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RESEARCH ARTICLE

## Therapeutic Apheresis, Immunosuppression, and Human Monoclonal Antibodies in Hematologic Diseases

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ABSTRACT

To cure a patient by removing his illness by extracting blood is a very old one. Now this old process, bloodletting, placed on a rational basis with therapeutic apheresis using hollow fiber membranes, is being our clinical practice. The authors herein give an overview of TA in hematologic diseases, with immunologic or non-immunologic origin. Immunology and molecular biology of the different hematologic diseases are discussed in relation to the rationale for apheresis therapies, and its place alone or in combination with other therapies, such as immunosuppression, HMAs, tyrosine kinase inhibitors, recombinant factor VVII, VIII, and others. With the introduction of effective biologic agents, therapeutic apheresis is indicated in severe cases such as rapid progression despite immunosuppressive therapy and/or other therapies. In mild forms of hematologic diseases, the treatment with immunosuppressive therapies and/or biologic agents seems to be sufficient. The prognosis of the most of the hematologic diseases has improved in recent years, due in part to very aggressive therapy methods. Therapeutic apheresis is indicated most only in severe hematologic diseases. Therapeutic apheresis can remove effectively toxins, autoantibodies, and other pathological substances from blood and lead to rapid clinical improvement. Adjuvant therapies are different for various diseases and are individualized in type, dose and duration. Therapeutic apheresis can safely be performed in all severe ill patients, most combine with an immunosuppression. Biologic agents are introduced more and more in hematologic diseases successfully. The guidelines of the Apheresis Application Committee of the American Society for Apheresis for the hematologic diseases, which could be treated with apheresis methods are cited.

**Keywords:** Therapeutic apheresis, immunosuppression, human monoclonal antibodies, hematologic diseases

## Abbreviations

AA: aplastic anemia; AAC: Apheresis Application Committee; ab: antibody; ACE: angiotensin converting enzyme; ADAMTS 13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aGVHD: acute Graft-Versus-Host disease; AIHA: autoimmune hemolytic anemia; AKI: acute kidney injury; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ASFA: American Society for Apheresis; ATG: antithymocyte globulin; BM: Bethesda units; BM-MSCs: bone marrow mesenchymal stem cells; BW: body weight; C3b: complement fragment 3b; cGVHD: chronic Graft-Versus-Host disease; DC: dendritic cell; DIC: disseminated intravascular coagulation; ECP: extracorporeal photopheresis; EHEC: enterohemorrhagic *E. coli*; EPO: erythropoietin; ET: essential thrombocythemia; EX TX: exchange transfusion; FV III: factor VIII; FFP: fresh frozen plasma; GI: gastrointestinal tract; GVHD: Graft-Versus-Host disease; HA: human albumin; Hb: hemoglobin; HbS: hemoglobin S; Hct: hematocrit; HDN: hemolytic disease in newborns; HMA: human monoclonal antibody; HP: hemoperfusion; HPA: human platelet antigen; HPC: hematopoietic progenitor cell; HPCT: allogenic progenitor cell transplantation; HUS: hemolytic uremic syndrome; IA: immunoadsorption; IFN $\alpha$ : interferon- $\alpha$ ; IgG: immunoglobulin G; IgM: immunoglobulin M; IMB: internal medicines board; ITP: idiopathic thrombocytopenic purpura; IVIG: intravenous immunoglobulin; JAK2: Janus kinase 2; LDH: lactate-dehydrogenase; MIU: Malmö inhibitor units; 8-MOP: 8-methoxypsoralen; PAlg: platelet associated IgG; PCR: plasma cryoprecipitate reduced; PF4: platelet factor 4; PoV: polycythemia Vera; PRCA: pure red cell aplasia; PTP: post-transfusion purpura; RBC: red blood cell; RG: recommendation grade; Rh: Rhesus; RT: essential thrombocythemia; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SCD: sickle cell anemia; TA: therapeutic apheresis; TPE: therapeutic plasma exchange; TPO: thrombopoietin; TPO-RA: thrombopoietin receptor agonist; TPV: total plasma volume; TTP: thrombotic thrombocytopenia purpura; TX: transfusion; UVA: ultraviolet A light, vWF: von Willebrandt factor; WBC: white blood cell;

## Introduction

Since more than 50 years, new process for therapeutic apheresis (TA) became available which used hollow fiber modules instead centrifuges (1). The advantage of these hollow fiber modules is a complete separation of the cellular components from plasma and due to increased blood flow rate higher efficacy. However, cell damage – especially to thrombocytes – occurs less using membranes than

centrifuges for blood separation methods (2). The adsorption technologies with special columns allow the best selective separation of plasma components without the use of substitution solution. Therapeutic Apheresis with hollow fiber membranes is simple and safe to apply and can be competitive to other extracorporeal detoxification methods (3). The advantage of the membrane technology is its simplicity to use with blood pumps and no observed white blood cell or platelet loss (4). The use of centrifuge for TA has a shorter treatment time such as the use of hollow fiber membranes is shown (5). However, this is no advantage. Important is to keep the blood levels with antibodies, and/or pathogenic substances on a very low level over long time of the treatment, and the substances that should be eliminated by the hollow fiber module could invade intravascular and be eliminated.

