Chapter 1

Therapeutic Apheresis in Blood Disorders

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First Published **January 18, 2017**

Blood Disorders

Abstract

Since the mid 1970s, membrane modules became available plasma separation techniques have gained in importance in the past few years. Therapeutic plasma exchange (TPE) with hollow fiber modules is used in different severe diseases since more than 38 years. The updated information and molecular biology of different hematologic diseases are discussed in relation for apheresis therapy and its place in combination with other modern treatments. The different hematologic diseases can be treated by various apheresis methods such as TPE with substitution solution or with online plasma or blood purification using adsorber columns which contain biological or non biological agents. The following diseases are discussed: hemolytic anemia, aplastic anemia, ABO incompatible diseases, thrombocytopenia, thrombocytosis, hyperleukocytosis, coagulopathy and others. Pathogenetical aspects are demonstrated in these diseases, in which they are clarified. Therapeutic apheresis (TA) has been shown to effectively remove the autoantibodies from blood and lead to rapid clinical improvement. In mild forms of autoimmune disease, treatment with immunosuppressive therapies and/or biologics agents seems to be sufficient. The prognosis of autoimmune diseases with varying organ manifestation has improved considerably in recent years, due to very aggressive therapy schemes. For the hematologic diseases which can be treated with TA the guidelines

of Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) are cited. The aim of the present review is to describe the solutions adopted to solve clinical and technical difficulties.

Keywords

Therapeutic Plasma Exchange; Immunoadsorption; Hemolytic Disease; Thrombocytopenia; Thrombocytosis; Hyperleukocytosis; Coagulopathy

Introduction

To cure a patient by removing his illness by extracting blood is a very old one. Many years ago, phlebotomy was practiced to cure illness. In 1914, Abel, Rowntree, and Turner studied the effect of plasma removal in dogs. They created the term plasmapheresis [1]. Only 18 years later, this new therapeutic of plasma removal would find further application in human medicine. This old process, placed on a rational basis with therapeutic plasma exchange, is being followed in clinical practice. Until the development of hollow fiber membranes, TPE was almost exclusively carried out by centrifugal technique [2].

Due to new therapeutic strategies, apheresis techniques have experienced a tremendous revival in recent years. Therapeutic Apheresis has been successfully used in various antibody-mediated diseases. More selective plasma separation methods can remove non-specific immunoglobulins from the patient's blood by new developed adsorbers [2]. Since the pathogenetic relevance of autoantibodies could be defined in various diseases, disease-specific adsorbers have been developed [3-5]. These adsorbers also remove selective, immune complexes, immunoglobulins, and other substances from the patient's blood.

Autoimmune diseases relate to diseases caused by antibodies acting against the body's own tissue. They are also referred to as auto aggressional diseases. Autoimmune diseases, with exception of rheumatoid arthritis and autoimmune thyreoid it is, are individually rare, but together they affect approximately 5 % of the population in western countries [6]. The cause of autoimmune reactions is still generally unknown.

Autoantibodies directly cause the destruction of the target cells in lysis. The cytotoxic antibodies react through complement activation with antigens of the cell surface and cause an intravascular lysis of erythrocytes through stages, (e.g., paroxymal hemoglobulin uremia) particularly in the cause of hematological diseases. In autoimmune hemolytic anemia for example, the affected erythrocytes can be opsonized by the antibodies. The process of binding of antibodies with complement participation changes the cells such that they are increasingly phagocytized, whereby the Fc-parts of the bound antibodies are recognized by the Fc-receptors of the phagocytizing cells

and by the cells of the RES in the liver and the spleen. The so-called immune clearance is the opsonization process, a physiologically effective way of removing intruding cells through immune bodies [2,7].

Antibodies are transport via efferent lymphatics into the venous and circulate with the blood through the body and can be detected in all tissues and can be directed against many non-hematogenous tissues.. Antibodies of the IgG class can transverse blood vessels wall and enter extravascular tissue spaces [2].

Antibody occupation of cells or tissue structures does not necessarily mean that damage occurs. This only happens when mediators are involved. Autoantibodies can have a serious effect on an organ even without the activation of the complement system, especially when either functionally important receptors are blocked by antibodies or else important proteins are rendered inactive through the combination with antibodies, such as hormones or enzymes. Myasthenia gravis is a classic example of a receptor blockade.

TPE is indicated in the management of various hematological diseases. The authors give an overview of the most important pathogenetic aspects indicating that TA can be a support therapy in hematologic disorders.

Methods

During the mid-1970s, the TPE with membrane modules became available. The advantages of this method are a complete separation of the corpuscular components from the plasma and due to increased blood flow rate higher efficacy. Furthermore cell damage especially to thrombocytes – occurs less using membranes than centrifuge for cell separation [2]. The TPE equipment currently available is, however, not yet perfect, because the filtered plasma fraction have to be discarded. Substitution solutions, electrolyte solutions supplemented with human albumin, human serum protein solutions, or fresh frozen plasma are used to replace the discarded fractions.

The physicians who have chosen the TA method must be knowledgeable concerning the half-life time, the compartment distribution of pathogenic plasma proteins, and the elimination of other toxic substances and complement components. TA with hollow fiber moduls is the most used therapy method in nephrology. Nephrologists have an extensive training in the management of blood purification treatments including vascular access, anticoagulation, volume management and prescription for solute clearance [8]. The renal indications for TPE expand the clinical practice of nephrologists [9].

TA methods, such as TPE, and semi- or selective plasma exchange methods, such as selective adsorbers, or IA,

were discussed by Bambauer et al. [10]. Erythro-, leuko-, and thrombocytapheresis are therapeutic procedures in which the different blood cells are removed from the patient's blood. Adsorptive cytapheresis mentioned in previous studies is a therapeutic procedure in which blood from the patient is passed through a medical device that contains a column or filter that selectively adsorbs activated monocytes and granulocytes and the remaining part of the blood is returned to the patient [11,12]. Extracorporeal photopheresis (ECP) is a procedure in which buffy coat separated from patient´s blood, is treated extracorporeally with a photoactive compound (e.g., psolens) and exposed to ultraviolet A light and subsequently reinfused to the patient during the same treatment [11,12]. The diseases for which the use of TA is discussed and the guidelines on the use of TA provided by the Apheresis Applications Committee of the American Society for Apheresis have been discussed in previous studies [11-13].

TA is indicated in the management of various hematological diseases. For most of these diseases, clear pathogenetic mechanisms of the diseases, are understood, and there are well-defined criteria with regard to the therapy [7]. Most medical management of immunohematological disorders requires the use of TA, serological immunomodulation, and classical pharmacological immunosuppression with steroids, cytotoxic agents, and antimetabolites,

where overall therapy is individually tailored to the needs of the patient. Controlled trials are difficult if not impossible because of variables such as severity of diseases, degree of organ system damage before intervention, age and the existence of co-morbid conditions. In some rare hematological diseases, it is impossible to recruit a large number of cases to perform a controlled clinical trial. Therefore, for most of theses diseases only small series of cases are available for analysis.

TPE, semi-selective cascade filtration or IA aimed at the causative antibodies can be used in diseases caused by antibodies or immune complexes. Adjuvant drug therapies are different for different diseases and are typically individualized in type, dose and duration of use. The TA method chosen depends on the pathophysiological origin of a given disease. The physician who has chosen the TA method must be knowledgeable concerning the half-life time, the compartmental distribution of pathogenic plasma proteins, and the elimination of other toxic substances and complement components. Table 1 shows a selection of hematolgical and hemostasiological diseases in which TA has been implemented [2,11-13].

