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RESEARCH ARTICLE

Therapeutic Apheresis, Immunosuppression and Human Monoclonal Antibodies in Hematologic diseases most with immunologic origin

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ABSTRACT

Therapeutic plasma exchange with hollow fiber modules has been used in different severe diseases for more than 45 years. Updated information on molecular biology and immunology of different diseases, the authors discuss in relation to the rationale for apheresis therapy and its place in combination with other modern therapies such as immunosuppressive drugs, cytotoxic agents, and/or human monoclonal antibodies. With the introduction of novel and effective biologic agents, therapeutic apheresis is indicated in severe cases, such as in rapid progression despite immunosuppressive therapy and/or biologic agents. In mild forms of immunologic diseases, treatment with immunosuppressive therapies and/or biologic agents seems to be sufficient. The prognosis of hematologic diseases has improved in recent years, due in part to very aggressive therapy schemes. For the hematologic diseases, especially diseases with an immunologic origin, such as various anemias, erythrocytosis, thrombocytopenia, hyperleukocytosis and coagulation inhibitors that can be treated with therapeutic apheresis, the guidelines of the Apheresis Application Committee of the American Society for Apheresis are cited. Therapeutic apheresis has been shown to effectively remove the toxins, autoantibodies, and other substances from blood and lead to rapid clinical improvement. Therapeutic plasma exchange or immunoadsorption 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. Therapeutic apheresis can safely be performed in all severe ill patients and is most combined with an immunosuppression therapy. Human monoclonal antibodies are more introduced in hematologic diseases in recent years.

Keywords: Therapeutic Apheresis, therapeutic plasma exchange, immunoadsorption, extracorporeal photopheresis, human monoclonal antibodies, hematologic diseases

Introduction

During the mid-1970, new process for therapeutic apheresis (TA) with membrane modules instead of centrifuges 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 centrifuges for cell separation. The adsorption technologies allow the most selective separation of plasma components without the use of any substitution (1). Membrane techniques are simple and safe to apply and can be competitive to other plasma separation and treatment technologies (2).

Therapeutic apheresis using centrifuges has shorter treatment times such as TA using hollow fibers shown by Hafer et al. is no of advantage (3). To keep the blood levels with antibodies, and/or pathogenic substances on a very low level over long time during treatment is more important. However, the substances that should be eliminated could invade into the intravascular space and be eliminated by the membrane hollow fiber. Furthermore, cell damage – especially to thrombocytes – occurs less using membranes than centrifuges for all cell separation. The adsorption technologies allow the most selective separation of plasma components without the use of any substitution solution (4).

Therapeutic apheresis is indicated in the treatment of various hematological diseases. For most of these diseases, clear pathogenetic mechanisms of the diseases are understood, and there are well-defined criteria. In hematological diseases, TA often requires on one side in which the plasma containing the offending material is removed and discarded and normal plasma containing physiological concentrations of normal plasma constituents necessary for homeostasis are provided example disseminated intravascular coagulation (DIC), sepsis (4). In diseases caused by antibodies or immune complexes, semi-selective cascade filtration or immunoadsorption aimed at the causative antibodies can be used. Adjuvant drug therapies are different for the different diseases and are typically individualized in type, dose and duration of use. Therapeutic apheresis method chosen depends on the physiological origin of a given disease. Furthermore, the physician must be knowledgeable concerning the half-life time, and the compartmental distribution of pathogenic plasma proteins, and the elimination of other toxic

substances and complements that determine the best with regard to the therapy. Best medical management of immunohematological disorders requires the use of TA, serological immunomodulation, and classical pharmacological immunosuppression with steroids, cytotoxic agents, antimetabolites, and human monoclonal antibodies were overall therapy is individually tailored to the needs of the patient. Variables such as severity of disease, degree of organ system damage before intervention, age and the existents of comorbid conditions make controlled trials difficult if not impossible. It is impossible to recruit a large number of patients to perform a controlled clinical trial, in some rare hematological diseases. For most of these diseases, only small series for cases are available for analysis.

The authors try to give an overview of the most important pathogenic aspects indicating that TA can be a supportive therapy in hematologic disorders. For hematologic diseases, which can be treated with TA, the guidelines of the Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) are cited (5, 6).

Therapeutic Apheresis Methods

TA includes the following methods, which are mentioned here (7):

- **Therapeutic plasma exchange (TPE)** in which the whole blood is pumped through a hollow fiber module, which separates the plasma from the cellular components of blood. The plasma is removed and replaced with albumin-electrolyte- and/or plasma solution and/or fresh frozen plasma.
- **Immunoadsorption (IA)**, in which the plasma after separation from the blood is passed through a medical device with special binding to active component of the devices. The active components can be staphylococcal protein A, or other organic or synthetic adsorber, which contains synthetic peptid-goat-antimouse, which works like a mini-receptor together with an epitop, and adsorber with covalently bound tryptophan.
- **Hemoperfusion (HP)** whole blood adsorption: lipoprotein apheresis is a selective method to remove low-density lipoproteins from the blood with the return of the remaining blood. The removal of LDL cholesterol based upon charge (dextran-sulfate or polyacrylate or precipitation at low pH), or IA with anti-Apo B-100 antibodies.

- **Red-blood-cell (RBC-) exchange**, in which the blood is passed through a medical device, which separates erythrocytes for other blood components. RBCs are removed and replaced with donor RBCs and/or with colloid solution.
- **Erythrocytapheresis** comparable with RBC-exchange.
- **Thrombocytapheresis**, in which blood is passed through a medical device, which separates thrombocytes from blood and removed them. The remaining blood is returned to the patient.
- **Extracorporeal photopheresis (ECP)**, in which buffy coat, separated from patient's blood, is treated in the extracorporeal device with a photoactive compound (e.g., psoralens), exposed to ultraviolet A light, and then reinfused to the patient during the same treatment.
- In addition, other adsorption methods which are mentioned elsewhere (7).

Hematologic Disorders with Immunologic Origin

Many hematologic disorders have an immunological origin. The term autoimmune disease relates to diseases caused by antibodies acting against the body's own tissue. They are also referred to as auto-aggressive diseases. Autoimmune disease, with exception of rheumatoid arthritis and immune thyroiditis, are individually rare, but together they affect approximately 5 % of the population in western countries (8). 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 antigen of the cell surface and cause an intravascular lysis of erythrocytes through stages (e.g., paroxysmal hemoglobinuria) particularly in the case of hematological diseases. In autoimmune hemolytic anemia for example, the antibodies can opsonize the affected erythrocytes. The binding of antibodies with complement participation changes the cell 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 reticulo-endothelial system (RES) in the liver and the spleen. The opsonization process is the so-called immune clearance, a physiologically effective way of removing intruding cells through immune bodies (4).

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 antibodies block functionally important receptors 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.

Immune complex (IC) diseases are diseases caused by antigen-antibody complexes. The antigen is sometimes of infectious origin. In most cases, however, neither the origin nor the structure of the antigen is clear. IC formation is a physiological process for eliminating foreign material, such as bacteria, their components and viruses. Normally ICs are removed from the blood by adhesion of the Fc-fragments of the antibodies to the corresponding phagocyte in the liver and spleen. If the ICs activate the complement system, (immune clearance) phagocytosis can even be enhanced. For example, more than 80% of glomerulonephritis cases are caused by intra renal deposited circulating immune complexes (CIC). If the antigen adheres to the basal membrane and binds circulating antibodies, the IC probably, first form in situ (4).

Rhesus (Rh) Disease, Hemolytic Disease in Newborns (HDN)

Rhesus disease or incompatibility during pregnancy is an indication for TPE as a supportive therapy (9). It has been common practice for years to carry out anti-D gamma globulin prophylaxis in Rh-negative women after the 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 kernicterus. Exchange transfusion is the therapy of choice. Recently, TA has also become possible (10). The diagnosis can be 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 could be a lifesaving procedure but involve a high risk. The earlier Rh incompatibility manifests itself in pregnancy, the poorer the prognosis. It occurs prior to the 26th week of pregnancy, more than 93% of fetuses die by the 31th week. When after the 26th week the Rh incompatibility manifests itself, the mother receives TPE treatment, and the child receives intrauterine or postpartal exchange transfusion.

sion. Seventy one percent of these children can survive whereas without treatment most die (11).