Therapeutic apheresis is the generic term for different extracorporeal blood purification methods to remove inflammatory mediators, antibodies, and other toxic substances. This method is used successfully in different immunological and non-immunological diseases (6,7). Therapeutic apheresis is indicated in the management of different hematological diseases. For many of these diseases, clear pathogenetic mechanisms of the diseases are understood, and there are well-defined criteria with regard to therapy. Most medical management of immunohematological disorders requires TA, serological immunomodulation, and immuno-suppression with steroids, cytotoxic agents, metabolites, and human monoclonal antibodies (HMA). The overall therapy is individually tailored to the needs of the patient. Controlled trials are difficult if not possible because of variables such as severity of disease, degree of organ system damage before treatment, age and the existence of co-morbid conditions, or in rare hematological diseases. It is impossible to recruit a large number of cases. For most of these disorders only small series of cases are available (8).

The destruction of the target cell in lysis is caused directly by autoantibodies. The cytotoxic antibodies react through complement activation with antigen of the cell surface and cause intravascular lysis of erythrocytes through stages. The antibodies can opsonize the affected erythrocytes, for example in autoimmune hemolytic anemia. The binding of antibodies with complement participation changes the cell such that they are increasingly phagocytized. The opsonization process is the so-called immune clearance, the effective way to remove intruding cells through immune bodies (8). The therapeutic apheresis methods, which are used in hematology, are therapeutic plasma exchange

(TPE), immunoadsorption (IA) hemoperfusion (HP), red-blood-cell (RBC) exchange, erythrocytapheresis, thrombocytapheresis, and extracorporeal photopheresis (2). The TA method chosen depends on the pathophysiological origin of a given disease. Physician must be knowledgeable concerning the half-life time, the compartmental distribution of pathogenic proteins, and the elimination of other toxic substances and complement components, when he chose the TA method.

In addition to TA, HMA and thrombopoietin agents, combinations of different diagnostic and therapeutic modalities and different therapeutic approaches are the main strategy for severe thrombocytopenia (9). The efficacy and safety of the HMAs have improved in the treatment of

different cardiovascular, cancers, respiratory, hematology, autoimmune, and infection diseases (10). Thrombopoietin (TPO) is the major regulator of platelet production. It is produced by the liver and cleared from the circulation by TPO receptors on circulating platelet (11). The new second-line drugs for thrombocytopenia are the thrombopoietin receptor agonist (TPO-RAs).

The authors try to give a review of the most important pathogenic aspects indicating that TA and/or HMAs could be a supportive therapy in hematology. The guidelines of the Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) are cited for these hematologic diseases which can be treated with TA (3, 12) (Table 1).

**Table 1: TA in hematological and hemostasiological diseases.**

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 under taken (3, 12)

Hematological and hemostasiological diseases	Category	RG	TA modality	Exchange volume (TPV)	Replacement
Rhesus incompatibility, Red cell alloimmunization in pregnancy	II II	2C 2C	TPE	1-1.5	5% HA-Electrolyte solution
Autoimmune hemolytic anemia -warm autoimmune hemolytic Disease -cold agglutinin disease	III II	2C 2C	TPE		
Sickle cell anemia - acute stroke - acute chest syndrome - prophylaxis for primary or secondary stroke; prevention of transfusion iron overload	I II III	1C 1C 1C	RBC-exchange		
Babesiosis - severe - high risk population	I II	1B 2C		1-1.5	5% HA-electrolyte solution
Hemolytic uremic syndrome - complement gene mutations - Factor H antibodies - MCP	II I IV	2C 2C 1C	TPE		
Aplastic anemia Pure red cell aplasia	III II	2C 1B	TPE		
ABO incompatible hematopoietic progenitor cell transplantation	II	1B-2B	TPE		
Graft-versus-host disease - skin, acute - skin, chronic - non skin, acute/chronic	II II III	1C 1B 2B	ECP	270 ml	Plasma
Erythrocytosis Polycythemia Vera	III I	1C 1B	Erythrocytapher	RBC	

Hematological and hemostasiological diseases	Category	RG	TA modality	Exchange volume (TPV)	Replacement
Thrombocytopenia -thrombotic thrombocytopenia Purpura -idiopathic thrombocytopenia Purpura -Post-transfusion purpura	I IV II III	1A 1C 1C 2C	TPE TPE IA TPE	1-1.5	5%-HA Electrolyte solution  --- 5% HA
Thrombosis - symptomatic - prophylactic or secondary	II III	2C 2C	Thrombocytapher		---
Hyperleukocytosis - leukostasis - prophylaxis	I III	1B 2C	Leukocytapheresis		---
Coagulation factor inhibitors -alloantibody -autoantibody	IV III III III	2C 2B 2C 1C	TPE IA TPE IA		FFP --- FFP ---

TA: therapeutic apheresis, RG: recommendation grade, TPE: therapeutic plasma exchange TPV: total plasma volume, ECP: extracorporeal photopheresis, IA: immunoadsorption with staphylococcal protein, HA: human albumin, RBC: red blood cell; FFP: fresh frozen plasma