Table 1: Selection of hematological and hemostaiological diseases, in which TPE has been implemented (modified after 2, 11-13):

ABO incompatibility, hematopoietic progenitor cell transplantation
Aplastic anemia, pure red cell aplasia
Autoimmune hemolytic anemia (AIHA)
Babesios
Coagulation factor inhibitors (CFI)
Disseminated intravascular coagulation (DIC)
Erythrocytosis, polycythemia vera
Evan´s syndrome (ES)
Graft-versus-host disease
Hemolytic disease in newborn (HDN)
Hemophilia A
Heaprin-induced thrombocytopenia
Hyperviscosity syndrome (different diseases)
Hyperleukocytosis
Immune thrombocytopenic purpura (ITP)
Malaria
Post transfusion purpura
Red cell aloimmunization
Schönlein-Henoch purpura
Sicle cell disease
Thrombocytopenia + thrombosis, Herpatin-induced
Thrombocytosis
Thrombotic thromobocytopenic purpura

Hemolytic Disease in Newborns (HDN), Rhesus Disease

Rh disease or incompatibility during pregnancy is an indication for TPE as a supportive therapy [12]. Although it has been common practice for years to carry out anti-D gamma globulin phrophylaxis in Rh-negative women after birth of an Rh-positive child, increased anti-D antibodies still occur in up to 3 % of subsequent pregnancies. This can lead to life-threatening morbus hemolyticus neonatorum for the fetus. Newborn babies rapidly develop anemia and hyperbilirubinemia with kernikterus. Exchange transfusion is the therapy of choice. Recently, TA has also become possible [14]. The diagnosis can be quickly made through the detection of anti-D antibodies in the mother and examination of the amniotic fluid for bilirubin and anti-D antibodies. Intrauterine exchange transfusions can be life saving procedure but involve a high risk. The earlier Rh incompatibility manifests itself in pregnancy, the poorer the prognosis. If it occurs prior to the 26th week of pregnancy, more than 93 % of fetuses die by the 32st week. If after the 26th week the Rh incompatibility manifests itself, and the mother receives TPE treatment, and the child receives intrauterine or postpartal exchange transfusion, 71 % of these children can survive whereas without treatment most die [2].

Hemolytic anemia in newborns presents as icterus neonatorum or hydrops fetalis. Both are caused by allo-

immunization against RhD-positive red blood cells of a RhD-negative mother bearing a RhD positive fetus. Alloimmunization of the mother occurs after fetomaternal hemorrhage during first pregnancy. The anti-RhD antibodies, which all belong to IgG subclasses, are able to transverse the placental barrier into the fetal circulation. The antibodies destroy fetal red blood cells by non-complement-dependant mechanism [2]. Hemolytic anemia in newborns usually occurs during the second pregnancy with an RhD-positive fetus. Intravascular fetal transfusion with RhD-negative erythrocytes compatible with the mother´s serum indicated in severe fetal hemolysis in a sensitised mother. After birth the newborn may receive a phototherapy and/or a neonatal exchange transfusion, or TPE, depending on the severity of hemolysis disease in newborns (HDN) [15].

The widespread use of fetal intravascular transfusion and the advent of IVIg therapy have now reduced the former significance of this disease. Towards the beginning of the second trimester in women who have developed hydrops fetalis before the 22nd week of a previous pregnancy combined with IVIg. TA can be administered [2]. TPE with human albumin-electrolyte solution (HAE) may bridge the gap between the onset of severe fetal anemia and the feasibility of fetal transfusion. To save the fetus for alloimmunization against other red cell antigens, which makes fetal intra-vascular transfusion impossible, maternal TA may be the only therapeutic option. Filbey et al. reported

in 1995 of 707 infants born to 538 alloimmunized women in Sweden [15]. Maternal TPE was performed in 2.4 % of the cases with a response rate of 100 %. TPE is recommended, therefore, only in severe HDN in the early stage of pregnancy before fetal transfusion is possible. TPE has been successfully performed thousands of times in recent years for Rhesus incompatibility. The physician must be aware that anti-D antibodies can also increase with TPE.

In 2006 Bing et al. reported successfully treating 44 pregnant women with Rh incompatibility using a combination of anti-D immunoglobulin and TPE, and intrauterine transfusion. The effects gained from the therapy lasted for approximately 6 weeks for the patients. The study demonstrated that systematic management (including routine test for the presence or absence of D antigen in pregnant women, series test and of anti-D antibody titer and ultrasonography, amniocentesis and cordocentesis) and timely treatment (including anti-D immunoglobulin, TPE, intrauterine transfusion, and delivery) can improve the perinatal outcomes of Rh-negative women [16].

The AAC of the ASFA has given HDN category III with recommendation grade (RG) 2C (Table 2) [11,12]. The rationale for TA is that TPE removes the maternal red cell alloantibodies that responsible for HDN [12]. TPE can decrease the maternal antibody titer and, in turn, the amount transferred to the fetus, thereby protecting it from HDN. Survival in severe cases of HDN with the use of

TPE and/or IVIg prior to ultrasound tomography (IUT) is about 70 %. Category III for TPE is assigned for patients when there is a previous history of a severely affected pregnancy and the fetus is than 20 weeks gestational age [12]. Typically, IUT can be performed after the fetus reaches 20 weeks of gestation.

TPE can safely be performed during pregnancy. During pregnancy, blood volume and especially the plasma volume increases. In the second or third trimester, it is preferable to place the patient on her left side to avoid compression of the inferior vena cava by the gravid uterus. Hypotension should be avoided as it may result in decreased perfusion to the fetus [2]. TPE should be considered early in pregnancy (from the 7th to 20th week) and continued until IUT can safely be administered (about 20th week of gestation). Close monitoring of the fetus for signs of hydrops will aid in guiding treatment. If the fetus is known to be at high risk for hydrops fatalism a more aggressive approach during early pregnancy is warranted. One approach is than to use TPE for the first week (3 procedures) followed by IVIg at 1 g/kg weekly [12,17]. The incidence in the United States is 100/100.000 newborns [16].

Table 2: Therapeutic apheresis in erythrocyte diseases (modified after 7, 12, 13).

Apheresis Application Committee of the ASFA, 2013, 2016 (12,13)						
Disease	**TA modality**	**Category**	**Recommendation grade**	**Treated Volume (TPV)**	**Replacement Solution**	**Frequency**
Rhesus incompatibility	TPE	III	2C	1-1.5	Human-albumin-electrolyte (HAE)	daily or 1-3/week
Red cell Alloimmunization in pregnancy	TPE	III	2C			
Autoimmune hemolytic anemia	TPE					
-warm AIHA		III	2C	1-1.5		
-cold AIHA		II	2C			
Sicle cell anemia						
-primary, prophylaxis	RBC exchange	I	1A	to achieve Hb S level 1-2 TBV	RBC* units	daily, or every other day, Series weekly
-multi-organ failure		III	2C			
Babesios		II	2C			
Aplastic anemia	TPE	III	2C	1-1.5	HAE	
Pure red cell aplasia	TPE	III	2 C			
HPC TX, ABO incompatible	TPE, RBC exchange	II III	1B-2B 2C			
HPC TX, HLA desensitization	TPE	III	2C	---	Group O RBCs	1 treatment
Graft-versus-host-disease						
-skin (acute)	ECP	II	1B-1C	200-270 ml	HAE	daily, series weekly
-skin (chronic)		II	1B			
non skin (acute/ chronic)	TPE	II	1B-1C			
Polycythemia vera	Erythrocyt-apheresis	I	1B	TBV		one or more
Erythrocytosis						
-secondary		III	1C			

TPV: Total Plasma Volume, TBV: Total Blood Volume, RBV: Red Blood Volume, ECP: Extracorporeal Photopheresis, * Hb S negative leuko-reduced RBCs, (category I: accepted for TA as first-line therapy; Category II accepted for TA as second-line therapy; Category III: not accepted for TA, decision should be individualized: Category IV: not accepted for TA, Institutional Review Board (IRB) approval is desirable if TA if TA is under taken [12,13].