Hemolytic disease in newborns presents as icterus neonatorum or hydrops fetalis. Both diseases are caused by alloimmunization against RhD-positive red blood cells of an RhD-negative mother bearing an RhD-positive fetus. Alloimmunization of the mother occurs after fetomaternal hemorrhage during the 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 blood cells by a non-complement-dependent mechanism (4). Hemolytic disease 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 is indicated in severe fetal hemolysis in a sensitized mother. After birth, the newborn may receive a phototherapy and/or a neonatal exchange transfusion, or TPE, depending on the severity of hemolytic disease in newborns (9).

The intravascular transfusion, which is widespread use and the advent of intravenous immunoglobulin (IVIG) therapy have now reduced the former significance of this disease. The combination of TA and IVIG can be administered towards the beginning of the second trimester in women who have developed hydrops fetalis before the 22nd week of a previous pregnancy (11). Therapeutic plasma exchange/human albumin may bridge the gap between the onset of severe fetal anemia and the feasibility of fetal transfusion. Alloimmunization against other red cell antigens makes fetal intravascular transfusion impossible, but maternal TPE may be the only therapeutic option to save the fetus. Filbey et al. reported in 1995 of 707 infants born to 583 alloimmunized women in Sweden (12). Maternal TPE was performed in 2.4% of the cases with a response rate of 100 %. Therefore, TPE is recommended 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 Rh incompatibility. The physician must be aware that anti-D antibodies can also increase with TPE. Bing et al. reported in 2006, successfully treating 44 pregnant women with Rh incompatibility using a combination of anti-D immunoglobulin and TPE, and intrauterine transfusion (13). The effects gained from the therapy lasted for approximately six weeks for the patients the study demonstrates that systematic management (including routine test for the presence or absence of D antigen in pregnant

women, series test of anti D antibody titer and ultrasonography, amniocentesis and cordocentesis) and timely treatment (including anti-D immunoglobulin, TPE, intrauterine transfusion (IUT), and delivery) can improve the perinatal outcomes of Rh-negative women.

Given that intrauterine exchange transfusion involves a considerable risk to the child and available data suggests that TPE for the mother is safe and effective, it seems reasonable to attempt control of the disease by TPE for the mother first and if control is inadequate then reconsider intrauterine exchange transfusion. Application of IgG after TPE treatment might have a further positive influence on the prognosis by delaying the time to reaccumulation of cytotoxic antibodies. Ultrasound can detect signs of anemia (middle cerebral artery velocity) or hydrops (ascites) (5). Amniocentesis provides samples for fetal genotype amniotic fluid spectral analysis, and fetal lung maturity. The measurement of fetal hematocrit allows, if needed, an IUT, which cannot occur until 20 weeks' gestational age. The fetus transfused with RBCs negative for the antigen against which maternal antibody is directed. Fetal mortality related to IUT is 1-2%. Intrauterine transfusion can be repeated, approximately every 1-2 weeks, until the fetus is ready for delivery.

The AAC of the ASFA has given the HDN the category II with the recommendation grade (RG) 2C (Table 1): The rationale for TPE is the removing the maternal red cell alloantibody that is responsible for HDN (5, 6). Therapeutic plasma exchange 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 IUT is about 70%. Category II for TPE is assigned for patients when there is a previous history of a severely affected pregnancy and the fetus is less than 20 weeks gestational age. Intrauterine transfusion can be performed after the fetus reaches 20 weeks of gestation (13-15).

Therapeutic plasma exchange can safely be performed during pregnancy during pregnancy (16). During pregnancy blood volume, 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 decrease perfusion to the fetus (4). Therapeutic plasma exchange should be considered early in pregnancy

(from 7th to 20th week) and continued until IUT can safely be administered, about 20th week of gestation. The use of TPE is the first week (three procedures) followed by IVIG at 1 g/kg weekly (17).

Hemolytic Anemia

The etiology of hemolysis often are categorized as acquired or hereditary. The 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, COVID-19, and transfusion reactions (4, 18). Microangiopathic hemolytic anemia occurs when the red cell membrane is damaged in circulation, leading to intravascular hemolysis and the appearance of schistocytes. Infectious agents such as malaria and babesiosis invade red blood cells (19). The severity of hemolytic anemia is quite variable depending on the cause it can be mild and compensated for by increased erythropoiesis so that there is no decrease in red cell mass. The treatment for mild forms and forms of such severity as to decrease red cell mass is directed at correction of the underlying cause. For example, proper antibiotics and supportive care for infections, surgical debridement and antibiotics for *Clostridia Welchii*, stopping the offending drugs in the case of G6PD deficiency. In severe hemolytic anemia with hemoglobinemia, heme saturation of albumin and hemoglobinuria regardless of whether it is mediated by exogenous or endogenous toxins, timely implementation of TPE and IVIG appears justified.

Autoimmune Hemolytic Anemia (AIHA)

Autoimmune hemolytic anemia is characterized by reduced erythrocytes in vivo survival time and by the presence of warm or cold agglutinating antibodies against autologous erythrocytes. The differentiation between the following antibodies is made based on their serological features (19, 20):

- Thermo-type (warm agglutination) autoantibodies. This group consists 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 temperature (0 – 10°C). They become of clinical importance

when a temperature of 30°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).

The diagnosis of autoimmune hemolytic anemia is an anemia direct microscopic of the peripheral blood film, hyperbilirubinemia, reticulocytosis, positive direct antiglobulin test (direct Coombs test), and elevated serum LDH (20). Immune hemolytic anemia is a result of antibody fixation to a red cell antigen. This triggers either intravascular red cell destruction mediated by the terminal lytic complement complex (C5b-C9) or extravascular destruction mediated by macrophage phagocytic system (20). Both mechanisms require opsonization by antibodies or C3b complement. The antibodies mostly belong to the IgM (cryo-type abs) and IgG groups, or occasionally also to the IgA (thermo-type abs).

The pathogenesis of warm AIHA is complex. The mononuclear phagocytic system in the spleen plays a major role in the breakdown of opsonized erythrocytes (extravascular hemolysis) (21, 22). The complement system, activated by the classical pathway, is involved in approximately half the cases (22, 23). Most of the complement-mediated erythrocyte destruction occurs through phagocytosis of complement fragment 3b (C3b)-coated cells (extravascular hemolysis). Recently, several cases have been described in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (24). C3b can also react to form C5 convertase, which initiates the terminal complement cascade (22). Terminal complement activation, in turn, leads to formation of the membrane attack complex and intravascular hemolysis, at least in some patients and situations (25). The reason for the formation of the antibodies is still unknown.

When warm autoantibodies attach to red blood cell surface antigens, these IgG-coated red blood cells are partially ingested by the macrophages of the spleen, leaving microspherocytes, the characteristic cells of AIHA. Cold autoantibodies (IgM) temporarily bind to the red blood cell membrane, activate complement, and deposit complement factor C3 on the cell surface. These C3-coated red blood cells are cleared slowly by the macrophage of the liver (extravascular hemolysis) (25).

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 autoimmune hemolytic anemia (WAIHA) also is associated with autoimmune disease (e.g., systemic lupus erythematosus), while cold AIHA may occur following infections, particularly infectious mononucleosis and *Mycoplasma pneumoniae* infection. Human immunodeficiency virus infection can induce both warm and cold AIHA. With conventional therapy of corticosteroids and cytostatics or even splenectomy, TA and/or HMA such as eculizumab are increasingly being implemented with success (26, 27).

The AAC of the ASFA has given the AIHA the category III with the RG 2C for the warm AIHA and for the cold agglutinin disease the category II with the RG 2C (Table 1) (5, 6). The symptoms are 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 antiglobulin (Coombs) test. The degree of hemolysis in AIHA is shown by the titer of the autoantibody, its avidity for the relevant red blood autoantigens, and, for cold autoantibodies, its ability to fix complement, and its thermal amplitude (5). Cold autoantibodies with high thermal amplitude could be active within in vivo temperatures ranges (i.e., 30 – 37°C), and in these cases the thermal amplitude most accurately predicts the severity of the disease (25).