## Rhesus Disease, Hemolytic Disease in Newborns

Rhesus (Rh) disease or incompatibility during pregnancy is an indication for TPE as a supportive therapy (3). To carry out anti-D gamma globulin prophylaxis in Rh-negative women after the birth of a Rh-positive child has been common practice for several years. Increased anti-D antibodies still occur in up to 3% of subsequent pregnancies, which can lead to life-threatening morbus hemolyticus neonatorum for the fetus. The newborns rapidly develop anemia and hyperbilirubinemia with kernicterus. Here, exchange transfusion and/or TPE is the therapy of choice (8,13,14). Through the detection of anti-D antibodies in the mother and the detection of bilirubin in the amniotic fluid, the diagnosis can be quickly made. The earlier Rh incompatibility manifests, the poorer the prognosis. Prior to the 26<sup>th</sup> week of pregnancy, more than 93% of the fetuses die by the 31<sup>th</sup> week. If after the 26<sup>th</sup> week the Rh disease manifests itself, the mother is treated with TPE, and the child receives intrauterine or postpartal exchange transfusion, 71% of these children survive, whereas without treatment most die (15). Intrauterine exchange transfusions can be a lifesaving procedure but involve a high risk.

Hemolytic disease in newborns (HDN), which presents as icterus neonatorum or hydrops fetalis are caused by alloimmunization 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 the first pregnancy. The anti-RhD antibodies transverse the placenta barrier into the fetal circulation and destroy their fetal red blood cells by non-complement-dependent mechanism, often during the second pregnancy (16). After the birth, the newborn receives a phototherapy and/or a neonatal exchange transfusion, or TPE, which is depending on the severity of hemolytic disease in newborns (13).

The fetal intravascular transfusion and the intravenous immunoglobulin (IVIG) therapy have reduced the former significance of the disease. Towards the beginning of the second trimester in women who have developed hydrops fetalis before the 22<sup>nd</sup> week of a previous pregnancy combined with IVIG, TPE can be administered (8). Maternal TPE may be the only therapeutic option to save the fetus for alloimmunization against other red blood cell antigen, which makes intravascular transfusion impossible. Therapeutic plasma exchange is recommended only on severe HDN in the early stage of pregnancy before fetal transfusion is possible.

TPE has been successfully performed thousands of times for Rh incompatibility, however, anti-D antibodies can also increase under TPE (17,18). Intrauterine exchange transfusion involves a considerable risk to the child, however, TPE for the mother is safe and effective. To attempt control of the disease by TPE and IVIG for the mother seems to be the first step, and if control is ineffective then reconsider intrauterine exchange transfusion.

The AAC of the ASFA has given the HDN the category II and the recommendation grade (RG) 2C (Table 1) (3, 12). The removing of the maternal red cell alloantibodies, that are responsible for HDN, is the rationale for TPE, and thereby it protected the child from HDN. Category II for TPE is assigned for patients who has 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 (18,19,20).

During pregnancy, TPE can safely be performed, and it should be considered early in pregnancy, from the 7<sup>th</sup> to 20<sup>th</sup> week and continued until intrauterine exchange transfusion can safely be administered, about 20<sup>th</sup> week of gestation (21,22). In the first week three procedures of TPE are performed followed by IVIG at 1 g/kg BW weekly.

## Hemolytic Anemia

Most causes, acquired or hereditary, of hemolytic anemia are autoimmunity, microangiopathy, and infections. Anti-erythrocyte antibodies cause immune-mediated hemolysis, which can be secondary to malignancies, autoimmune disorders, drugs, Covid-19, and transfusion reactions (8,23). When the red cell membrane is damaged in circulation a microangiopathic hemolytic anemia follows, leading to intravascular hemolysis and the appearance of schistocytes. Infectious agents such as malaria and/or babesiosis invade the red blood cells (8,24). Hemolytic anemia has a quite variable severity depending on the cause it can be mild and compensated for by increased erythropoiesis so that there is no decrease in red cell mass. For mild forms and forms of such severity as to decrease red cell mass, the treatment is directed at correction of the underlying cause. In severe hemolytic anemia, with hemoglobinemia, heme saturation of albumin and hemoglobinuria regardless of whether it is mediated by exogenous or endogenous noxae, timely implementation of TPE appears indicated (8). Another successful therapy is rituximab alone or in combination with TPE (25):

## Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is characterized by reduced erythrocyte in vivo survival time and by the presence of warm or cold agglutinating antibodies against the autologous erythrocytes. Based on their serological features a differentiation between the following antibodies is possible (24,26):

- Thermo-type: Warm agglutination autoantibodies, which mostly consist of IgG and its various

subclasses. At body temperature (37°C), the optimum antibody activities are reached  
Cryo-type: Cold agglutination autoantibodies, which belong to the group of IgM antibodies, display their strongest reaction to antigen-bearing cells at low temperature (0-10°C). If temperature of 30°C or more is reached, they become of clinical importance.

Bithermal autoantibodies belong to the IgG antibodies. Contrary to thermo-type, antibodies bind at low temperature (0-10°C) and hemolyze erythrocytes at body temperature (37°C).

Autoimmune hemolytic anemia is diagnosed by direct microscopic evaluation of the peripheral blood film, hyperbilirubinemia, reticulocytosis, positive direct antiglobulin test (direct Coomb's test), and elevated LDH (26). The AIHA is a result of antibody fixation to a red cell antigen, which triggers either intravascular red cell destruction mediated by the terminal lytic complement complex (C5b-C9) or extravascular destruction mediate by macrophage phagocytic system (27). Both mechanisms require opsonization by antibodies or complement factor 3b (C3b) complement. The antibodies mostly belong to the IgM (cryo-type abs) and IgG groups, or occasionally also to the IgA (thermo-type abs).