Autoimmune Hemolytic Anemia (AIHA)

The etiologies of hemolysis often are categorized as acquired or hereditary. Most acquired causes of hemolytic anemia are autoimmunity, microangiopathy, and infections. Immune-mediated hemolysis, caused by anti-erythrocyte antibodies, can be secondary to malignancies, autoimmune disorders, drugs and transfusion reactions. When the red cell membrane is damaged in circulation a microangiopathic hemolytic anemia is the consequence, leading to intravascular hemolysis and the appearance of shistocytes. Infectious agents such as malaria and babesios invade red blood cells [7].

The severity of hemolytic anemia is quite variable. Depening on the cause it can be mild and compensated for by increased erythropoiesis. The treatment for mild forms and forms of such severity as to decreased cell mass is directed at correction of the underlying cause. For example, proper antibodies and supportive care for infections, surgical debridement and antibodies for Clostridium welchii, and stopping the offending drugs in the case of G6PD deficiency. In severe hemolytic anemia, with hemoglobinuria regardless of wether it is mediated by exogenous or endogenous noxae, timely implementation of TPE appears justified [2].

Autoimmune hemolytic diseases are characterized by reduced erythrocyte in vivo survival time and by the presence of warm or could agglutinizing antibodies against the autologous erythrocytes. Differentiation between the following antibodies is made on the basis of their serological features [17,18].

- **Thermo-type:** Warm agglutination autoantibodies. These autoantibodies consist mostly of IgG and its various subclasses. Optimum antibody binding activities is reached at body temperature (37°C).

- **Cryo-type:** Cold agglutination autoantibodies. These belong to the group of IgM antibodies and display their strongest reaction to antigen-bearing cells at low temperatures (0-10°C). They become of clinical importance when a temperature of 20°C or more is reached.

- **Bithermal autoantibodies:** These belong to the IgG antibodies. Contrary to thermo-type, antibodies bind at low temperature (0-10°C) and hemolyse erythrocytes at body temperature (37°C) [2].

Autoimmune hemolytic anemia is diagnosed by direct microscopic evaluation of the peripheral blood film, hyperbilirubinemia, reticulocytosis, positive direct Coomb´s test, and elevated serum LDH [18]. Immune hemolytic anemia is a result of antibody fixation to a red cell antigen. This autoantibody triggers either intravascular red cell destruction mediated by the terminal lytic complement complex (C5b-C9) or extravascular destruction mediated by macrophage-phagocytic system [19]. Both mechanisms require opsonization by antibodies or

C3b complement [20]. The antibodies mostly belong to the IgM (cryo-type abs) and IgG groups, or occasionally also to the IgA (thermo-type abs). The reason for the formation of the autoantibodies is still unknown.

When warm autoantibodies attach to red blood cell surface antigens, theses IgG-coated red blood cells are partially ingested by the macrophages of the spleen, leaving macropherocytes, the characteristic cells of AIHA. Cold autoantibodies (IgM) temporarily bind to the red blood cell membrane, can activate complement, and deposit complement factor C3 on the cell surface. The macrophages of the liver (extra-vascular hemolysis) slowly clear these C3-coated red blood cells [18].

Although most cases of autoimmune hemolysis are idiopathic, potential causes should always be sought. Lymphoproliferative disorders (e.g., chronic lymphocyte leukemia, non Hodgkin´s lymphoma) may produce warm or cold autoantibodies. A number of commonly prescribed drugs can induce production of both types of antibodies. Warm AIHA (WAIHA) also associated with autoimmune disease (e.g., systemic lupus erythematosus), while cold AIHA (CAIHA) may occur following infections, particularly infectious mononucleosis and *Mycoplasma pneumoniae* infection. Human immunodeficiency virus infection can include both warm and cold AIHA [16,18]. Along with conventional therapy with corticosteroids and cytostatics or even splenectomy. TA is increasingly being implemented with success [21]. The observed symptoms include fatigue and jaundice. The laboratory findings are the signs of hemolysis such as anemia, hyperbilirubinemia, elevated serum LDH, reticulocytosis, as well as a positive direct Coombs test [12].

The AAC of the ASFA has given autoimmune hemolytic anemia category III with RG 2C for the WAIHA and for the CAIHA category II with RG 2C (Table 2) [12,13]. Antibody removal by TPE is also effective here. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction [21]. TPE can remove effectively pathogenic immune complexes, activated complements, and autoantibodies [12]. The duration of the TPE treatment is until the hemolysis is controlled and the need for transfusions is limited. More and more new substances such as rituximab, everolimus, sirolimus are introduced in the therapy of AIHA in combination with steroids or TPE [22,23].

Other hemolytic anemia diseases such as sickle cell anemia (SCD) and Babesios have also been treated with TA, especially with erythrocytapheresis.

Sickle cell anemia is an inherited disorder caused by a point mutation leading to a substitution of valine for glutamic acid in the sixth position of the ß-chain of hemoglobin. Membrane abnormalities from sickling and oxidative damage caused by hemoglobin S, along with impaired

deformability of sickle cell, leads to splenic trapping and removal cells. Some degree of intravascular hemolysis occurs as well. Hemoglobin electropheresis reveals a predominance of hemoglobin S. Sickle cells are observed on the peripheral smear [11].

Variants of SCD include Hb SC, Hb Sß-thalassemia, Hb SD etc. Morbidity and mortality are significantly higher in Hb SS than in SCD variants [11]. Hb S polymerises upon deoxygenation, causing red blood cells to become rigid and deformed (sickled RBCs). Sickled RCBs have a shortened lifespan, producing hemolytic anemia and occluding the microvasculature leading to tissue hypoxia and infarction. Major manifestations are vaso-occlusive events (VOE), splenic sequestration, and transient red cell aplasia (TRCA). Among VOE, painful episodes are the most common. Other serious VOE include acute chest syndrome (AVS), stroke, priapism, and splenic hepatic and renal dysfunction. Leading causes of death are sepsis, ACS, stroke, and acute multiorgan failure. Infection is the most common cause of death in children, primarily due to auto splenectomy. Overall mortality rate for SCD is 2.6 percent (0.5 death/100 person years) with the peak at 1-3 years of age. Median ages of death in males and females with Hb SS in the mid 1990s were 42 and 48 years old, respectively [11].

Standard therapies include penicillin prohylaxis, folic acid, pneumococcal and *Haemophilus influenzae* vaccinations, analgesis for painful episodes, and antibodies for

infections. Hydroxyurea may be used to reduce frequency of severe pain and ACS. RBC transfusion (TX) can be primary or a first-line adjunct therapy. Methods include simple RBC TX or RBC exchange TX (EX-TX).

In severe anemia, single RBC-TX is the best transfusion method to improve oxygen-carrying capacity of blood by increasing RBC mass [11]. In acute ischemic stroke, ACS, or acute life- organ-threatening complications, erythrocytapheresis is preferred over single RBC-TX since the Hb S concentration is reduced rapidly by removing and relapsing sickled RBCs with normal RBCs without increasing blood viscosity and volume overload. Long-term erythrocytapheresis has the distinctive advantage of preventing or markedly reducing transfusions associated iron accumulation, but is associated higher (1.5 – 3 times higher) blood requirements than single RBC-TX. Increased blood exposure can potentially increase rates of viral transmission and RBC alloimmunization. Strategies to reduce the risk of alloimmunization include the use of pheno-typically-matched RBC [11].

In the guidelines of the AAC of the ASFA, the sickle cell disease has the category I with RG 1A for life organ threatening complications with the RG 1A for primary and secondary stroke prohylaxis and for prevention of transfusion iron load for erythrocytapheresis. For multiorgan failure, there is the category III with RG 2C for RBC exchange (Table 2) [11,12].

The treated volume using the Cobe Spectra is 1 – 2 total RBC volume, the replacement fluid is Hb S negative leuko-reduced RBCs, and, if available, antigen matched for E, C, and Kell. The frequency in acute situations at required intervals to maitain the desired Hb S level < 30 – 50 percent [12].