First-line therapy for WAIHA includes prednisone at 1 – 2 mg/kg/day, until response becomes evident (5). Prednisone suppresses antibody production and down-regulates Fc-receptor-mediated red cell destruction in the spleen. Second-line therapies are splenectomy, IVIG, rituximab, eculizumab, bortezomib, danazol and immunomodulatory agents (e.g., Cyclophosphamide, azathioprine, cyclosporine A) and TA (26, 27).

Antibody removal by TPE is also effective. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized red cells (28). Therapeutic plasma exchange can remove pathogenic immune complexes, activated complements, and autoantibodies (5). Therapeutic plasma exchange in AIHA can reduce and eliminate autoantibody in severe situations (i.e., anemia not responding to transfusion) until immunosuppressive therapy takes effect or if

other treatments have failed. At body temperature, IgG, mostly extravascular, is absorbed. The improvement of AIHA after TPE is usually temporary, depending on the autoantibody, and its rate of production. The frequency of TPE is daily or every other day. The duration of the procedure is until hemolysis is controlled and the need for transfusion is limited (5).

Sickle Cell Anemia (SCD)

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 β -chain of hemoglobin (29). Membrane abnormalities from sickling and oxidative damage caused by the 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 electrophoresis reveals a predominance of hemoglobin S (HbS). Sick cells are observed on the peripheral smear. HbS polymerizes upon deoxygenation, causing red blood cells to become rigid and deformed sickled RBCs (5). The sickled RBCs have a shortened lifespan, producing hemolytic anemia and occluding the microvasculature leading to tissue hypoxia and infarction. The manifestations are vaso-occlusive events (VOE), splenic sequestration, and transient red cell aplasia (TRCA). Among VOE, painful episodes are the most common. Other VOE are acute chest syndrome (ACS), 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 autosplenectomy. Overall mortality rate for SCD is 2.6 % (=5 death/100 person years) with the peak at 1 – 3 years of age (6).

The main therapies include penicillin prophylaxis, folic acid, pneumococcal and Haemophilus influenzae vaccinations, analgesis for painful episodes, and antibiotics for infections (5). Red blood cell transfusion (TX) can be a primary or a first-line adjunct therapy with simple RBC TX or RBC exchange TX (EX-TX). In severe anemia RBC-TX is one of the best treatments to improve oxygen-carrying capacity of blood by increasing RBC mass and stop or decrease the splenic sequestration, or hyperhemolysis, ACS with hypoxia, stroke, and acute multiorgan failure, before surgery or in complicated pregnancy. Chronic TX to maintain Hb S < 30 percentage is indicated to prevent first/primary stroke and Hb S < 30 – 50 % to prevent secondary/recurrent stroke and to treat chronic debilitat-

ing pain, pulmonary hypertension, and anemia with chronic renal failure (5). However, in acute ischemic stroke or acute or 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 transfusion associated iron accumulation, but is associated higher (1.5 – 3 times higher) blood requirements than single RBC-TX (30). In patients with acute, severe sickle cell-related complications beside RBC TPE can be indicated and successfully (31 – 33). In milder forms of the diseases, monoclonal antibodies such as rituximab or alemtuzumab could be used (34).

In the guidelines of the AAC of the ASFA, the sickle cell disease has the category I for life organ threatening complications with the RG 1C and the category II with 1C for primary and secondary stroke prophylaxis and for prevention of transfusion iron load for erythrocytapheresis (5). For multi-organ failure, there is the category III with RG 2C for RBC exchange (Table 1). The replacement fluid is Hb S negative leukoreduced RBCs, and, if available, antigen matched for E, C, and Kell (5). The frequency in acute situations is one procedure, and in chronic situations at required intervals to maintain the desired Hb S level < 30 – 50 %. Only one procedure is sufficient to treat the acute complications of SCD. For chronic transfusion therapy, erythrocytapheresis is typically performed at patient specific intervals to maintain the desired Hb S < 30 – 50% (30).

Babesiosis

Babesiosis is another hemolytic anemia, which is a protozoal disease transmitted from an animal reservoir to humans by the bites of hardtacks, or, more rarely, by transfusion (5). Usually responsible for transmission of the disease from animal reservoirs to human hosts is the *Ixodes dammini*, the deer tick. Three out of 70 species of babesia (*B. bovis*, *B. divergens*, and *B. microti*) have been positively implicated in causing infection and diseases.

The incubation period is reported 1 – 3 weeks and with longer incubation period of (6 – 9 weeks)

with transfusion transmission (5) and the symptoms are usually nonspecific. 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, acute kidney injury (AKI), DIC, congestive heart failure, and pulmonary disease. Specific diagnosis is made through examination of a Giemsa-stained blood smear, DNA amplification using polymerase chain reaction, or detection of specific antibody. The first-line therapy includes a combination of antibiotics, most quinine sulfate and clindamycin.

Babesiosis is caused by intraerythrocytic protozoan of the genus *Babesia*, resulting in a febrile illness and a hemolytic anemia (35). It is endemic in the Northeast and upper Midwest. The number of cases reported to the United States centers for Disease Control and Prevention increased significantly over the last two decades, and babesiosis remains an emerging infectious disease (36, 37).

In the guidelines of the AAC of the ASFA the babesiosis has the category I with the RG 1B in severe cases for erythrocytapheresis and in high risk patients the category II with the RG 1C (Table 1) (5, 6). After the AAC of the ASFA is the mechanism of action of exchange transfusion twofold. First, it lowers the level of parasitemia by physically removing the infected RBC from blood stream and replacing them with noninfected RBC. Because babesia organism do not have an exo-erythrocyte phase, removal of RBC-associate parasites is potentially curative. Second, the hemolytic process produces vasoactive compounds, including a variety of cytokine and thromboplastin, which can promote renal failure and DIC. Red blood cell exchange may help to curtail the production of these substances. The greatest advantage of RBC exchange over antibiotic therapy is its rapid therapeutic effectiveness (5). The frequency is a single procedure but it can be repeated. The specific level of which parasitemia must be reduced to elicit the maximum therapeutic level to which parasitemia must be reduced to elicit the maximum therapeutic effect is not clear. Treatment is usually discontinued after achieving < 5 percentage residual parasitemia.

Table 1: TA in hematological and hemostasiological diseases in pediatrics

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, IMB approval is desirable if TA is undertaken (5, 6))

Hematological and hemostasiological diseases	Apheresis Applications Committee of ASFA 2016, 2019 (5, 6)				
	TA modality	Category	RG	Exchange volume (TPV)	Replacem. fluid
Rhesus incompatibility (HDN)	TPE	II	2C		
Red cell alloimmunization in pregnancy	TPE	II	2C		
Autoimmune hemolytic anemia				1-1.5 TPV	5% HA-electrolyte solution
- warm autoimmune hemolytic disease (WAIHA)	TPE	III	2C		
- cold agglutinin disease	TPE	II	2C		
Sickle cell anemia	RBC-exchange	I	1C	1-2 total RBC	RBC
- acute stroke		II	1C		
- acute chest syndrome		III	1C		
- prophylaxis for primary or secondary stroke; prevention of transfusion iron overload		III	2C		
- multi-organ failure		III	2C		
Babesiosis					
- severe		I	1B		
- high risk population		II	2C		
Hemolytic uremic syndrome (HUS)	TPE	II	2C	1-1.5 TPV	5% HA-electrolyte solution
- complement gene mutations		I	2C		
- Factor H ab		IV	1C		
- MCP mutations					
Aplastic anemia (AA)	TPE	III	2C	1-1.5 TPV	5% HA-electrolyte solution
Pure red cell aplasia		II	1B		
ABO incompatible hematopoietic Progenitor cell transplantation	TPE	II	1B-2B	270 ml	Plasma
Graft-versus-host disease (GVHD)			1C		
- skin (acute)	ECP	II	1B		
- skin (chronic)	ECP	II	2B		
- non skin (acute/chronic)	ECP	III			
Erythrocytosis	Erythrocyt-apheresis	III	1C	RBC	5% HA-electrolyte solution
Polycythemia Vera (PV)		I	1B		
Idiopathic thrombocytopenic purpura (ITP)	TPE, IA-Protein	IV	1C	1-1.5 TPV	5% HA electrolyte solution, FFP
		II	1C		
		I	1A		
Thrombotic thrombocytopenic purpura (TTP)	TPE	III	2C		
Post-transfusion purpura (PTP)					
Thrombocytosis	Thrombocyt-apheresis	II	2C		---
- symptomatic		III	2C		
- prophylactic or secondary					
Hyperleukocytosis	Leukocyt-apheresis	I	1B	1-1.5 TPV	5% HA electrolyte solution, FFP
- leukostasis		III	2C		
- prophylaxis					
Coagulation factor inhibitors					
- alloantibody	TPE, IA	IV	2C		FFP
		III	2B		---
- autoantibody	TPE, IA	III	2C		FFP
		III	1C		---