A prominent role in the breakdown of opsonized erythrocytes plays the mononuclear phagocytic system in the spleen (28). The classical pathway is activated by the complement system, which is involved in approximately half the patients (29). The complement-mediated erythrocyte destruction most occurs through phagocytosis of C3b-coated cells. Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have been described (30). Terminal complement activation leads to formation of the membrane attack complex and intravascular hemolysis in some patients (31). The IgG-coated red blood cells are partially ingested by the macrophages of the spleen, leaving micro spherocytes, if warm autoantibodies attach to red blood cell surface antigen. Cold autoantibodies (IgM) temporarily bind to the RBC membrane, active complement, and deposit complement factor C3 on the cell surface. The macrophages of the liver, extravascular hemolysis, slowly clear these C3 coated RBC (31). Autoimmune hemolysis in most cases is idiopathic. Lymphoproliferative disorders, e.g., chronic lymphocyte leukemia, non-Hodgkin's lymphoma, may produce warm or cold autoantibodies. Many of prescribed drugs can induce production of both types of antibodies (abs). 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 first-line therapy of corticosteroids and cytostatics or second-line therapy of splenectomy, and TA and/or HMA such as rituximab, or eculizumab and others are increasingly being implemented with success (32,33). Newer drugs are the proteasome inhibitor bortezomib, or tyrosine kinase inhibitors such as ibrutinib and rilzabrutinib etc. (34).

The AAC has given the autoimmune hemolytic anemia category III with RG 2C for the warm AIHA and for the cold agglutinin disease category II with RG 2C (Table 1) (3, 12). Symptoms include fatigue, and jaundice. Antibody, pathogenic immune complexes, activated complements removal by TPE is safe and effective in AIHA, especially in severe situations or if other treatments have failed. The frequency is daily or every other day. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized red cells (35). The improvement of AIHA after TPE is usually temporary, depending on the auto abs, and its rate of production. The duration of the TPE treatment is until the hemolysis is controlled and the need for transfusions is limited. The frequency is daily or every other day. Human monoclonal antibodies such rituximab, penpulimab, etc., are introduced with great success in cases and small patient groups (34,36,37). In severe cases AIHA, where other therapies failed, HMAs can combined with TPE.

## Sickle Cell Anemia

Sickle cell anemia (SCD) is an inherited disorder caused by a point mutation leading to a substitution of valine for glutamic acid in the sixth position of the  $\beta$ -chain of hemoglobin (38). Sickle cell anemia has a widely variable clinical course. Hemoglobin S (HbS) is the cause for membrane abnormalities sickling and oxidative damage, along with impaired deformability of sickle cell. Sickle cells are seen on the peripheral smear. The presence of HbS can lead to polymerization of hemoglobin molecules upon deoxygenation, resulting in RBCs that are poor carriers of oxygen compared to their HbA counterparts and more prone to obstruction of small vessels causing vaso-occlusions (3,39). Sickled RBCs have shortened lifespan, producing hemolytic anemia. The SCD can manifest clinically in many organs, including nervous system, such as stroke, silent cerebral infarcts; cardiopulmonary system, such as acute chest syndrome, pulmonary hypertension; reticuloendothelial system, such as splenic sequestration, functional hyposplenism; musculoskeletal system, such as a vascular necrosis; gastrointestinal system, such as hepatopathy,

cholelithiasis; and urogenital system, such as renal failure, priapism (39). Overall mortality rate for SCD is 2.6% (5 death/100 person per year) with the peak at 1–3 years of age (12).

The first-line therapies include penicillin prophylaxis, folic acid, pneumococcal and Hemophilus influenza vaccinations, analgesis for painful episodes and antibiotics for infections (16). Red blood cell transfusion (TX) can be also a first-line adjunct therapy with simple RBC TX or RBC exchange TX (EX-TX). In severe cases of SCD RBC-TX is one of best treatment to improve oxygen-carrying capacity of blood by increasing RBC mass and stop the organ failure, before surgery or in complicated pregnancy. Chronic TX to maintain HbS < 30% is indicated to prevent the different organ failure (40).

In acute ischemic stroke or acute or organ-threatening complications, erythrocytapheresis is preferred over single RBC-TX since the HbS concentrations reduced rapidly by removing and relapsing sickled RBCs with normal RBCs without on creasing blood viscosity and volume overload (41). Erythrocytapheresis, as long-term therapy, has an advantage of preventing or markedly reducing transfusion associated iron accumulation, but is 1.5–3 times higher blood requirements than single RBC-TX (42). In patients with acute severe sickle cell-related complications besides RBC, TPE can be used successfully (43–45).

The AA C of the ASFA has given the sickle cell disease the category I for life organ threatening complications with the RG 1C, and the category II with the RG of 1C for acute chest syndrome (3). The category III with the RG 1C has the prophylaxis for primary or secondary stroke, and prevention prevention of transfusion iron overload. The multi-organ failure has the category III with the RG 2C for RBC exchange (3,12) (Table 1). The replacement fluid is HbS negative leukoreduced RBCs, and, if available, antigen matched for E, C, and Kell (3). In acute situations only one procedure is sufficient to treat the acute complicates of SCD, and for chronic transfusion therapy, RBC-exchange is typically performed at patient specific intervals to maintain the desired HbS < 30-50% (42-45).