Babesios is a protozal disease transmitted from an animal reservoir to humans by the bites of hard ticks, or, more rarely, by transfusion. Ixodes dammini, the deer tick, is usually responsible for transmission of the disease from animal reservoirs to human hosts. Three out of 70 species (*B. bovis, B. divergens*, and *B. microti*) have been positively implicated in causing infection and diseases. In the U.S., *B. microti* appears to be the predominant human pathogen [12].

The incubation period is usually 1 – 3 weeks, with longer incubation period (6 – 9 weeks) reported with transfusion transmission. In clinical apparent cases, symptoms are usually non-specific. However immunocompromised patients, especially asplenic patients, patients with HIV, simultaneous infection with lyme disease, and elderly patients may have much more serious clinical course. In these patients, symptoms may include hemolytic anemia, AKI, DIC, congestive heart failure, and pulmonary disease. Specific diagnosis is made through examination of a Giemsa-stained blood smear, DNA amplication using polymerase chain reaction, or detection of specific

antibody [12]. Primary therapy includes a combination of antibiotics, most quinine sulfate and clindamycin.

In the guidelines of the AAC of the ASFA the babesios has the category II with the RG 2C in severe cases for erythrocytapheresis and in high risk patients (Table 2) [12,13]. After the AAC is the mechanism of action of exchange transfusion twofold. First, it helps to lower the level of parasitemia by physically removing the infected RBC from the blood stream and replacing them with non-infected RBC [12]. Because babesios organism do not have an exo-erythrocyte phase, removal of RBC associated parasites is potentially curative. Second, the hemolytic process produces vasoactive compounds, including a variety of cytokines (including TNF-α, IL-6, IL-10) and thromboplastin, which can promote renal failure and DIC. RBC exchange may help to curtail the production of these substances. The greatest advantage of RBC exchange over antibiotic therapy is it rapid therapeutic effectiveness.

The specific level to which parasitemia must be reduced to elicit the maximum therapeutic effect is not clear. Treatment is usually discontinued after achieving < 5 percent residual parasitemia. Decision to repeat the exchange depends on the level of parasitemia post exchange as well as the clinical condition [12,13].

Aplastic Anemia (AA)

Aplastic anemia and pure red cell aplasia (PRCA) are rare. AA is defined by pancytopenia/ reticulocytopenia

and a hepatocellular bone marrow in absences of neoplastic hematopoiesis. Until now only some case reports of AA, which have been treated with TPE, have been published. The pathogenesis of aplastic anemia is regarded as complex and mostly unclear. In some cases, hemopoietic and erythropoietic inhibitors have been found in serum, leading to it being considered an autoimmune disease [2]. In these patients it was possible to remove the circulating inhibitors by TPE. TPE is only indicated in the case of proven autoimmune pathogenesis. Successful therapy has also been conducted in recent years with cyclosporin A. The AAC of ASFA has given aplastic anemia and pure red cell aplasia category III with RG 2 C (Table 2) [12,17,24].

Allogenic hematopoietic progenitor cell (HPC) transplant is the treatment of choice for severe AA in newly diagnosed patients < 40 years old. Young patients with mild diseases or without a matched donor and older patients are treated with antilymphocyte globulin (ATG), cyclosporin A and/or rituximab [25,26]. Immunosuppressive therapy is usually sufficient until remission is obtained in primary acquired PRCA. Corticosteroids (prednisone at 1 mg/kg per day) are used first. Alternative treatment is required if no response is achieved after 2 – 3 months. Salvage agents include cyclophosphamide, azathioprine, cyclosporine, ATG, and high dose IVIg [27]. In diseases that may be immunologically mediated, TPE may be helpful by removing serum antibody and/or inhibitory activity.

ABO Incompatible Hematopoietic Progenitor Cell Transplantation

The presence of natural antibodies in the recipient against the donor´s ABO blood group, which may cause hemolysis of red cells present in the transplanted product, is the requirement of the major incompatibility [11]. In peripheral hematopoietic progenitor cells that are collected by apheresis, there is a lower risk of hemolysis due to reduced red cell contamination (2 – 5 %) as compared to HPCs derived from the bone marrow. To prevent an acute hemolytic reaction either the product needs to be red cell reduced or the patient´s antibody titer needs to be lowered. If the recipient has a high titer of antibodies, especially a group O patient receiving a group A transplant, a delayed erythroid engraftment or even pure red cell aplasia may result [12].

The AAC of the ASFA has given category II with RG 1 B – 2 B for TPE in ABO incompatible hematopoietic progenitor cell transplantation (HPC TX) and bone marrow transplants (Table 2) [12,13]. TPE can reduce ABO antibodies , which are responsible for hemolysis and PRCA. In most of the ABO incompatibility, removal of the high titer antibody from the recipient´s circulation can prevent hemolysis if red cells are unable to deplete the product.

In minor incompatibility with passenger lymphocytes making antibodies 7 – 12 days after infusions, prohylactic red cell exchange with group O red cell be performed to

deplete recipient type red cells [12,13]. If unable to red cell deplete the HPC product, TPE should be performed before infusion of HPCs and the replacement fluid is a combination of albumin and plasma (50:50) compatible with both donor and recipient [12]. Before HPC TX, the goal should be to reduce the IgM or IgG antibody titers to ≤ 1:16 immediately. Generally, 2 – 4 TPEs are sufficient and if the antibody titer is high in the case of delayed red cell recovery or PRCA, TPE may be performed in the transplantation period [12]. The HPC TX, HLA desensitisation has got the category III RG 2 C from the AAC of the ASFA [13]. HLA antibodies positive patients receive 4 – 5 treatments and complement-dependent cytotoxic crossmatch positive patients receive additional treatments.

Graft-Versus-Host Disease (GVHD)

The graft-versus-host diseases has category II with 1 B-1 C for acute or chronic skin, and II with 1 B – 1 C for acute or chronic non-skin for extracorporeal photopheresis (ECP) after the AAC [12,13] (Table 2). GVHD following allogenic cell transplantation (HPCT) is typically characterized as either acute (aGVHD) or chronic (cGVHD) [12]. Acute GVHD usually occurs within 3 months after allogenic stem cell transplantation and results from activation of donor T cells by host antigen-presenting cells, leading to immune and cytokine-mediated tissue injury. The skin, gastrointestinal tract, and liver are major targets of aGVHD. Chronic GVHD often evolves from

aGVHD and is mediated by donor allo- or autoreactive T cells that activate inflammatory cytokines, B cells, autoantibody production, and cytolytic process. End-organ complications of cGVHD include progressive fibrosis and/or dysfunction of the skin, eyes, lungs, gastrointestinal tract (GI), joints, and vagina [12,13]. Acute GVHD of grades II to IV severity is first treated with a calcineurin inhibitor and systemic corticosteroids. Treatment options include local/topical measures for the skin, eyes, mouth, and gastrointestinal tract along with systemic therapies such as calcineurin inhibitors, ATG, mycophenolate mofetil, rapamycin, thalidomide, hydroxychloroquine, sirolimus, pentostasin monoclonal antibodies against T cells, B cells or cytokines, and ECP [12].

The rational of extracorporeal photopheresis involves the collection of peripheral blood leukocytes by apheresis, the extracorporeal exposure of the leukocytes to 8-methoxypsoralen (8-MOP) followed by irradition with ultraviolet A (UVA) light, and the reinfusion of the photactivated cells [12].

The therapeutic effect of ECP for GVHD appears to involve induction of apotosis in treated lymphocytes, modulation of monocytes-derived dendritic cell (DC) differentiation, increased production of anti-inflammatory cytokines by monocytes and T cells, decreased DC antigen-presenting function, restoration of normal T helper cell and DC subsets and induction of regulatory T cells

that establish immune tolerance. For cGVHD, ECP improves skin or oral manifestations in 60-80 percents of steroid-dependant patients. Liver or GI complications respond in roughly 35-75 percents of cases, with the highest rates reported in children. Most responses with cGVHD are partial [12,13].

