>
<td>ATP</td>
<td>adenosintriphosphate</td>
</tr>
<tr>
<td>ASFA</td>
<td>American Society for Apheresis</td>
<td>BLSS®</td>
<td>bioartificial liver support system</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CTCL</td>
<td>cutaneous T cell lymphoma</td>
<td>DALI</td>
<td>LDL hemoperfusion</td>
</tr>
<tr>
<td>DFPP</td>
<td>double filtration plasmapheresis</td>
<td>DIC</td>
<td>disseminated intravascular coagulation</td>
</tr>
<tr>
<td>ECP</td>
<td>extracorporeal photopheresis</td>
<td>ELAD®</td>
<td>extracorporeal liver assist system</td>
</tr>
<tr>
<td>EPP</td>
<td>erythropoietic protoporphyria</td>
<td>FH</td>
<td>familial hypercholesterolemia</td>
</tr>
<tr>
<td>FPSA®</td>
<td>Prometheus system</td>
<td>Gd</td>
<td>gadolinium</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
<td>GTE</td>
<td>glyceroltryerucate</td>
</tr>
<tr>
<td>GTO</td>
<td>glyceroltriolsteate</td>
<td>HD</td>
<td>hemodialysis</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
<td>HELLP</td>
<td>elevated liver enzymes, low platelet count</td>
</tr>
<tr>
<td>HELP</td>
<td>heparin-induced LDL precipitation</td>
<td>HH</td>
<td>hereditary hemochromatosis</td>
</tr>
<tr>
<td>HMA</td>
<td>human monoclonal antibodies</td>
<td>HTG</td>
<td>Hypertriglyceridemia</td>
</tr>
</tbody>
</table>
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 understoodably 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 made 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
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 challenges 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 metabolism. 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 mercuric chloride (sublimate) and carbon tetrachloride. Further substances such as glycol and oxalic acid, however, cause extensive cortical necrosis, usually with irreversible renal damage. Further nephrotoxic 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 through 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 hepatorenal syndrome, decomposition products, toxic and phenols are released through the destruction of liver cells due to liver insufficiency. The pathogenesis of hepatorenal syndrome is presumably based on a reduced effective blood volume, and the increased presence of vasoactive, humoral, or neurohumoral 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 hepatorenal syndrome. Studies showing conclusive results, this speculation at this point. The role of prostaglandin is also still unknown. The application of prostaglandin A1 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 lyssolecithin 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 al-