## Babesiosis

Human babesiosis, another hemolytic anemia, is a worldwide problem and presents a significant health burden in areas where it is endemic (46). Babesiosis is a protozoal disease transmitted from an animal reservoir to humans by the bites of hardtacks, or, more rarely, by transfusion (3). The 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*, *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 (3). The symptoms are usually nonspecific. Patients, which are immunocompromised, asplenic patients, patients with HIV, simultaneous infection with Lyme disease, and elderly patients may have much more serious clinical course. These patients have symptoms, which may include hemolytic anemia, acute kidney injury (AKI), disseminated intravascular coagulation (DIC), congestive heart failure, and pulmonary disease. The diagnosis is made by examination of a Giemsa-stained, DNA implication using polymerase chain reaction, or detection of specific antibodies.

The hemoprotzoan parasites are transmitted by ticks, transfusion of contaminated blood products, solid organ transplantation, or from mother to fetus (47). Babesiosis is caused by intraerythrocytic protozoan of the genus *Babesia*, resulting in afebrile illness and hemolytic anemia. It is endemic in the Northwest and upper Midwest of the USA, and the number of cases reported increased significantly over the last two decades, and babesiosis remains an emerging infectious disease (48,49) Therefore, the first-line therapy includes a combination of antibiotics, most quinine and clindamycin.

The AAC of the ASFA has given the babesiosis 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) (3,12). The mechanism of action of exchange transfusion is to lower the level of parasitemia by physically removing the infected RBC from blood and replacing them with noninfected RBC. The babesia organism has not an exo-erythrocyte phase, removal of RBC-associated parasites is potentially curative. The hemolytic process produces vasoactive compounds, including a variety of cytokine and thromboplastin, which can promote renal failure and DIC. Red cell exchange may help to curtail the production of these substances. The advantage of RBC exchange over antibiotic therapy is its rapid therapeutic effectiveness (3, 12). 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 is not clear. Treatment is usually discontinued after achieving < 5% residual parasitemia

## Hemolytic-Uremic Syndrome

Hemolytic-uremic syndrome (HUS) is a severe disease, which can lead to AKI and often to other serious sequelae, including death. The disease is characterized by microangiopathy, hemolytic anemia, thrombocytopenia and AKI. The disease is associated with dysregulation of the immune complement system, especially of the alternative pathway (50). However, the etiology and pathogenesis of HUS are not completely understood, and the therapy is therefore complicated. Several authors reported successful treatment using TA as a supportive therapy in more than 87 percent of treated patients. Therapeutic apheresis is indicated in severe courses of HUS and is superior to other available therapy interventions (51). In recent years, several studies reported improvements in renal and hematological parameters under the treatment with HMA eculizumab (52).

Most patients have infections with enterohemorrhagic *E. coli* (EHEC). Through contaminated food, these bacteria can be transmitted, animal and person to person contact. Hemolytic-uremic syndrome is one of the most severe complications of a potentially avoidable food-borne infection. A further cause of HUS described as “typical” have to be differentiated since other factors including genetic disorders are of importance. Three main different pathogenetic types, which can lead to HUS, are distinguished, HUS caused by infections, idiopathic HUS (non-Shiga toxin HUS), and HUS in systemic diseases and after toxin exposure (53).

Spontaneous recovery from HUS have been reported. However, the total lethality in HUS was first reduced 5 to 20 % with the introduction of dialysis (54). If the dialysis is administered early enough, two-thirds of cases recover without any impairment. In 10 – 20 % of cases, however, lasting renal damage occurs.

Therapeutic plasma exchange and IA were successfully introduced in the treatment of HUS (55-58). Substitution of plasma or coagulation factors is often necessary due to severe coagulation problems in HUS. More effective than infusions alone, might be TA, as it removes potentially toxic substances from the circulation (51). Therapeutic plasma exchange or IA should be considered first-line therapy in situation that limit to amount of plasma that can be infused, such as renal or heart failure. Contraindicated is plasma infusion treatment in *S. pneumonia* induced non-Stix HUS. The disease may be exacerbated because adult

plasma contains antibodies against Thomas Friedenreich antigens (59)

Therapeutic plasma exchange and/or dialysis as supportive therapy are still the most effective treatments in HUS (60). None of the evaluated intervention such as fresh frozen plasma transfusion or dipyridamole, Shiga toxin binding protein and steroids was superior to supportive therapy alone for any outcomes. The advantage of TA over other therapeutic procedures is that it intervenes at an early stage in the pathogenetic processes by rapidly removing immune complexes and toxins. Therapeutic plasma exchange 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 HF 1 with a partial HF 1 deficiency and all other toxic substances can be rapidly removed by TA, which is the rationale for TA (3). Due the poor prognosis of HUS in adults, TA seems a reasonable option (51).

The AAC of the ASFA has divided HUS in three 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), which has the category I with the RG 2C. Group 3 is the typical HUS < 18 years. Group 3 has the category IV with RG 1C (Table 1) (3,12). There are no exact guidelines available for the therapy of HUS, due to the various and very different causes, which can lead to HUS. The supportive therapy of TA is indicated which include control of fluid and electrolyte imbalance, use of dialysis if required, control of hypertension, blood and plasma transfusion as required (57). Antibiotic therapy of *E. coli* O157:H7 colitis may stimulate further verotoxin production and can increase the risk of HUS. Hemodialysis or peritoneal dialysis as required must be daily, however, without dialysis in adults or children may progress to end in organ damage. Platelet transfusion may actually worsen outcome.