The treated volume is a mononuclear cell (MNC) product of approximately 270 ml consisting of mononuclear cells, plasma and saline [2]. The two-process method collects and treats MNC obtained from two times TPV processing. The replacement fluid is that all photoactivated leukocytes are reinfused with albumin and saline.

Erythrocytosis and Polycythemia Vera (PoV)

Erythrocytosis results from an increase in the red cell mass with concomitant increase in RBC number, red cell count, and hematocrit [28]. This finding may be generally attributed to hemoconcentration given the many cases of dehydration, hypovolemia and other relative low-volume states encountered in the emergency department.

The incidence of PoV is about 2.6 cases per 100.000 [29]. PoV is associated with a point mutation of an autoinhibitory Janus kinase 2 (JAK2) protein kinase domain [30] the activation on this domain results in erythropoiesis losing its dependence on erythropoietin signalling and becoming virually autonomous [31].

Hematopoiesis existes in a hemostatic balance between the body´s requirements for particular blood cell lines and loss or destruction of those cells. In the red cell line this balance is maintained by a feedback mechanism primarily involving the hormone erythropoietin [29]. Erythropoietin is primarily produced in the renal cortex, accounting for 90 percent of this circulating protein. Secondary sites of production consist of liver, spleen, lung, testis, brain, and erythroprogenitor cells. Erytropoietin stimulation results in the production of 2×10^{11} red blood cells per day [32]. All blood cell lines arise from a common hematopoietic stem cell. These stem cells begin their initial differentiation onto erythrocyte progenitors when stimulating by one of several cytokine factors [33]. A relative erythrocytosis occurs in cases of dehydration and low volume due to hemoconcentration. Correction in these cases can be accomplished by volume replacement and the condition may be short-lived.

In the guideline of the AAC of the ASFA the erythrocytosis and the polycythemia vera has the category I and the RG 1 B for erythrocytapheresis. Secondary erythrocytosis has the category III and the RG 1C (Table 2). Absolute erythrocytosis is defined as a red cell mass of at least 25 percent above the gender-specific mean predicted value [12]. Hct values > 60 percent for males and > 56 percent for female are always indicate of absolute erythrocytosis, as these levels cannot be achieved with plasma volume concentration alone or other causes of “apparent”

or "relative" erythrocytosis. Primary erythrocytosis refers to the myeloproliferative disorder polycythemia vera, in which an abnormal hematopoietic stem cell alone autonomously overproduces red cells. Additional features of PoV include splenomegaliy, granulocytosis, thrombocytosis and a point mutation in the tyrosine kinase JAK2 gene.

Secondary erythrocytosis refers to isolated red cell overproduction due to a congenital erythropoietic or hemoglobin defect, chronic hypoxemia related to a respiratory or cardiac disorder, etopic erythropoietin (Epo) production (e.g., from renal cell carcinoma, uterine leiomyoma), or Epo augmentation (e.g., post-renal transplantation). Idiopathic erythrocytosis refers to erythrocytosis in the absence of a primary disorder or features of PoV. Whole blood viscosity increases significantly as the Hct level exceeds 50 percent. Patients with PoV may experience hyperviscosity-related symptoms with modestly elevated Hct, whereas patients with secondary erythrocytosis are usually asymptomatic until Hct levels exceed 55 – 60 percent. Roughly 15 – 40 percent of patients with PoV develop arterial or venous thrombosis. Thrombotic risk factors with PoV include uncontrolled erythrocytosis, age > 60 years, history of prior thrombosis, cardiovascular comorbidities, immobilization, pregnancy and surgery. PoV may also induce microvascular ischemia of the digits or in the central nervous system (12).

The rationale for TA is the red cell reduction by automated centrifuge apheresis, like isovolemic phlebotomy,

corrects hyperviscosity by lowering the hematocrit, which reduces capillary shear rates, increases microcirculatory flow and improves tissue perfusion. For PoV patients with acute thromboembolism, severe microvascular complications or bleeding, therapeutic erythrocytapheresis may be useful alternative to emergent large-volume phlebotomy; particularly if the patient is hemodynamically unstable. Erythrocytapheresis may be appropiate prior to surgery the high risk of peri-operative thrombohemorrhagic complications in a PoV patient with uncontrolled Hct. With secondary erythrocytosis and symptomatic hyperviscosity or thrombosis, red cell reduction by apheresis may, selected cases, be a safer and more effective approach than simple phlebotomy [13].

The treated volume is the volume of blood, which is removed based on the total blood volume, the starting Hct and the desired post-procedure. Hct. The replacement fluid is an albumin-electrolyte solution and the frequency is one procedure. In patients with PoV, the goal is normalization of the Hct (i.e., < 45 percent). For secondary erythrocytosis, the goal is to relieve symptoms but retain a residual red cell mass is optimal for tissue perfusion and oxygen delivery. A post-procedure Hct of 50 – 52 percent may might be adequate for pulmonary hypoxia or high affinity hemoglobins, whereas Hct values 55 – 60 percent might be optimal for patients with cyanotic congenital heart disease. A single procedure should be designed to achieve the desired post-procedure Hct [13].

Idiopathic Thrombocytopenic Purpura (ITP)

Thrombocytopenia is an inherited or acquired disease that results in a reduction of circulating thrombocytes. This condition may be asymptomatic or manifests itself in hemorrhagic diathesis with petechial bleeding. The immune thrombocytopenias are a heterogenous group of bleeding disorders with similar hemostatic manifestations but different pathogenic etiologies. ITP caused by autoantibodies which, in severely progressing cases, are accompanied by hemorrhagic diathesis. ITP is the most common autoimmune hematologic disorder. The etiology is still for the most part unknown. The spleen plays an important role, since it not only produces a large part of the antibodies directed against thrombocytes, but also breaks down the damaged thrombocytes. As the antibodies can pass through the placenta barrier, the fetus can also be affected [34]. In more than 60 percent of the patients, part or full remission can be reached with steroid therapy . Splenectomy and cytostatics are further therapeutic measures. In recent years, in addition to being treated with TPE, therapy-resistant, acute and chronic cases have also been successfully treated with high doses of intravenous immunoglobulin of 400 mg/kg BW/day. The pathophysiological mechanism in ITP is the binding of auto- or alloantibodies to platelet antigens. Fixed antibodies may trigger complement activation [35]. The promised platelets are

destroyed by phagocytosis in the macrophage-phagocytic system mediated by the Fc receptors FcyRI-III and complement receptors CR1 And, CR3. Platelet destruction occurs mainly in the spleen (and accessory spleen), but also in liver and bone marrow. The spleen is a major site of antiplatelet antibody production; therefore, splenectomy is therapeutically very effective. The main antigenic determinants are the platelet membrane glycoproteins GP-Iib/IIIa and Ib/IX [36].

A further mechanism leading to platelet destruction in drug-induced immune thrombocytopenic purpura is the formation of antibodies against neoantigens expressed after adherence of the drug to the RBC membrane [37]. Recently, acquired autoimmune deficiency of a plasma metalloprotease named ADAMTSJB was shown in many cases of ITP [38]. Alloimmunization is the cause of neonatal autoimmune htrombocytopenia, platelet transfusion refractoriness, and post-transplant purpura. The alloantigens are classified on the human platelet antigen (HPA) system [39]. Neonatal immune thrombocytopenia is the platelet counterpart of hemolytic disease in newborns. A HPA-1a-negative mother is sensitised to HPA-1-positive platelets of the fetus. Alloimunization (IgG ab > IgM ab) against platelets induced by fetomaternal hemorrhage occurs during a HPA-incompatible pregnancy or after a HPA-incompatible platelet transfusion. In heparin-induced thrombocytopenia, type II immune complexes consisting of antibodies to heparin and platelet Factor 4

activate platelets after binding to platelet Fc receceptors. Excess platelet Factor 4 binds to endothelial glucosaminoglycan, resulting in endothelial damage and thrombi [37]. Heparin-induced thrombocytopenia type 1 refers to non-immunogenic thrombocytopenia due to heparin-induced aggregation of platelets.