RG: recommendation grade, TPV: total plasma volume, ECP: extracorporeal photopheresis, IA-Protein: IA-Protein with staphylococcal protein A, HA: Human albumin, RBC: red blood cell, FFP: fresh frozen plasma

Hemolytic-Uremic Syndrome (HUS)

Hemolytic-uremic syndrome is a disease that can lead to AKI and often to other serious sequelae, including death. The disease is characterized by microangiopathic hemolytic anemia, thrombocytopenia and AKI. The etiology and pathogenesis of HUS are not completely understood, and the therapy of HUS is complicated. After introduction of therapeutic apheresis as a supportive therapy in HUS, several authors reported successful treatment using TA in HUS in more than 87 percent of treated patients. The supportive therapy is indicated in severe courses of HUS and is superior to available therapy interventions. Bambauer et al. discuss the pathophysiologic aspects of the different pathogenic types of HUS (38).

Most cases are associated with infections with enterohemorrhagic *E. coli* (EHEC). These bacteria can be transmitted through contaminated food, animal and person to person contact. HUS is one of the most severe complications of a potentially avoidable food-borne infection. Other causes of HUS described as "typical" have to be differentiated since other factors including genetic disorders are of importance. A minimum of three different pathogenetic types, which lead to HUS, are subdivided. Hemolytic-uremic syndrome caused by infection, idiopathic HUS (non-Shiga toxin HUS), and HUS in systemic diseases and after toxin exposure (39). There have been reports of spontaneous recovery from HUS. The various etiological and pathogenetic assumptions have produced diverse therapy concepts. However, the total lethality in HUS was first reduced to 20 percent with the introduction of dialysis (40). If the therapy is administered early enough, two-thirds of cases recover without any impairment. In 10 - 20 percent of cases, however, lasting renal damage occurs.

Other authors reported successful in HUS using TPE and successful treatment in HUS using IA with protein-A (41-44). A compilation of therapeutic concepts for HUS implemented up to 2009 showed the success of HUS therapy with TPE/HD or IA/HD (38). Substitution of plasma or coagulation factors is often necessary due to the severe coagulation problems in HUS. Therapeutic apheresis might be more effective than infusions alone, as it removes potentially toxic substances from the circulation. Therapeutic plasma exchange or IA should be considered first-line therapy in situations that limit the amount of plasma that can be infused, such as renal or heart failure. Plasma infusion treatment is contraindicated in *S. pneumonia* induced non-

StxHUS. It may exacerbate the disease because adult plasma contains antibodies against Thomson Friedenreich antigen (45).

Different randomized controlled trials showed that TPE and/or dialysis as supportive therapy are still the most effective treatments in HUS (46). The outcome was listed for HUS, all-cause mortality, chronic reduced kidney function, and persistent proteinuria or hypertension at last follow up. None of the evaluated interventions such as fresh frozen plasma transfusion or dipyridamole, Shiga toxin binding protein and steroids was superior to supportive therapy alone for any outcomes (46).

The advantage of TA over other therapeutic procedures is that it intervenes at an early stage in the pathogenetic processes by quickly removing immune complexes and toxins. TA eliminates fibrinogen, fibrinogen degradation products, and other high molecular complexes, all of which can both support and inhibit coagulation. All other toxins produced by Bacteria and viruses like Shiga-toxin, the pathogenic pathway which follows the activation of the complement system of the factor HF1 with a partial HF1 deficiency and all other toxic substances can be quickly removed by TA.

Therapeutic apheresis methods, which are introduced in HUS as a supportive therapy, are TPE and IA with protein-A columns. Both methods are described elsewhere (38, 41, 44). The rationale for TA in HUS is discussed controversially because of the limited and/or conflicting data available in the literature. The rationale is that TA can effectively remove antibody or mutated circulating complements regulators (5). TA seems a reasonable option considering the poor prognosis of HUS in adults (38). The role of TA is uncertain but this treatment may be appropriate as supportive therapy.

The AAC of the ASFA divided HUS in 3 groups for TPE: Group 1 (diarrhea associated HUS) is a HUS due to complement factor gene mutations has the category II with the RG 2C. Group 2 is a HUS due to autoantibody to factor H (atypical HUS), and has the category I with the RG 2C. Group 3 is the typical HUS < 18 years. Group 3 has the category IV with the RG 1C (Table 1) (5, 6). Due to the various and very different causes, which can lead to a hemolytic-uremic syndrome, there are no exact guidelines available for the therapy of HUS. In HUS, a supportive therapy is indicated which include control of fluid and electrolyte imbalance, use of dialysis if required, control of hypertension, blood and plasma transfusion as required. Anti-

otic treatment of *E. coli* O157:H7 colitis may stimulate further verotoxin production and thereby increase the risk of HUS. The use of dialysis like hemodialysis or peritoneal dialysis as required daily. However, untreated HUS in adults and children may progress to end in organ damage (47). Platelet transfusion may actually worsen outcome. Therapeutic plasma exchange or IA is generally performed daily until the platelet count is normal. In TPE, the replacement fluid consists of human albumin electrolyte solution (5%) in 30 to 70 percent and FFP in the remainder. The exchange volume per treatment should be 1 – 1.5 total plasma volume (TPV) depending on the severity of the HUS. TPE may reverse the ongoing platelet consumption. By using IA, no replacement fluid is necessary only between the treatments FFP or coagulation factors may be transfused if required. The hemodialysis treatment can be combined with the TA.

A large outbreak of diarrhea and the HUS caused by an unusual serotype of Shiga-toxin-producing *Escherichia coli* (O104:H4) was in Germany in May to July 2011 with 3,167 without HUS and 16 deaths in the patients, and 908 with HUS and 34 deaths (48). 241 patients with HUS were treated with TPE and 193 patients with TPE and eculizumab. The treatment strategy was dependent on disease severity (49). Therapeutic plasma exchange and eculizumab in combination seems to be prudent and necessary prior to establishing new treatment guidelines.

Aplastic Anemia (AA)

Only some cases of aplastic anemia that have been treated with TPE have been published (11). 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 a consideration of it as an autoimmune disease. In these patients, it was possible to remove the circulating inhibitors with the aid of TPE. As only a few controlled studies have been carried out so far, 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 the ASFA has given the aplastic anemia (pure red cell aplasia, (PRCA)) the category III with RG 2C and for TPE and for pure red cell aplasia the category II with RG 1B (5, 6) (Table 1). The aplastic anemia and the pure red cell aplasia are rare hematopoietic stem cell disorders.

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 disease or without a matched donor and older patients are treated with antithymocyte globulin (ATG) and cyclosporine A (5, 50, 51). Cao et al. used a modified protocol of post-transplantation cyclophosphamide and TPE to decrease the levels of antibodies (52). Primary acquired PRCA is usually responsive to immunosuppressive therapy until remission is obtained. Corticosteroids (prednisone at 1mg/kg/day) are used as 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 (53). These diseases, which may be immunologically mediated, TPE may be helpful by removing serum antibody and/or inhibitory activity.

ABO Incompatible Hematopoietic Progenitor Cell Transplantation

After the guidelines of the AAC of the ASFA, the major incompatibility refers to 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 (5). A lower risk of hemolysis due to reduced red cell contamination (2 – 5 percent) as compared to HPCs derived from the bone marrow is observed in peripheral hematopoietic progenitor cells that are collected by apheresis. If the recipient has a high titer of antibodies, a delayed erythroid engraftment or even pure red cell aplasia may result.