Therapeutic apheresis is generally performed daily until the platelet count is normal. In TPE, the replacement solution consists of human albumin electrolyte solution of 5% in 30 – 70 % and FFP in remainder. The exchange volume per treatment should be 1–1.5 total plasma volume (TPV) depending on the severity of the HUS. In IA no replacement solution is required. The hemodialysis treatment can be combined with the TA. In recent

years, there are more and more reports of HMA in the treatment of HUS (6,61). The studies reported improvement in renal and hematological parameters in most of the patients treated with eculizumab (52). Especially in atypical HUS, the treatment with eculizumab is effective (62,63).

In May to July 2011 in Germany was a large outbreak of diarrhea and HUS caused by an unusual serotype of Shiga-toxin-producing *Escheria coli* (O104:H4) with 3,167 without HUS and 16 death in the patients, and 908 with HUS and 34 deaths (64). With HUS, 241 patients were treated with TPE and 193 patients with HUS were treated with TPE and eculizumab. The treatment strategy depended on the severity of the disease (65). Therapeutic plasma exchange and eculizumab in combination seems to be prudent and necessary prior to establishing new treatment guidelines. Further studies are necessary to prove TPE in combination with HMA or alone, what would be the best therapy in HUS.

## Aplastic Anemia

The pathogenesis of aplastic anemia (AA) is regarded as complex and mostly unclear. Hemopoietic and erythropoietic inhibitors have found in the serum of some cases, which could be an autoimmune disease. In these patients, it was possible to remove the circulating inhibitors by TPE. Therapeutic plasma exchange is only indicated in the case of proven autoimmune pathogenesis. Until now only some case reports of AA, which have treated with TPE have been published (8). Successful therapy has also been conducted with Cyclosporin A. Another study showed human leukocyte antigen-haploidentical hematopoietic stem cells transplantation combine with allogenic mesenchymal stem cell infusion in the therapy of severe AA (66). Besides immunosuppression, more and more HMA such as eculizumab or alemtuzumab are applied in severe AA with success (67,68).

The AAC of the ASFA has given the aplastic anemia the category III and the RG 2C, and the pure red cell aplasia (PRCA) the category II with the RG 1B (3,12) (Table 1). The AA and PRCA are rare hematopoietic stem cell diseases. In newly diagnosed patients < 40 years old, allogenic hematopoietic progenitor cell (HPC) transplant is the treatment of choice for severe AA. In young patients with mild disease or without a matched donor and older patients, the treatment is with antithymocyte globulin (ATG) and cyclosporine A (3,69,70). Immunosuppressive therapy is usually sufficient until remission is obtained in primary acquired PRCA. Corticosteroids such as prednisone at 1 mg/kg BW per day, are used as first. If no



response is achieved after 2-3 months, salvage agents include cyclophosphamide, azathioprine, Cyclosporine A, ATG and high dose IVIg are indicated (71). In diseases that may be immunologically mediated, TPE and/or HMAs 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 (3). In the 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 higher titer of antibodies, especially a group of patient receiving a group A transplant, a delayed erythroid engraftment or even pure red cell aplasia may result (3).

Various therapy strategies have been published for the treatment of delayed erythroid engraftment or PRCA, such as post transplantation, including high-dose erythropoietin (EPO), TPE, or IA, donor lymphocyte infusions, discontinuation of cyclosporine, antithymocyte globulin, rituximab, and steroids. An optimal treatment is until today not well defined (3,72).

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 transplantation (3,12) (Table 1). The ABO antibodies, which are responsible for hemolysis and PRCA can be successfully reduced by TPE or selective ABO IA (73,74). The removal of the high titer antibody from the recipient's circulation can prevent hemolysis, in most of the ABO incompatibility patients; if red cells are unable to deplete the product. In minor incompatibility with passenger lymphocytes making antibodies 7-12 days after infusions, prophylactic red cell exchange with group O red blood cell can be performed to deplete recipient type red cells (3,12). Therapeutic apheresis 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, if unable or red cell deplete the HPC product (3). Before HPC transplantation, the goal should be reduced IgM or IgG antibody

titers to  $\leq 1:16$  immediately. Generally, 2-4 TPE 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 (3,75). The therapy with calcineurin inhibitors and TPE showed a response rate of 64% (76).

Monoclonal antibodies such as datumab, an IgG1k anti-CD38 monoclonal antibody that can target plasma cells producing anti-donor isohemagglutinins is specific to disease, and is applied in PRCA after major ABO-mismatched allogeneic hematopoietic stem cell transplantation (77). Further studies are necessary.

## Graft-Versus-Host Disease

The Graft-Versus-Host disease (GVHD) following allogeneic cell transplantation (HPCT) is characterized as either acute (aGVHD) or chronic (cGVHD). Acute GVHD usually occurs within 3 months after HPCT and results from activation of donor T cells by host antigen-presenting cells, leading to immune and cytokine-mediated tissue injury (3). The skin, gastrointestinal tract (GI), and liver are major targets 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. Progressive fibrosis, and/or dysfunction of the skin, eyes, mouth, lungs, GI, joints and vagina are the end-organ complications of cGVHD (3,12). 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 GI along with systemic therapies such as calcineurin inhibitors, ATG, mycophenolate mofetil, rapamycin, thalidomide, hydroxychloroquine, sirolimus, pentostatin, monoclonal antibodies against T cells, B cells or cytokine, and extracorporeal photopheresis (ECP) (12).