Acute abrupt onset ITP is seen in childhood, and often follows a viral illness or immunization. The majority of children require no treatment and in 80 – 85 percent of cases the disorder resolves within 6 months. Some 15 – 20 percent of children develop a chronic form of ITP, which, in some cases, resembles the more typical adult. Chronic ITP in childhood has an estimated incidence of 0.46 per 100.000 children per year and prevalence of 4.6 per 100.000 children at any one time [40]. This form of ITP affects mainly women of childhood age (female: male: 3:1). Childhood ITP has an incidence of between 4.0 and 5.3 per 100.000 [35].

The diagnosis of ITP based principally on blood count, clinical symptoms, autoimmune profile and other investigation, and on the exclusion of other causes of thrombocytopenia using the history, physical examination. Further investigations are not indicated, blood count and film are typical of the diagnosis of ITP and do not include unusual features that are uncommon in ITP [40]. Platelet associated IgG (PAIg) is elevated in both immune and non-immune thrombocytopenia and therefore has no role in the diagnosis of uncomplicated ITP. In patients

refractory to therapy although some patients have shown improvement in platelet counts following eradication therapy, it is worth determining the presence of H. pylori [40]. The first-line therapy comprises oral corticosteroids and intravenous immunoglobulins.

The successful use of high doses of IgG and anti-D therapy has reduced TA second-line or third-line treatment in these cases [41]. The second-line therapy is splenectomy and high dose corticosteroids, high dose IVIg, intravenous anti-D, cyclosporin A and dapsone. Patients who failed the first- and second-line therapies must be treated with interferon-α (IFNα), rituximab, campath-1H, mycophenolate mofetil and TA [34]. TA can include remissions in approximately 80 percent of patients with ITP. TA becomes a legitimise option for maintenance therapy in chronic ITP patients, if the application of IgG is not possible due to allergic reactions, Rh-negative status, or splenectomy.

The most important part of TA is to remove antiplatelet antibodies to prevent bleeding by keeping the platelet count above a critical level. The goal of therapy is to obtain sustained remission with a minimum platelet count of over 50.000 platelets/μL. The measurements of antiplatelet autoantibodies is a useful test for determining whether TA is indicated and if so, to assess its efficacy. As some severely progressing cases of ITP do not respond to steroids and/or high doses of immunoglobulin, immunosuppressive drugs, TPE are indicated [40].

As there are only a few controlled studies yet available, it is not possible to reliably conclude which form of therapy should be given preference. Thus, in ITP, initial treatment should consist of high doses of IgG, and immunosuppressive drugs as mentioned above. Should no significant improvement be observed within one or two weeks (thrombocytes > 80.000/µL), then TA treatment should be commenced immediately. The authors recommend TPE with 1 to 1.5 plasma volumes a day for 4 days. Treatment with two to four sections of TPE per month can also have a positive effect in chronic cases. TPE is recommended prior to surgery in acute respectively chronic uncontrollable bleeding [2]. IA with Protein-A was also induced successfully in the treatment of ITP.

In the AAC of the ASFA, ITP has the category III and the RG 2C for TPE and IA in refractory cases [12,13] (Table 3). First-line therapies are oral corticosteroids, IVIg (1-2mg of prednisone/kg per day, IVIg at 1 g/kg for 1-2 days), and iv anti-Rh (D) (50-74µg/kg) [12].If thrombocytopenia persists or recurs, splenectomy is recommended in adults but is deferred to prevent overwhelming post splenectomy infection or allow for spontaneous remission. TPE and IA with Protein-A columns may be considered in patients with refractory ITP, with life-threatening bleeding or in whom splenectomy is contraindicated. IgG antibodies and IgG-containing circulating immune complexes can be selectively removed by IA with protein-A. The use of this column is contraindicated when the patient is on ACE inhibitors, has a history of hypercoagulability, or thromboembolic events [42]. There are no clear guidelines concerning treatment schedule and duration of treatment. The procedure is generally discontinued when either the patients shows improvement in platelet count > 50 x 10^9/L or no improvement after about six treatments. The columns with protein-A are no longer available in the United States but may be available in other countries [12].

Table **3:** Therapeutic apheresis in a selection of thrombocyte diseases (modified after 7,12,13).

Apheresis Application Committee of the ASFA, 2013, 2016 [12,13]						
Disease	**TA modality**	**Category**	**Recommendation grade**	**Treated Volume (TPV)**	**Replacement Solution**	**Frequency**
Idiopathic thrombocytopenic purpura	TPE,	III	2C	2-4	HAE	daily or every other day
Post-transfusion purpura	IA-Protein-A	III	2C	1-1.5		
Thrombocytosis						
- prohylactic	Thrombocytapheresis	II	2C	1.5-2	--	daily
- secondary		III		TBV	--	

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

Post-Transfusion Purpura (PTP)

Post-transfusion purpura occurs when donor B lymphocytes and dendritic cells migrated as passenger cells to the recipients´s system, where they undergo clonal expansion after "homing in" on, and producing alloantibodies to the incompatible HPA allele [43]. PTP is rare bleeding

disorder caused by alloantibody specific to platelet antigens. The antibody against the human platelet alloantigen HPA-1a is responsible for most of the cases. The majority of affected patients are multiparous women who presumably have been previously sensitised during pregnancy [44]. Blood transfusions rarely have been implicated as the primary cause for alloimmunization in PTP. Thrombocytopenia is usually severe and resolves spontaneously within several weeks. However, patients may develop severe if not fatal bleeding during the course of the disease. The diagnosis is confirmed by demonstrating that the patient´s serum contains antibodies to platelet-specific antigens. Treatments for PTP include IVIg, corticosteroids, and TPE [44].

The treatment is high IVIg (0.4 g/kg BW/day for 2-5 days or 1 g/kg BW/day for 2 days) [12]. It is possibly acts by Fc receptor blockade of RES. The removal of HPA1a alloantibodies by TPE results in a decrease of antibody titer, removal of any unattached HPA-1a antigen, and an increase in platelet count and cessation of bleeding. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIg therapy is not effective [12]. In the AAC of the ASFA the PTP has the category III with RG 2C for TPE based on limted data available in the literature (Table 3) [12,13]. TPE can be discontinued when platelet count starts increasing (> 20 x 10^9/l) and non-cutaneous bleeding stops.

Thrombocytosis

Thrombocytosis, defined as circulating platelet count ≥ 500 x 10^9/L, is most commonly phenomenon related to acute bleeding, hemolysis, infection, inflammation, asplenic, cancer, or iron deficiency [12]. The increased normal platelet in these cases do not predispose to thrombosis or bleeding. Patients with PoV and essential thrombocythemia (Etr) are at significant risk of arterial and, less commonly, venous thromboembolic events. These occur either sponteounsly or during situational hypercoagulability, such as surgery, immobilization and pregnancy. Additional risk factors include age > 60 years, history of prior thrombosis, cardiovascular comorbidities and, for PoV, uncontrolled erythrocytosis. Thromboembolism with ET occurs in 11 – 25 percent at diagnosis and in 11 – 27 percent during follow-up [12,45].

The current treatment includes the following low-dose aspirin is indicated for thromboprophylaxis in patients with Etr or PoV who do not have a bleeding tendency. Phlebotomy is required to maintain normal Hct with PoV. The platelet count also be normalized before general anesthesia and surgery. Hydroxyurea is preferred platelet-lowering agent. Alternatives includes anagrelide and interferon alpha. Thromboembolic complications are treated acutely with unfractionated or low-molecular-weight heparin followed by transition to therapeutic warfarin [12,46].