For treatment of delayed erythroid engraftment or PRCA, post transplantation various management strategies have been reported including high-dose erythropoietin (EPO), TPE, IA, donor lymphocyte infusions, discontinuation of cyclosporine, antithymocyte globulin, and rituximab. The optimal treatment is currently not well defined (5).

The AAC of the ASFA has given the category II with RG 1B – 2B for TPE in ABO incompatible hematopoietic progenitor cell transplantation and bone marrow transplants (5, 6) (Table 1). 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 unable to red cell deplete the product. In minor

incompatibility with passenger lymphocytes making antibody 7 – 12 days after infusions, prophylactic red cell exchange with group O red cells can be performed to deplete recipient type red cells.

If unable to red cell deplete the HPC product, TPE should be performed before infusion of HPCs and replacement fluid is combination of albumin and plasma (50:50) compatible with both donor and recipient. The frequency of TPE is daily. The goal should be to reduce the IgM or IgG antibody titers to $\leq 1:16$ immediately before HPC transplantation. Generally, 2 – 4 TPEs are sufficient. If the antibody titer is high in the case of delayed red cell recovery or PRCA, TPE may be performed in the transplantation period (6, 54).

Graft-Versus-Host Disease (GVHD)

The GVHD after allogeneic progenitor cell transplantation (HPCT) is typically characterized as either acute (aGVHD) or chronic (cGVHD). Within 3 months after HPCT, acute GVHD usually occurs 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 (GI), and liver are major organs of aGVHD. Chronic GVHD often results 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 are progressive fibrosis and/or dysfunction of the skin, eyes, mouth, lungs, GI, joints, and vagina. Treatment options include local/topical measures for the skin, eyes, mouth, and GI along with systemic therapies such as calcineurin inhibitors, ATG, mycophenolate mofetil, rapamycin, thalidomide, hydroxychloroquine, pentostatin, monoclonal antibodies against T cells, B cells or cytokines, and ECP (5).

In the guidelines on the use of TA of the ASFA, the graft-versus-host disease has the category II with RG 1B for acute or chronic skin, and III with RG 2B for acute or chronic non-skin for extracorporeal photopheresis (ECP) (5, 6) (Table 1). The rationale of ECP involves the following steps: Collection of peripheral blood leukocytes by apheresis, extracorporeal exposure of the leukocytes to 8-methoxypsoralen followed by irradiation with ultraviolet A (UVA) light, and reinfusion of the photo-activated cells (5). For cGVHD, ECP improves skin or oral manifestations in 60-80 % of steroid-dependant patients. Liver or GI complications respond in roughly 35-75 percent of cases, with the highest rates reported in children. Most

responses with cGVHD are partial. Extracorporeal photopheresis does not induce general immunosuppression the greatest benefit may be in facilitating a rapid corticosteroid taper (5).

The treated volume is a mononuclear cell product of approximately 270 ml consisting of mononuclear cells, plasma and saline (5). The two-process method collects and treats mononuclear cells obtained from two times TBV processing. The replacement fluid is that all photo-activated leukocytes are reinfused lower weight patients: albumin, saline. The frequency is on two consecutive days (one series) every one to 2 weeks. Extracorporeal photopheresis is often performed one series weekly for aGVHD until disease response, usually within 4 weeks, and then tapered to every other week before discontinuation. For cGVHD, one series weekly ECP treatments are continued every week or biweekly either until a response or for 8 – 12 weeks followed by a taper to every 2 – 4 weeks until maximal response. The technical data of the ECP in graft-versus-host disease are reported elsewhere (55, 56).

The results of ECP are associated with a low infection rate and an optimal clinical efficacy. ECP is still a suitable treatment for GVHD. However further studies with larger group of patients will be necessary (57). In recent years, the combination therapy of the Janus kinase inhibitor ruxolitinib and ECP is reported very successful (58, 59).

Erythrocytosis and Polycythemia Vera (PoV)

Erythrocytosis results from an increase in the red cell mass with concomitant increase in RBC number, red cell count at least 25 percent above the gender-specific mean predicted value (60-62). Hematocrit (Hct) values > 60 percent for males and > 56 percent for female are always indicative of absolute erythrocytosis, as these levels cannot be achieved with plasma volume contraction alone or other causes of “apparent” or “relative” erythrocytosis (5). These findings may be generally attributed to hemo-concentration 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 persons (63). PoV is associated with a point mutation of an auto-inhibitory Janus kinase 2 (JAK2) protein kinase domains (64, 65). The activation on this domain results in erythropoiesis los-

ing its dependence on erythropoietin signaling and becoming virally autonomous (66).

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 erythropoietin cells. Erythropoietin stimulation results in the production of 2×10^{11} red blood cells per day (67). All blood cell lines arise from a common hematopoietic stem cell. These stem cells begin their initial differentiation onto erythrocyte progenitors when stimulated by one of several cytokine factors (68).

Erythrocytosis is identified by the increased in hematocrit and red blood cell count, but it is important that these indices are dependent on red blood cell mass and plasma volume. In the guidelines on the use of TA of the ASFA the erythrocytosis has the category III with RG 1C and the PoV has the category I with RG 1B for erythrocytapheresis (5) (Table 1).

Polycythemia Vera include splenomegaly, granulocytosis, thrombocytosis and a point mutation in the tyrosine kinase JAK2 gene. The erythrocytosis refers to the myeloproliferative disorder PoV, in which an abnormal hematopoietic stem cell clone autonomously overproduces red cells to isolated red cell overproduction due to a congenital erythropoietic or hemoglobin defect, chronic hypoxemia related to a respiratory or cardiac disorder, ectopic EPO production (e.g., from renal cell carcinoma, uterine leiomyoma), or EPO augmentation (e.g., post-renal transplantation) and to erythrocytosis in the absence of a primary disorder or features of PoV (5, 69).

The rationale for TA is the red cell reduction by apheresis, like isovolemic phlebotomy, corrects hyperviscosity by lowering the hematocrit, which reduces capillary shear rates, increases microcirculatory flow and improves tissue perfusion. For patients with PoV and acute thromboembolism, severe microvascular complications or bleeding, therapeutic erythrocytapheresis may be useful alternative to emergent large-volume phlebotomy, especially the patient who is hemodynamically unstable. Erythrocytapheresis may be appropriate prior to surgery the high risk of perioperative thrombohemorrhagic complications in a PoV patient with uncontrolled Hct. Thrombocytapheresis, as well as erythrocytapheresis may be indicated for patients with PoV and an acute complication associated with uncontrolled thrombocytosis and erythrocytosis. Red cell reduction by apheresis is a

safer and more effective approach than simple phlebotomy (5). Therapeutic erythrocytapheresis is a secure strategy to can achieve hematocrit depletion in a shorter time than phlebotomy especially in PV and secondary erythrocytosis patients (70)

The treated volume will be 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 PoV patients, the goal is the normalization of the Hct (i.e., < 45 percent). For acquired erythrocytosis, the goal is to relieve symptoms but retain a residual red cell mass that is optimal for tissue perfusion and oxygen delivery. A post-procedure Hct of 50 – 52 percent might be adequate for pulmonary hypoxia or high oxygen affinity hemoglobin, whereas Hct values of 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 (6).

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic purpura is a rare disease of unclear genesis that carries a poor prognosis (71). It is probably a polyetiological complex, with the kidneys and brain as target organs (72). Primarily there is endothelial damage triggered by different factors, which, can be regarded as the basic physiologic process. Both the thrombocytes and the endothelial cells seem to be damaged, such that it is still not clear whether the destroyed endothelial cells cause activity and deposition of the thrombocytes in the micro vessels, or whether disseminated intravascular coagulation is responsible for the morphological changes. Possibly von Willebrand factor and fibronectins, which are formed and released by endothelial cells, play an important role in the pathomechanism of TTP (73). Deficiency of von Willebrand factor (vWF) cleaving protease ADAMT 13 has been demonstrated to be the proximate cause of a subset of TTP.