The AAC of the ASFA has given the HVHD the category II (skin, acute and skin, chronic) with RG 1B-1C, and the category III with the RG 2B for acute or chronic non skin for ECP (Table 1) (3,12). The rationale for ECP involves the collection of peripheral blood leukocytes by apheresis, the extracorporeal exposure of the leukocytes to 8-methoxypsoralen (8-MOP) followed by irradiation with ultraviolet A (UVA) light, and reinfusion of the photoactivated cells (12). The therapeutic effect of ECP for GVHD appears to involve induction of apoptosis 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 cell that establish immune tolerance. Extracorporeal photopheresis in cGVHD improves skin or oral manifestations in 60-80% of steroid-dependant patients. In 35-75% of cases respond of liver or GI complications in children. The most responses of GVHD are partial. The greatest benefit may be in facilitating a rapid corticosteroid taper, ECP does not induce general immunosuppression.

Approximately 270 ml consisting of mononuclear cells, plasma and saline is the treated volume (3). All photo-activated leukocytes are reinfused lower weight patients is the replacement fluid with albumin and saline. The frequency is on two consecutive days every to 2 weeks. For aGVHD, ECP is often performed one series weekly, 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 (78,79). Low infection rate and an optimal clinical efficacy are the results of ECP (80).

The combination therapy of the Janus kinase inhibitor ruxolitinib or ibrutinib and ECP is reported very successful in CVHD in recent years (81-84). Further Therapy possibility is the mesenchymal stem cells, which show considerable promise in the treatment of GVHD because of their potential immunomodulatory activity (85). A therapy protocol was developed for baxilimab in steroid-refractory aGVHD. Baxilimab is safe and effective for treating aGVHD (86). However, further studies are necessary, which is the most effective therapy for GVHD.

### **Erythrocytosis and Polycythemia Vera**

An increase in the red cell mass with concomitant increase in RBC is called erythrocytosis. Red cell counts at least 25 % above the gender-specific mean predicted value (87-89). Hematocrit (Hct) > 56% for female and > 60% for males are always indicate of absolute erythrocytosis, as these levels cannot be achieved with plasma volume contraction alone or other causes of “apparent” or “relative” erythrocytosis (3). These attributed to hemo-concentration given the many cases of dehydration, hypovolemia and other relatively low-volume states encountered in the emergency department.

Polycythemia Vera (PoV) is a myeloproliferative neoplasm, which follows by excessive proliferation of erythroid, myeloid, and megakaryocytic components in the bone marrow due to mutations in the Janus kinase 2 (JAK2) (90). With a point-

mutation of an auto-inhibitory Janus kinase 2 protein kinase domain is PoV associated (91,92). About 2.6 cases per 100.000 persons is the incidence of PoV (93). Polycythemia Vera include splenomegaly, granulocytosis, thrombocytosis and a point mutation in the tyrosine kinase JAK2 gene. Erythropoiesis follows the activation on this domain, which losing its dependence on erythropoietin signaling and becoming virtually autonomous (94). About 90 % of the circulating erythropoietin are produced in the renal cortex, and in the liver, spleen, lung, testis, brain, and erythroprogenitor cells are produced the rest. Erythropoietin stimulation results in the production of  $2 \times 10^{11}$  red blood cells per day (95). From a common hematopoietic stem cell arise all blood cell lines. These stem cells begin their initial differentiation onto erythrocyte progenitors when stimulated by one of several cytokine factors (96). A congenital erythropoietic or hemoglobin defect, chronic hypoxemia related to a respiratory or cardiac disorder, ectopic EPO production are from renal cell carcinoma or uterine leiomyoma, or EPO augmentation, post-renal transplantation, and to erythrocytosis in the absence of a primary disorder or features of PoV (3,97).

The AAC of the ASFA has given the erythrocytosis the category III with the RG 1C and the PoV the category I with RG 1B for erythrocytapheresis (3, 12) (Table 1). The red cell reduction by apheresis is the rationale for TA, like isovolemic phlebotomy, corrects hyperviscosity by lowering the Hct, which reduces capillary shear rates, increases microcirculatory flow and improves tissue perfusion. Erythrocytapheresis may be useful in patients with PoV and acute thromboembolism, severe microvascular complications or bleeding, as an alternative method to emergent large-volume phlebotomy, especially the patient who is hemodynamically unstable. The erythrocytapheresis may be appropriate prior to surgery the high risk of perioperative thrombohemorrhagic complications in a patient with PoV with uncontrolled Hct. Erythrocytapheresis as well as thrombocytapheresis may be indicated in patients with PoV and an acute complication associated with uncontrolled thrombocytosis and erythrocytosis. Red cell reduction by TA is safer and more effective approach than simple phlebotomy (3). Erythrocytapheresis is a secure strategy to can achieve Hct depletion in a shorter time than Phlebotomy especially in PoV and secondary erythrocytosis patients (98).

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.