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 < 30 ml/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 erythematous 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 diaphragm, 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).
<table>
<thead>
<tr>
<th>Diseases</th>
<th>TA modality</th>
<th>Category</th>
<th>RG</th>
<th>Exch. volume (TPV)</th>
<th>Replace-ment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrogenic systemic fibrosis (NSF)</td>
<td>TPE/ECP</td>
<td>III</td>
<td>2C</td>
<td>1-1.5 TPV/1.5L blood</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>Familial Hypercholesterinemia (FH)</td>
<td>LA</td>
<td>I</td>
<td>1A</td>
<td>1-1.5L blood</td>
<td>none</td>
</tr>
<tr>
<td>- homozygotes</td>
<td></td>
<td>II</td>
<td>1A</td>
<td>or plasma*</td>
<td>none</td>
</tr>
<tr>
<td>- heterozygotes</td>
<td></td>
<td>II</td>
<td>1A</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>- homozygotes/heterozygotes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Hyperlipoproteinemia, Lipoprotein (a) (Lp(a))</td>
<td>LA</td>
<td>II</td>
<td>1B</td>
<td>1-1.5L blood or plasma*</td>
<td>none</td>
</tr>
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<td>Nephrogenic systemic fibrosis (NSF) TPE/ECP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Liver Failure (ALF)</td>
<td>TPE/LA</td>
<td>III</td>
<td>1C</td>
<td>1-1.5L blood or plasma*</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>- prevention of HTG-AP relapse</td>
<td></td>
<td>III</td>
<td>2C</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Hypertriglyceridemic pancreatitis</td>
<td>TPE/LA</td>
<td>III</td>
<td>1C</td>
<td>1-1.5L blood or plasma*</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>- severe HTG-AP</td>
<td></td>
<td>III</td>
<td>2C</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>- prevention of HTG-AP relapse</td>
<td></td>
<td>III</td>
<td>2C</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Fulminant hepatic Failure (FHF)</td>
<td>TPE</td>
<td>III</td>
<td>2B</td>
<td>1.5LTPV 8-12L P depends of the method</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>- prevention of HTG-AP relapse</td>
<td></td>
<td>III</td>
<td>2B</td>
<td></td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>Erythropoietic Protoporphryia (EPP)</td>
<td>TPE</td>
<td>III</td>
<td>2C</td>
<td>1.5LTPV exchange+</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>RBC exch.</td>
<td>III</td>
<td>2C</td>
<td>1.5LTPV exchange+</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>Phytanic Acid Storage Disease Refsum’s Disease</td>
<td>TPE/LA</td>
<td>III</td>
<td>1B</td>
<td>1-1.5L TPV 3L</td>
<td>albumin</td>
</tr>
<tr>
<td>Systemic Amyloidosis</td>
<td>TPE</td>
<td>IV</td>
<td>2B</td>
<td>1-1.5L TPV</td>
<td>Albumin, Plasma</td>
</tr>
<tr>
<td>- β2-micro-globulin column</td>
<td></td>
<td>II</td>
<td>2B</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Hereditary Hemochromatosis (HH)</td>
<td>Erythrocyt-apheresis</td>
<td>I</td>
<td>1B</td>
<td>up to 800 ml RBCs</td>
<td>-1/2 of removed RBC</td>
</tr>
<tr>
<td>Hyperviscosity in Hypergamma-globulinemia (HVS)</td>
<td>TPE</td>
<td>IV</td>
<td>2B</td>
<td>1-1.5L TPV</td>
<td>Albumin, Plasma</td>
</tr>
<tr>
<td>- symptomatic</td>
<td></td>
<td>II</td>
<td>2B</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>- prophylaxis for rituximab</td>
<td></td>
<td>II</td>
<td>2B</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Age related macular Degeneration, dry (AMD)</td>
<td>Rheo-apheresis</td>
<td>II</td>
<td>2B</td>
<td>0.8-1.5L TPV</td>
<td>none</td>
</tr>
<tr>
<td>Wilson Disease, fulminating</td>
<td>TPE</td>
<td>I</td>
<td>1C</td>
<td>1-1.5L TPV</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>Cutaneous T Cell Lymphoma(CTCL)</td>
<td>ECP</td>
<td>I</td>
<td>1B</td>
<td>1.5L blood</td>
<td>none</td>
</tr>
<tr>
<td>Mycosis fungoides, Sézary Syndrome</td>
<td>ECP</td>
<td>III</td>
<td>2C</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Infections (Septicemia)</td>
<td>RBC exchange</td>
<td>III</td>
<td>2B</td>
<td>1-2 total RBC vol.</td>
<td>RBCs</td>
</tr>
<tr>
<td>- Malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overdose, Envenomation, Poisoning</td>
<td>TPE</td>
<td>II</td>
<td>2C</td>
<td>1-2 TVP</td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>- mushroom poisoning</td>
<td></td>
<td>III</td>
<td>2C</td>
<td></td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>- envenomation</td>
<td></td>
<td>III</td>
<td>2C</td>
<td></td>
<td>albumin, plasma</td>
</tr>
<tr>
<td>- Drug overdose/poisoning</td>
<td></td>
<td>III</td>
<td>2C</td>
<td></td>
<td>albumin, plasma</td>
</tr>
</tbody>
</table>


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 triacylglycerides [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 lipoprotein (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 medicinal 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 cardiology, 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].

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Methods / drugs</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Gennes et al. (46), 1967</td>
<td>Therapeutic plasma exchange</td>
<td>Quick and well-tolerated elimination of pathologic substances</td>
<td>Unselectively of infection, bleeding, risks of human albumin</td>
</tr>
<tr>
<td>Agishi et al. (61), 1980</td>
<td>Cascade filtration</td>
<td>Semi-selectivity</td>
<td>Expensive technology</td>
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<tr>
<td>Stoffel et al. (62), 1981</td>
<td>Immunoadsorption</td>
<td>Selectivity, effectiveness, regeneration, reusable</td>
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<td>Seidel et al. (63), 1982</td>
<td>Heparin-induced LDL precipitation (HELP)</td>
<td>Selectivity, effectiveness</td>
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<tr>
<td>Nosé et al. (64), 1985</td>
<td>Thermo-filtration</td>
<td>Selectivity, effectiveness</td>
<td>Expensive technology, not available</td>
</tr>
<tr>
<td>Mabuchi et al. (65), 1987</td>
<td>Dextran sulfate LDL adsorption</td>
<td>Selectivity, effectiveness</td>
<td>Expensive technology</td>
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<tr>
<td>Pokrovski et al. (66), 1991</td>
<td>Lp(a) immunoadsorption</td>
<td>Selectivity, effectiveness</td>
<td>Expensive technology</td>
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<tr>
<td>Bosch et al. (67), 1993</td>
<td>LDL hemoperfusion (DALI)</td>
<td>Selectivity, effectiveness</td>
<td>Technology not expensive</td>
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<td>Klingel et al. (68), 2002</td>
<td>Lipid filtration</td>
<td>Semi-selectivity</td>
<td>Expensive technology</td>
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<tr>
<td>Otto et al. (69), 2003</td>
<td>LDL hemoperfusion (Liposorber D)</td>
<td>Selectivity, effectiveness</td>
<td>Expensive technology</td>
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<tr>
<td>Kreuzer et al. (70), 2010</td>
<td>Lipoprotein filtration</td>
<td>Semi-selectivity</td>
<td>Expensive technology</td>
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<tr>
<td>Grossmann et al. (71), 1995</td>
<td>Lomitapide, Mipomersan</td>
<td>Low effectiveness</td>
<td>Unknown, not available</td>
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<tr>
<td>Raal et al. (57), 2014</td>
<td>Evolocumab</td>
<td>Selectivity, effectiveness</td>
<td>Unknown</td>
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<tr>
<td>Gaudet et al. (72), 2014</td>
<td>Alirocumab</td>
<td>Selectivity, effectiveness</td>
<td>Unknown</td>
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Table 2: Extracorporeal methods, human monoclonal antibodies and other new drugs for elimination of LDL and Lp(a) (modified after 46)
vascular risk in these patients [85]. Further studies are necessary
atherosclerotic diseases showed a significantly reduced cardio-
study Evolocumab versus placebo included 27,564 patients with
controls showed that PCSK9 inhibitors improve lipid profiles
and that these lifetime reductions confer substantial protection
against CAD [80]. The PCSK9 gene expression is regulated by
nuclear transcription factor sterol regulatory element-bind-
ing protein-2. Concentration of sterol regulatory element-bind-
ing protein-2 are increased by statin therapy, which thus also
increases PCSK9-concentration [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 func-
tion of circulating PCSK9 is to regulate receptor in the liver [81].
Human monoclonal antibodies are target-specific antibodies cre-
ated 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 asso-
ciated 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 reticuloendotheli-
al system [81]. The monoclonal antibody inhibition of PCSK9
have demonstrated reduction in LDL and Lp(a) blood concen-
tration. The PCSK9 inhibition with HMA offers substantial LDL
lowering in patients with dyslipoproteinemia and those with
clinical atherosclerotic cardiovascular disease who are on maxi-
mally tolerated statins. Evolocumab and Alirocumab are gener-
ally well tolerated and the prolonging 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 admin-
istered as monotherapy or in combination with statins and or
ezetimibe in patients with dyslipoproteinemia [81, 87-90]. A me-
ta-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 cardio-
vascular 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 ther-
apeutic 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-apher-
esis 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 (week-
ly 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 ex-
pression 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 onco-
genes, 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]. Li-
oprotein apheresis is the gold standard for patients with homo-
zygous FH [101, 102]. The treatment with PCSK9 inhibitors is
safe and effective, too [103]. Evolocumab or Evinacumab may
have excellent reduction of LDL and Lp(a) [104, 105].