Many studies show a defective function of perforin in these two conditions. Perforin is a protein found in the cytoplasmic granules of both T cytotoxic lymphocytes and natural killer cells (4). This protein is implicated in target cell lysis by the above cells. TTP is a clinical syndrome defined by the presence of thrombocytopenia and microangiopathic hemolytic anemia. The damage triggers cascade of biochemical events that ultimately leads to the

characteristic feature of TTP – widespread dissemination of hyaline thrombi, composed predominantly of platelets and fibrin, which occlude the terminal arterioles and capillaries (microcirculation) of most of the body organs: commonly, the heart, brain, kidneys, pancreas, and adrenals. Other organs are involved to a lesser degree. Disseminated intravascular coagulation is an explosive life-threatening bleeding disorder in most cases secondary to activation of coagulation factors including tissue factor.

The mortality rate was significantly reduced by the implementation of TPE and/or fresh frozen plasma (FFP) substitution. However, whether the effect of TPE therapy is due to the removal of toxins or to the infusion of certain plasma components or both cannot be definitely stated at present. A defect in prostaglandin metabolism has also been implicated (74). This uncertainty is reflected in the numerous therapeutic approaches, which includes sole substitution of FFP and TPE, besides, splenectomy, corticosteroids, aggregation inhibitors, cytostatics and other drugs. TPE is superior to all other forms of therapy, if implemented in TTP at an early stage (74). The mainstay of treatment for TTP is TPE but the role of splenectomy is still undefined. Therapeutic plasma exchange with FFP replacement is the most effective therapy and should be started as soon as the diagnosis is established and continued daily until neurologic symptoms resolve, renal failure improves and platelet count normalises (75).

In the guidelines on the use of TA of the AAC of the ASFA, the TTP has the category I with RG 1A for TPE (5, 6) (Table 1). Therapeutic plasma exchange decreased the overall mortality from uniformly fatal to < 10 percent. If TPE is not immediately available, plasma infusions should be started at approximately 30 – 40 ml/kg BW per day, until TPE can be initiated. Both plasma and plasma cryoprecipitate reduced (PCR) have been used as replacement fluid for TPE, with similar results in patient outcome. The TPE is effective in treatment of TTP. Once TTP is diagnosed or suspected, patients should be treated with plasma exchange as soon as possible. During treatment, physicians should monitor the occurrence of adverse reactions in TTP patients, deal with adverse reactions in a timely manner, and ensure the safety of patients during plasma exchange (76). Corticosteroids are often used as an adjunct at 1 mg/kg/day. Other adjuncts include rituximab, vincristine, and splenectomy (73). Bleeding, if present, is typically limited to skin and mucous membranes. Platelets should not

be transferred unless clinically indicated. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10 – 15 ml/kg) or cryoprecipitate (which contains ADAMTS13) are used (5).

TPE with plasma replacement has significantly improved patient clinical outcomes. No other intervention has had as significant of an impact on the treatment of TTP. The hypothesis is that TPE removes the anti-ADAMTS13 autoantibody, while restoring ADAMTS13 protease activity (6). Transfusion of RBC, when necessary, may be given emergently during TPE. TPE is performed daily until the platelet count is above $150 \times 10^9/L$ and LDH near normal for 2 – 3 consecutive days. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment (5).

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 heterogeneous group of bleeding disorders with similar hemostatic manifestations but different pathogenic etiologies (71).

Idiopathic thrombocytopenic purpura is 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 (77). 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 (78), 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 (70). The opsonized platelets are destroyed by phagocytosis in the macrophage-

phagocytic system mediated by the Fc receptors FcγRI-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-1b/IIIa and Ib/IX (79, 80).

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 (81). Recently, acquired autoimmune deficiency of a plasma metalloprotease named ADAMTSJB was shown in many cases of ITP (82). Alloimmunization is the cause of neonatal alloimmune thrombocytopenia, platelet transfusion refractoriness, and post-transplant purpura. The alloantigens are classified in the human platelet antigen (HPA) system (83). Neonatal immune thrombocytopenia is the platelet counterpart of hemolytic disease in newborns. A HPA-1a-negative mother is sensitized to HPA-1-positive platelets of the fetus. Alloimmunization (IgG ab >IgM ab) against platelets induced by fetomaternal hemorrhage occurs during an HPA-incompatible pregnancy or after a HPA-incompatible platelet transfusion (79, 84). In heparin-induced thrombocytopenia, type II immune complexes consisting of antibodies to heparin and platelet factor 4 active platelets after binding to platelet Fc receptors. Excess platelet factor 4 binds to endothelial glycosaminoglycan, resulting in endothelial damage and thrombi (71). Heparin-induced thrombocytopenia type I 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 disease. 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 (85). 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 (80).

The diagnosis of ITP based principally on blood count, clinical symptoms, autoimmune profile and other investigation, and on 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 (85). 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 patient's refractory to therapy although some patients have shown improvement in platelet counts following eradication therapy. It is worth determining the presence of *H. pylori*.

The successful use of high doses of IgG and anti-D therapy has reduced TA to second-line or third-line treatment in these cases. The second-line therapy is splenectomy and high dose corticosteroids, high dose IVIG, intravenous anti-D, Cyclosporine 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 (80, 85). Therapeutic apheresis can induce remissions in approximately 80 percent of patients with ITP. Therapeutic apheresis becomes a legitimate 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 objective 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 measurement of free antiplatelet autoantibodies is a useful test for determining whether TPE is indicated and if so, to assess its efficacy (71). In the last years, vaccine-induced ITPs, which are associated with high titers of IgG class antibodies against platelet chemokine platelet factor (PF4), are reported (86-88).

In the guidelines on the use of TA of the ASFA, the ITP has the category II for immunoadsorption in refractory cases and the category IV for TPE. (5) (Table 1). Only a few controlled studies are 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 oral corticosteroids, IVIG (1 – 2 mg of prednisone/kg/day, IVIG at 1 g/kg/day for 1-2 day), and IV anti-Rh (D) (50 – 75 μg/kg). Should no significant improvement be observed within one or

two weeks (thrombocytes $> 80\,000/\mu\text{L}$), then TA treatment should be commenced immediately. The authors recommend plasma exchange with 1 – 1.5 TPV a day for 4 days. Treatment with two to four sessions of TPE per month can also have a positive effect in chronic cases. TPE is recommended prior to surgery in acute resp. chronic uncontrollable bleeding (71). Immunoadsorption with Protein-A was introduced successfully in the treatment of ITP (89, 90).

If thrombocytopenia persists or recurs, splenectomy is recommended in adults but is deferred to prevent overwhelming postsplenectomy infection or allow for spontaneous remission (5). Therapeutic plasma exchange and IA with Protein-A columns may be considered in patients with refractory ITP, with life threatening bleeding or in whom splenectomy is contraindicated. The 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. The frequency is once a week or every 2 – 3 weeks. There are no clear guidelines concerning treatment schedule and duration of treatment. Procedure is generally discontinued when either the patient shows improvement in platelet count $>50 \times 10^9/\text{L}$ or no improvement after about 6 treatments (5). The column with protein-A is no longer in the United States but may be available in other countries.

Great progress has been made in recent years in developing new treatment options for thrombocytopenic patients, especially in ITP. In addition to TA, human monoclonal antibodies and thrombopoietin agents, combination of different diagnosis and therapeutic approaches are the main strategy for difficult cases (71). Especially rituximab is a novel second-line agent for the treatment of ITP with encouraged results of some studies. Thrombopoietin (TPO) is the major physiology regular of platelet production. Thrombopoietin is produced by the liver at a constant rate and cleared from the circulation by TPO receptors on circulating platelets thereby providing an efficient feedback system regulating platelet production by bone marrow megakaryocytes (91). The further new second-line drugs for ITP are the thrombopoietin receptor agonists (TPO-RAs). For platelet response, eltrombopag, and romiplostim were the best. Romiplostim and eltrombopag have high efficacy and safety as second-line treatments in the short term for adult patients with persistent ITP. Eltrombopag and romiplostim stimulate the platelet and

megakaryocyte production. Both substances are approved in the United States and EU for treatment of different forms of thrombocytopenia (92).

Post-Transfusion Purpura (PTP)

Post-transfusion purpura occurs when donor B lymphocytes and dendritic cells migrated as passenger cells to the recipients' system, where they undergo clonal expansion after "homing in" on, and producing alloantibodies to the incompatible HPA allele (93). Post-transfusion purpura is a 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 sensitized during pregnancy (94). 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 intravenous immunoglobulin, corticosteroids, and TPE.