Thrombocytapheresis is an exceptional treatment modality to prevent recurrent or progressive thromboembolism or hemorrhage in a patient with a myeloproliferative disease (MPD) und uncontrolled thrombocytosis [12]. Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believed to ameliorate pro thrombosis factors associated with the dysfunctional platelets. The rationale for thrombocytapheresis is undefined and the efficacy unproven; therefore the category II with RG 2C for symptomatic thrombocytosis and for prophylatic and the category III with the RG 2C for secondary thrombocytosis based on conflicting and limited date available in the literature (Table 3) [12].

The treated volume is 1 – 2 TBV, the replacement fluid is not necessary, and the frequency is daily, or as indicated for chronic treatment. With acute thromboembolism or hemorrhage, the goal is normalization of the platelet count and maintenance of a normal count until cytoreductive therapy takes effect. With very high pre-treatment counts more than one procedure may be required to achieve a normal count.

Hyperleukocytosis

The many early complications and death are directly attributed to hyperleukocytosis and its resultant microcirculatory dysfunction, a phenomenon known as leukostasis, where the sludging of leukemic blasts in capillary vessels and their adhesive interactions give rise to deleterious

effects [47]. Symptoms may rise from the involvement of any organ system, but intraparenchymal brain heorrhage and respiratory failure account for the majority of deaths. The rapid destruction of leukemic cells in response to chemotherapy also causes metabolic disturbances (tumor lysis syndrome).

After the AAC of the ASFA hyperleukocytosis is defined as a circulating white blood cell (WBC) or leukemic blast cell count > 100 x 10^9/L. Leukostasis complications associated with hyperleukocytosis include organ or tissue dysfunction directly attributable to the high burden of circulation leukemic myeloid or lymphoid blast cells in the absence of infection, thromboembolism, or other underlying etiology. In general, leukostasis is observed in acute myeloid leukemia (AML) when WBC is > 100 x10^9/L and in acute lymphoblastic leukemic (ALL) when WBC is > 400 x 10^9/L [12].

The monoblastic/monocytic subtypes of AML appear particularly pathogenic, as pulmonary complications are reported at blast counts > 50 x 10^9/L. Central nervous system manifestations include confusion, somnolence , delirium, coma, and parenchymal hemorrhage with focal neurological deficits. Pulmonary complications include dyspnoea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure, and radiographic findings of interstitial and/or alveolar infiltrates [12,13].

Definitive treatment is with induction chemotherapy. Hydroxyurea may be a useful temporising cytoreduc-

tive agent. Associated tumor lysis syndrome and hyperuricemia are treated with intravenous fluids, electrolyte replacement, allopurinol or rasburicase, alkalinization of the urine, and dialysis. Plasma cryoprecipitate, and/or platelets are given, as indicated, for bleeding or coagulopathy. Because of concerns of adding more cell mass to the circulation, RBC transfusion is generally avoided prior to cytoreduction. Adjunctive radiation therapy may be considered in invidividual cases with perenchymal brain lesions [12]. In the guidelines of the AAC of the ASFA, the hyperleukocytosis has the category II (leukostasis) with RB 1B, and III (prophylaxis or secondary) with RG 1B for leukocytapheresis Table 4) [12,13]. Leukocytapheresis has been widely used following anecdotal case reports describing striking clinical improvements with prompt leukoreduction. Although introduced more than 20 years ago, there are still no convincing data that leukocytapheresis is essential in the immediate treatment of hyperleukcytic leukaemia and the effectiveness of this technique remains in question [48].

Despite the inability to accurately predict leukostasis complications and the lack of a clear treatment goal, prophylactic leukocytapheresis should be considered for AML patients with a blast count > 100 x 10^9/L; and especially for those with a monocytric/monoblastic subtype. Among children and adults with ALL, clinical leukostasis occurs in < 10 percent of those with WBC counts < 400 x 10^9/L. Prophylatic leukotapheresis offers no advantages over aggressive induction chemotherapy and supportive care, including those with tumor lysis syndrome. The category III and R 2C for prophylaxis or secondary of hyperleukocytosis was assigned because of the limited and conflicting data available in the literature. Severe end-organ injure or hemorrhage may not improve, however, in patients with extensive and/or severe preexisting tissue damage. Leukocytapheresis should be repeated in persistently symptomatic patients until clinical manifestation resolve or a maximum benefit is achieved. Concurrent chemotherapy is also required in order to prevent rapid reacumulation of circulating blasts [13,48,49].

A single leukocytapheresis can reduce the WBC count by 30 – 60 percent. The treated volume is 1.5 – 2 TBV; the replacement fluid is a human-electrolyte solution and/or plasma. For prophylaxis of asympromatic AML patients discontinue treatments when the blast count is < 100 x 10^9/L. For AML patients with leukostasis complications, discontinue when the blast cell count is < 50 – 100 x 10^9/L and clinical manifestation are resolved. For prophylaxis of asymptomatic ALL patients, discontinue treatment when blast cell counts is < 400 x 10^9/L. For ALL patients with leukostasis complications, discontinue treatment when the blast cell count is < 4oo x 10^9/L and clinical manifestation are resolved [12,13].

Table 4: Therapeutic apheresis in leukocyte diseases (modified after 7, 12,13).

Apheresis Application Committee of the ASFA, 2013, 2016 (12,13)						
Disease	**TA modality**	**Category**	**Recommendation grade**	**Treated Volume (TBV)**	**Replacement Solution**	**Frequency**
Hyperleukocytosis						
– symptomatic	Leukocyt-	II	1B	1,5-2	HAE	daily
– prophylactic	apheresis	III	2C			
or secondary						

Category II accepted for TA as second-line therapy; Category III: not accepted for TA, decision should be individualized.

Coagulopathy

This is a defect of the endogenous coagulation system, either inherited or acquired. It includes diseases which result from reduction, lack, or malformation of the factors VIII, IX, XII, or prekallikrein. Hemophilia A is the longest-known hemorrhage diathesis. As a result of substitution therapy, 5 – 20 percent of hemophiliacs develop antibodies against factor VIII administered during the course of treatment. Factor VIII antibodies belong to the IgG immunoglobulin group [50,51]. Antibodies can, however, also occur spontaneously in older patients or after pregnancy. These are antibodies that are directed against the patient´s own factor VIII and can lead to an acquired factor VIII deficiency. Hemophiliacs may become sensitised to concentrates of their deficient coagulation factors. This occurs in about 15 percent of hemophilic patients. Low and high responders can be distinguished. The activity of the inhibitor can be measured in Bethesda units (BM) or Malmö inhibitor units (MiU). The F VIII inhibitors are IgG subclass 4 antibodies. F VIII inhibitors are the most common pathogenic antibodies directed against the blood coagulation factors. They develop in approximately 30 percent of patients with severe and moderately severe hemophilia A in response to infusions of FVIII. Patients develop inhibitors usually within the first year of treatment. The mechanisms underlying the state of apparent immune tolerance in the remaining non-inhibitor patients are known. The greatest risk of inhibitor development is associated with no sense mutations, large deletions and intrachromosomal recombinations (inversion) in the F VIII gene that are predicted or cause a complete lack of endogenous FVIII. The risk of inhibitor development in patients with mild hemophilia A increases with the amount of exposure F VIII [52].

Many patients with antibody formation display a rapid increase in antibodies after administration of F VIII. Attempts to suppress the formation of antibodies in these patients through immunosuppressive therapy have, for the most part, been unsuccessful. TA is used to reduce these antibodies prior to infusing F VIII. TA in combination with F VIII has been successful in interrupting severe bleeding in hemophilics who are unresponsive to F VIII and as hematologic preparation to normalize these inhibitors prior to major surgery [53]. TA is indicated in severely bleeding patients classified as immunological high responders. TA can be considered when plasma concen-

tration of the inhibitors exceeds either 10 BM or 3 MiU. TA should be implemented prior to high-dose administration of human VIII concentrates.