A reduction in costs is a valid demand in view of the scare re-
sources available in the healthcare system. Physicians are com-
mitted to help all patients entrusted to them to the best of their
knowledge, and this means that medical treatment – and particu-
larly 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. Humor-
al 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 pa-
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 protease, 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, hepato-splenomegaly, 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 pancreatic 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-effects. 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 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].
Total hepatectomy
• Products arising from the necrotic liver.

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, noradrenaline 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 to liver transplantation in patients with acute-on-chronic liver failure or RBC exchange alone or in combination with transfusions, heparin, 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 polyneuropitiformis, 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 tissues, myelitis sheaths, heart, kidneys and retina, leading to retinitis pigmen-tosa, peripheral dissociative polyneuropathy, cerebral ataxia, “sailors walk”, renal, cardiac and liver dysfunction 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].

Erythropoietic Protoporphyrin (EPP), Liver Disease
Erythropoietic protoporphyria 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, heparin, 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].
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 β₂-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 β₂-microglobulin adsorption column treatment to be at least partial 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. Dara-tumumab 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 qX28 region of the X-chromosome [139], possibly resulting in a defect of lipoxygen-C0A 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 cortices 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 glyceroltrioleate (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 glyceroltrioleate, (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 onset 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, fatigueability 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 ibritinib. 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 retinal 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 wet 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 choriodal 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 copper 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 antitiglobulin 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 enterohemoplastic 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 mainstay 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 1 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 Cu²⁺ ion [179].

Cutaneous T Cell Lymphoma (CTCL); Mycosis Fungoides: Sézary SyndromeMycosis 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 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

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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, paralyser and seizures, spasms, 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 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, chlorellacon, aluminium, tricyclic antidepressants, benzozidepine, 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 excretery 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...
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 intoxications 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


https://doi.org/10.1159/000517699.


impact of lipoprotein (a) levels and apolipoprotein (a) isoform size on risk of coronary heart disease. Journal of internal medicine, 276(3), 260-268.
Treatment of acute hepatic failure by extracorporeal methods and results in five patients with acute fulminant hepatic necrosis. Annals of internal medicine, 72(2), 165-174.


Fractionated plasma separation and adsorption system: a novel system for blood purification to remove albumin bound substances. Artificial organs, 23(1), 81-86.

Molecular absorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. Artificial organs, 23(4), 319-330.

Brain edema and intracranial hypertension in fulminant hepatic failure: pathophysiology and management. World journal of gastroenterology: WJG, 12(46), 7405.


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, 72(2), 165-174.

Variability of internal medicine, 72(2), 165-174.


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, 72(2), 165-174.


blood phlebotomy for the treatment of hereditary hemochromatosis. Blood Transfusion, 12(Suppl 1), s84.


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.org/10.18103/mro.01Oil0.3147.