The treatment is high IVIG (0.4 g/kg BW/day for 2 – 5 day or 1 g/kg BW/day for 2 days). It possibly acts by Fc receptor blockade of reticuloendothelial system (5). Patients are also given high dose of corticosteroids. The TPE is indicated only if IVIG is not effective and severe thrombocytopenia persists. Recombinant FVIIa may be considered in a bleeding patient when HPA-1a negative platelets are not available. The removal of HPA-1a alloantibodies by TPE is a decrease of antibody titer, removal of any unattached HPA-1a antigen, and an increase in platelet count and cessation of bleeding. Therapeutic plasma exchange should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG therapy is not effective (5).

In the guidelines on the use of TA of the ASFA the PTP has the category III with RG 2C for TPE based on limited data available in the literature (Table 1) (5, 6). The treated volume, replacement fluid, and the frequency of TPE are the same such in ITP and TTP. Therapeutic plasma exchange can be discontinued when platelet count starts increasing ($> 20 \times 10^9/\text{L}$) and non-cutaneous bleedings stops. Therapeutic plasma exchange is effective as treatment for PTP. Once TTP is diagnosed or sus-

pected, patients should be treated with TPE as soon as possible. During treatment, patients should be monitored to observe possible adverse reactions in TTP,

Thrombocytosis

The thrombocytosis is defined as a circulating platelet count $\geq 500 \times 10^9/L$, and most commonly, phenomenon related to acute bleeding, hemolysis, infection, inflammation, asplenia, cancer, or iron deficiency (5). Patients with PoV and essential thrombocythemia (ET) have a significant risk of arterial and less venous thromboembolic events. These occur either spontaneously or during situational hypercoagulability, such as surgery, immobilization and pregnancy.

The current treatment includes low dose aspirin, which is indicated for thromboprophylaxis in patients with ET, or PoV who do not have a bleeding tendency. Phlebotomy is required to maintain normal hematocrit with PoV. The platelet count should also be normalized before general anesthesia and surgery. Hydroxyurea is the preferred platelet-lowering agent. Further treatments include anagrelide and interferon alpha. Thromboembolic complications are treated acutely with unfractionated or low-molecular-weight heparin followed by transition to therapeutic warfarin (95).

Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believed to ameliorate prothrombotic factors associated with the dysfunctional platelets (5). The rationale for thrombocytapheresis is undefined and the efficacy unproven; therefore the category is II for symptomatic thrombocytosis and III and the RG 2C for prophylactic or secondary thrombocytosis based on conflicting and limited data available in the literature (Table 1). A replacement fluid is not necessary, and the frequency is daily, or as indicated for chronic treatment, 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, the goal is normalization of the platelet count and maintenance of a normal count until cytoreductive therapy takes effect (4). Therapeutic thrombocytapheresis provides an immediate symptomatic relief and is an efficient useful emergency lifesaving procedure in patients with thrombocytosis (96-98).

Hyperleukocytosis

Hyperleukocytosis is a hematologic crisis caused by excessive proliferation of leukemic cells and has a relatively high mortality due to a series of severe complications. 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 (99, 100). Symptoms may rise from the involvement of any organ system, but intraparenchymal brain hemorrhage 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).

The AAC of the ASFA has defined the hyperleukocytosis as a circulating white blood cell (WBC) or leukemic blast cell count $> 100 \times 10^9/L$ (5). Complications of hyperleukocytosis are organ or issue 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. Leukostasis is observed in acute myeloid leukemia (AML) when the WBC is $>100 \times 10^9/L$ and in acute lymphoblastic leukemia (ALL) when the WBC is $> 400 \times 10^9/L$ (6). The symptoms in the central nervous system manifestations are confusion, somnolence, delirium, coma, and parenchymal hemorrhage with focal neurological deficits. Pulmonary complications are dyspnea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure, radiographic findings of interstitial and/or alveolar infiltrates (5).

The important treatment is with induction chemotherapy. Hydroxyurea may be a useful temporizing cytoreductive agent (5). The tumor lysis syndrome and hyperuricemia, which can follow hyperleukocytosis, are treated with intravenous fluids, electrolyte replacement, allopurinol or rasburicase, alkalisation of the urine, and dialysis. RBC transfusions are generally avoided prior to cytoreduction.

In the guidelines of the use of TA of the AAC of the ASFA, the hyperleukocytosis has the category I for leukostasis with RG 1B, and III for prophylaxis with RG 2C for leukocytapheresis (Table 1) (5, 6). Leukocytapheresis has been widely used following anecdotal case reports describing striking clinical improvements with prompt leukoreduction. Leukocytapheresis appears to be effective on early mor-

tality and overall survival (101, 102). Prophylactic leukocytapheresis before appearance of leukostasis symptoms is effective on overall survival and possibly early mortality.

Among children and adults with ALL, clinical leukostasis occurs in < 10 percent of those with WBC counts < $400 \times 10^9/L$ (4). Prophylactic leukocytapheresis offers no advantage over aggressive induction chemotherapy and supportive care. The category III indication for prophylaxis of hyperleukocytosis was assigned because of the limited and conflicting data. Severe end-organ failure 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 manifestations resolve or a maximum benefit is achieved. Concurrent chemotherapy is also required in order to prevent rapid reaccumulation of circulating blasts (103, 104).

A single leukocytapheresis can reduce the WBC count by 30 – 60 % (5). For AML patients with leukostasis complications, discontinue when the blast cell count is < $50 - 100 \times 10^9/L$ and clinical manifestations are resolved. For prophylaxis of asymptomatic ALL patients, discontinue treatment when the blast cell count is < $400 \times 10^9/L$. For ALL patients with leukostasis complications, discontinue treatment when the blast cell count is < $400 \times 10^9/L$ and clinical manifestation are resolved. However, multicentre studies are necessary to better define the role of leukocytapheresis (105).

Coagulation Factor Inhibitions, Disseminated Intravascular Coagulation (DIC)

In patients with DIC, the platelet count is invariably low or rapid decreasing. Disseminated intravascular coagulation may complicate a variety of underlying disease processes, including sepsis, trauma, cancer, or obstetrical calamities, such as placental abruption. The mortality rate of sepsis-associated disseminated intravascular coagulation is high (106).

Major alterations in the coagulation process, offer various theoretical approaches for Therapeutic plasma exchange. There are three stages in the pathomechanism of consumption coagulopathy reaction: hypercoagulable state, intravascular formation of clots, and consumption coagulopathy with reactive hyperfibrinolysis (107). 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 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 formation and/or degradation, such as D-dimer or fibrin degradation products.

The process of consumption coagulopathy can be interrupted in the hypercoagulable stage by eliminating or reducing the levels of active pro-coagulation factors example heparin, depletion of factors II, VII, IX and X with Coumadin or TPE. Therapeutic plasma exchange interrupts the pathogenic chain reaction in the second stage, in which intravascular clot formation occurs, pro-coagulant, anti-coagulant, and depleted and failure of the clearing function of the reticuloendothelial system 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-coagulants with FFP (4).

Stegmayr et al. treated 15 patients with multi-organ failure because 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 normalized (108). More and more case reports are presented of successful treatments of DIC with HMA (e.g., eculizumab) (109).

Hemophilia A

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, XI, XII, or Prekallikrein. Hemophilia A is the longest-known hemorrhagic diathesis. Because 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 (110). Antibodies, however, can also occur spontaneously in older patients or after pregnancy. These antibodies are directed against the patient's own factor VIII and can lead to an acquired factor VIII deficiency. Hemophiliacs may become sensitized 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.

Factor 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 in response to infusions of F VIII (111). 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 unknown. The greatest risk of inhibitor development is associated with nonsense mutations, large deletions and intrachromosomal recombinations (inversion) in the F VIII gene that are predicted to cause a complete lack of endogenous F VIII. The risk of inhibitor development in patients with mild hemophilia increases with the amount of exposure F VIII (112). Often patients present with large ecchymosis, extensive muscle hemorrhages, gastrointestinal bleeding, or even intracerebral hemorrhage (113). The mortality is high because of bleeding complications and treatment complications such as infection.