The use of IA with anti-immunoglobulin columns may be safer and more effective. A further indication for TA is in cases where inhibitors occur after factor substitution to induce immune tolerance according to the Malmö or similar protocols. Serial TPE and simultaneous administration of factor VIII/IX concentrates, high-dose IgG (0.4 g/kg per day), and cyclophosphamide is recommended. This protocol has a success rate of 80 percent. Chronic immunosuppression may be necessary in some cases [35].

IA is being increasingly applied in the treatment of F VIII inhibitors. Several types of IA methods have been used, although reports are mainly anecdotal. But IA may be clinically effective and cost-effective and should be considered early in the treatment of patients (Table 5) [54].

Antibodies against F VIII can occur in many diseases such as immunolgical diseases, after pregnancy, as a reduction to medication (e.g., phenylbutanzone), skin complaints, tumors, and diabetes mellitus. In the case of most patients with acquired F VIII antibodies, it is not possible to determine the cause. If the underlying disease is known and treated, a drop in antibody titer can be expected.

F VIII autoantibodies in non-hemophiliacs produce a condition sometimes called acquired hemophilia A. It is the most common autoimmune bleeding disorder in-

volving the coagulation system. For unknown reasons, acquired Hemophilia A patients are more likely to have a more severe bleeding diathesis than hemophilia A inhibitor patients. Approximately 50 percent of acquired hemophilia A patients have underlying conditions, including autoimmune disorders, malignancy, and pregnancy [55]. The remaining idiopathic cases most commonly occur in elderly patients of either sex.

Treatment of bleeding episodes for patients with acquired hemophilia A or congenital hemophilia A with inhibitors depends on the inhibitor titer. Low-titer inhibitors can be overwhelmed with F VIII bypassing agents (prothrombin complex concentrates, activated prothrombin complex concentrates), or recombinant F VIIa or porcine F VIII concentrates can be used to treat patients with high-titer inhibitors. Recombinant F VIIa is effective in controlling most bleeding episodes. There have been no reports of inhibitory antibodies developing to the product [55].

Acute bleeding complications are an indication not only for the application of highly dosed concentrated F VIII, but also for the removal of circulating antibodies through TPE. Substitution with fresh frozen plasma also includes the administration of F VIII. The advantage of TPE and IA is in its rapid removal of antibodies and absence of excessive antibody formation. A disadvantage is an increased risk of bleeding with TPE treatment, if anti-

coagulation becomes necessary. With IA a selective elimination of acquired F VIII antibodies is available [56].

The AAC has given the coagulation factor inhibitors in hemophilia A and acquired factor antibodies in non-hemophilia patients has category III with RG 2B for TPE and IA with RG 2B (Table 5) [12,13]. Factor deficiency can either be congenital or acquired; the majority of acquired deficiencies result from autoantibodies. In addition, congenital factor deficient patients can develop inhibitors, allo-antibodies, to the factors. The treatment options for inhibitor suppression include high dose corticosteroids, cyclophosphamide, cyclosporin A rituximab and high dose IVIg [2]. For coagulation factor inhibitors, the extracorporeal removal by IA is more effective than TPE [56].

Table 5: Therapeutic apheresis in a selection of coagulopathy diseases (modified after 7, 12, 13).

Apheresis Application Committee of the ASFA, 2013, 2016 (12,13)						
Disease	**TA modality**	**Category**	**Recommendation grade**	**Treated Volume (TBV)**	**Replacement Solution**	**Frequency**
Coagulator factor inhibitor				1-1.5	HAE, plasma	daily, or every other day
– alloantibody	TPE, IA-protein-A	III IV	2C 2B			
– autoantibody	TPE, IA-Protein-A	III III	1C-2C 1C			
Disseminated intravascular coagulation	TPE	III	1C			

Category III: not accepted for TA, decision should be individualized:
Category IV: not accepted for TA, Institutional Review Board (IRB) approval is desirable if TA if TA is under taken.

Disseminated Intravascular Coagulation (DIC)

In patients with DIC, the platelet count is invariable low or rapid decreasing. DIC may complicate a variety of underlying disease processes, including sepsis, trauma, cancer or obstetrical calamities such as placental abruption.

Major alterations in the coagulation process, offer various theoretical approaches for TPE [57]. As the blood flow is interrupted to tissue, the tissue in the affected areas dies and releases tissue thromboplastin. Tissue thromboplastin activates Factor VII and the extrinsic pathway leading to local clotting and with sufficient thromboplastin, disseminated intravascular clotting with activation of both the extrinsic and intrinsic systems. As the process continues more tissue dies due to clotting in capillary beds. In the process, both pro-coagulant as well as anti-coagulant factors (protein C and S and antithrombin III), and plasminogen are used up. The clinical picture of excessive blood clotting and uncontrolled bleeding is produced often with fatal consequences

Patients with DIC have a low or rapidly decreasing platelet count, prolonged coagulation tests, low plasma levels of coagulation factors and inhibitors, and increased markers of fibrin and/or degradation, such a D-dimer or fibrin degradation products [58].

The process of consumption coagulopathy can be interrupted in the hypercoagulemic stage by eliminating or

reducing the levels of active pro-coagulation factors example heparin, depletion of factors II, VII, IX with coumadin or TPE [2]. TPE interrupts the pathogenic chain reaction in second stage, in which intravascular clot formation occurs, pro-coagulant and anticoagulant and depleted and failure of the clearing function of the RES occurs. Even in the third stage, high molecule fibrin split products can be eliminated by TPE and the coagulation status normalized through the substitution of clotting factors and normal levels of anti-coagulant with FFP.

Stegmayr et al. treated 15 patients with multi-organ failure as a result of acute intravascular coagulation with TPE. Such multi-organ failure normally has very poor prognosis and is associated with high mortality. Eleven of these patients survived their multi-organ failure through TPE, and their renal function also normalized [59].

The following diseases in Table 1 such as Evan´s syndrome, different forms of the hyperviscosity syndrome, Malaria, Schönlein-Hennoch purpura, Heaprin-induced thrombocytopenia and thrombosis, etc. are not mentioned here, because they are most depended from other diseases and are discussed elsewhere.

Conclusion

TA has been successfully used in varies anti-body-mediated and other diseases, but all mentioned therapeutic apheresis methods are still technically complicated and very expensive. A reduction in costs is a valid demand in

view of the scare resources available in the healthscare system. Commissions consisting of physicians, administration specialists and representatives of the health insurance funds and others nowadays decide at a “round table” who will be granted medical facilities and who will not; this is a clinical routine adopted only in Germany. Physicians are committed to helping of the patients entrusted to them to the best of their knowledge, and this means that medical treatment-and particularly the apheresis process-must become affordable. This represents a great demand to physicians, politicians, health organizations, and above all, to the manufacturers. Industry constantly justifies the high costs with the extensive research and development required. All those involved in healthcare must intensify their cooperation in this respect.

Simple and user-friendly systems are necessary for routine clinical use. It is therefore desirable that only one machine (hardware) is available for different extracorporeal methods. This hardware should be equipped with various software programs for running different apheresis methods. The membrane, adsorber and tube sets should be different for different methods. These sets should be only used with special software programs. Only one hardware system for all different apheresis methods could be a great advantage because the machine park in nephrological and intensive medical care units could be reduced. For the physicians and the staff this will be a simplification of their daily work, because they can work with different sets and only one hardware system [2].

Nevertheless, medical processes are advancing and will not be stopped. Since the introduction of hollow fiber membranes, exceptional efforts in research and development have been undertaken in the apheresis sector alone, enabling, for example, the introduction of selective separation techniques into everyday clinical practice-techniques that were unsought of at the beginning of the 1980s. This reflected in the numerous national and international specialist congresses, which take place each year.

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