Many patients with antibody formation display a rapid increase in antibodies after administration of factor VIII. Attempts to suppress the formation of antibodies in these patients through immunosuppressive therapy have, for the most part, been unsuccessful. Therapeutic plasma exchange is used to reduce these antibodies prior to infusing factor VIII. TA in combination with factor VIII has been successful in stopping severe bleeding in hemophiliacs who are unresponsive to Factor VIII and as hematologic preparation to normalize these inhibitors prior to major surgery (114).

Therapeutic plasma exchange is indicated in severely bleeding patients classified as immunological high responders (115). Therapeutic plasma exchange can be considered when plasma concentration of the inhibitors exceeds either 10 BM or 3 MiU. TPE should be implemented prior to high-dose administration of human VIII concentrates. The

use of Immunoabsorption (IA) with anti-immunoglobulin columns may be safer and more effective (116). 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 (0.4g/kg/day), and cyclophosphamide is recommended. This protocol has a success rate of 80 percent. Chronic immunosuppression may be necessary in some cases.

Immunoabsorption is being increasingly applied in the treatment of F VIII inhibitors. Several types of IA methods have been used, although reports are mainly anecdotal, consisting of relatively small numbers of patients. However, IA may be clinically effective and cost-effective and should be considered early in the treatment of patients (Table 1) (5, 113). Multimodal therapy including corticosteroids, rituximab, and emicizumab are reported in the last years (117-120).

Acquired Factor VIII (F VIII) Antibodies in Non-Hemophilic Patients

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

Factor VIII autoantibodies in non-hemophiliacs produce a condition sometimes called acquired hemophilia A. It is the most common autoimmune bleeding disorder involving 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 (121). 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 by passing agents (prothrombin complex concentrates, activated prothrombin complex concentrates), or

recombinant F VIII or porcine F VIII concentrates can be used to treat patients with high-titer inhibitors. Recombinant F VIII is effective in controlling most bleeding episodes. There have been no reports of inhibitory antibodies developing to the product (121).

Acute bleeding complications are an indication not only for the administration of highly dosed concentrated factor VIII, but also for the removal of circulating antibodies through TPE. Substitution with fresh frozen plasma also includes the administration of factor VIII. The advantage of TPE or 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 anticoagulation becomes necessary. With IA, a selective elimination of acquired factor VIII antibodies is available (122).

In the guidelines on the use of TA of the ASFA the coagulation factor inhibitors by hemophilia A and acquired factor antibodies in non-hemophilia patients has the category III with RG 2B for IA and IV with RG 2C for TPE (Table 1) (5, 6). Factor deficiency can be either congenital or acquired; the majority of acquired deficiencies result from auto-antibodies. In addition, congenital factor deficient patients can develop inhibitors, alloantibodies, to the factors. The treatment options for inhibitor suppression include high dose corticosteroids, cyclophosphamide, cyclosporine, rituximab, and high dose IVIG (5). For coagulation factor inhibitors, the extracorporeal removal by immunoadsorption is more effective than TPE (123). The replacement fluid in TPE is plasma in IA none, and the frequency as needed in TPE for congenital, rare factor deficiencies, and in IA for inhibitors daily.

Hyperviscosity Syndrome

Hyperviscosity syndrome caused by cryoglobulinemia, macroglobulinemia, multiple myeloma, or hypergammaglobulinemia, and the Waldenström's Macroglobulinemia (WM) (hyperviscosity in monoclonal gammopathies) are now a generally recognized indication for TPE in adults but in children these diseases are very rare or unknown (124, 125).

Common Remarks

Not only are physical issues important do physical problems play an important role, but also technical ones such as the apparatus required, and, above all, vascular access (126-130). In addition to indi-

cation for TPE and early commencement of therapy, the following are of important considerations:

- The selection of good vascular access, an adequate exchange amount (40 ml/kg BW), and a lowest possible extracorporeal volume.

The substitution medium considerations for replacement fluids are the same for adults and children. The patients must be monitored during and between TPE sessions. Particular attention must be paid to circulation, consciousness, coagulation status, and blood count. If a large-bore catheter is in place in a central vein, sterile procedures must be adhered to, to prevent catheter infection and sepsis.

The indications for TA, calculations for the ordering of blood products, and several important and practical details to consider, must be discussed, thus preventing delays in starting the apheresis procedure. In the experience of Wright et al. TPE appears to be benefit during the acute phase of illness, especially in children with organ-specific disease (130).

The use of TA is regarded to be an extreme therapeutic measure in patients. However, when the need for such treatment is undebatable, TA must be done. A well-trained and experienced team can overcome the technical difficulties in order to complete the procedure without complications. The most frequently observed adverse effects are vascular relative access insufficiency (2%), and mild hypotension (2%) (130).

However, all mentioned therapeutic apheresis methods are still technically complicated and very expensive. A reduction in costs is a valid demand in view of the scarce resources available in the healthcare 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 in German. Physicians are committed to helping all patients entrusted to them to the best of their knowledge, and this means that medical treatment – and particularly the apheresis processes – must become affordable. This demand represents a great challenge 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 the health-care system must intensify their cooperation in this respect.

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 un-thought of at the beginning of the 1980s. This is reflected in the numerous national and international specialist congresses, which take place each year.

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. After Malchesky, every effort should be made to delay the progression of acute and chronic diseases. TA is clearly an important tool in treatment of many complex conditions now and in the future (131).

Conclusion

Therapeutic apheresis with hollow fiber modules has been used successfully in various hematologic diseases most with immunological origin. The therapy of TA is always combined with an immunosuppression therapy and/or human monoclonal antibodies or other drugs. The prognosis of anemias, erythrocytosis, thrombopenia, hyperleukocytosis and coagulation inhibitors has improved in recent years, with TA alone or in combination with other drugs. Especially in severe hematologic diseases, these therapy schemata, TA with immunosuppression with steroids, cytotoxic agents, and/or HMA, are indicated. It is impossible to recruit a large number of cases to perform a controlled trial, in some rare hematological diseases. Therefore in some of these diseases, a definitive conclusion of the therapeutic value of these therapy regiments cannot be done.

List of abbreviations

AA: aplastic anemia, AAC: Apheresis Application Committee, ABO: blood groups, ACS: acute chest syndrome, ADAMT 3, 13: desintegrin and metalloproteinase with thrombospondin motifs 3, 13, AIHA: autoimmune hemolytic anemia, AKI: acute kidney injury, ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, ATG: antithymocyte globulin, ASFA: American Society for Apheresis, BM: Bethesda units, CIC: circulating immune complex, DIC: disseminated intravascular coagulation, ECP: extracorporeal photopheresis, EHEC: enterohemorrhagic E. coli, EPO: erythropoietin, ET: essential thrombocythemia, EX-TX: exchange transfusion, FFP: fresh frozen plasma, F VIII: factor 8, G6PD: glucose-6-phosphate-dehydrogenase, GI: gastrointestinal tract, GVHD: graft-versus-host disease, HbS: hemoglobin S, Hct: hematocrit, HDN: hemolytic disease in newborns, HMA: human monoclonal antibody, HP: hemoperfusion, HPC: hematopoietic progenitor cell, HPA: human platelet antigen, HPCT: allogenic progenitor cell transplantation, HUS: hemolytic-uremic syndrome, IA: immunoadsorption, IC: immune complex, ITP: idiopathic thrombocytopenic purpura; IUT: intrauterine transfusion, IVIG: intravenous immunoglobulin, JAK 2: Janus kinase 2, MiU: Malmö inhibitor units. PAI: plasminogen-activator inhibitor, PCR: plasma cryoprecipitate reduced, PoV: polycythemia Vera, PRCA: pure red cell aplasia, PTP: post-transfusion purpura, RBC: red blood cell, RES: reticulo-endothelial system, RG: recommendation grade, Rh: Rhesus, SCD: sickle cell anemia, TA: therapeutic apheresis, TBV: total blood volume, TPE: therapeutic plasma exchange, TPO: thrombopoietin, TPO-RAs: thrombopoietin receptor agonists, TPV: total plasma volume, TRCA: transient red cell aplasia, TTP: thrombotic thrombocytopenic purpura, TX: transfusion, UVA: ultraviolet A, VOE: vaso-occlusive events, WAIHA: warm AIHA, WBC: white blood cell, vWF: von Willebrand factor

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