Albumin-electrolyte solution is the replacement fluid and the frequency are one procedure. In PoV patients, the goal is the normalization of the Hct < 45 %. 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 % might be adequate for pulmonary hypoxia or high oxygen affinity hemoglobin, whereas CT values of 55 – 60 % might be optimal for patients with cyanotic congenital heart disease. A single procedure should be enough to achieve the desired post-procedure Hct (12).

An important component of the hematopoietic microenvironment, bone marrow mesenchymal stem cells (BM-MSCs) play a high role in the hemostasis and pathogenesis of the hematopoietic system by regulating the fate of hematopoietic stem cells. Remodeled CD146\*CD271 BM-MSCs might contribute to the pathogenesis of PoV, a finding that will shed light on potential therapeutic strategies for PoV (99). A new monoropegylated formulation of Interferon alpha-2b and ruxolitinib, a JAK 1 and JAK 2 inhibitor are safe and effective long-term treatment option for patients with PoV who are resistant or to intolerant of hydroxyurea (90). Interferon alpha 2b and/or ruxolitinib are indicated in these patients (100). Dupilumab, a HMA, was given a patient with PoV, which was failed and later successfully treated with upadacitinib (101). Further studies are necessary, which are the most effective for PoV and erythrocytosis.

## Thrombocytopenia

Thrombocytopenia is defined as a platelet count of less than  $150 \times 10^3$  per  $\mu\text{L}$ , and is one of the most common hematologic diseases (102). The clinical expression of thrombocytopenia has a variation from asymptomatic to life-threatening bleeding. Different syndromes and diseases are associated with thrombocytopenia. Thrombocytopenia is often sometimes a first sign of hematologic malignancies, infection diseases, thrombotic microangiopathies, or autoimmune diseases, and is sometimes a common side effect of different medications.

## Thrombotic Thrombocytopenia Purpura

The thrombotic thrombocytopenia purpura (TTP) is a clinical syndrome defined by the presence of thrombocytopenia and microangiopathic hemolytic anemia, and, is a rare disease of unclear genesis that carries a poor prognosis (103). It is a polyetiological complex, with the kidneys and brain as target organs. An endothelial damage is

triggered by different factors. The thrombocytes and the endothelial cells seem to be damaged, such that 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. Von Willebrand factor and fibronectin are formed and released by endothelial cells, and play an important role in the pathomechanism of TTP (104). The proximate cause of a subset of TTP has been demonstrated a deficiency von Willebrand factor (vWF) cleaving protease ADAMT 13. A defective function of perforin is seen in these two conditions. Perforin is a protein found in the cytoplasmatic granules of both T cytotoxic lymphocytes and natural killer cells (8). This protein is implicated in target cell lysis by the above cells.

A cascade of biochemical events that ultimately leads to the characteristic feature of TTP is triggered by the damage. Hyaline thrombi, composed predominantly of platelets and fibrin, which occlude the terminal arterioles and capillaries of most of the body organs, the heart, brain, kidneys, pancreas, and adrenals follow. Other organs are involved to a lesser degree. The DIC is an explosive life-threatening bleeding disease in most cases secondary to activation of coagulation factors including tissue factors.

The implementation of TPE in TTP and/or fresh frozen plasma has reduced significantly the mortality. Whether the effect of TPE therapy is due to the removal of toxins or the infusion of certain plasma components or both cannot be definitely stated at present. A defect in prostaglandin metabolism has also been implicated (103). Besides numerous therapeutic approaches include sole infusion of FFP and TPE, splenectomy, corticosteroids, aggregation inhibitors, cytostatics, and other drugs, TPE is superior to all other forms of therapy, if TPE is implemented in TTP at an early stage. The mainstay of treatment for TTP is TPE, however, the role of splenectomy is still undefined. Therefore, TPE with FFP replacement is the most effective therapy and should started as soon as the diagnosis is established and continued daily until neurologic symptoms, renal failure improves, and platelet count normalizes (105).

The AAC of the ASFA has given the TTP the category I with the RG 1A for TPE (Table 1) (3,12). The mortality from uniformly fatal is decreased < 10 % by TPE. If TPE is not immediately available, plasma infusions could be started at approximately 30 – 40 ml/kg BW per day, until TPE can be started. As replacement fluid for TPE, plasma and

plasma cryoprecipitate reduced (PCR) are used. The patients under TPE should be monitored to register possible adverse reactions (106).

Often, corticosteroids are used as an adjunct at 1 mg/kg BW/day. Other adjuncts include rituximab, vincristine, and splenectomy (103). The bleeding, if present, is typically limited to skin and mucous membranes. Platelets should not be transferred unless clinically indicated. Congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, here simple plasma infusions (10–15 ml/kg BW) or cryoprecipitate (which contains ADAMTS13) are necessary (3).

A significant improvement in patient clinical outcome is reached with TPE. Therapeutic plasma exchange removes the anti-ADAMTS13 autoantibodies, while restoring ADAMTS13 protease activity (12). Until the platelet count is above  $150 \times 10^9/L$  and LDL near normal for 2-3 consecutive days, TPE is performed daily and is with immunosuppression the mainstay of initial therapy (107). In TTP after Covid-19 vaccination, TPE was successful, too (108). Besides rituximab another HMA caplacizumab with TPE or alone is immediately applied to all patients with an acute episode of TTP (109,110). Caplacizumab is well tolerated with minor bleeds as the most important effect.

### Idiopathic Thrombocytopenic Purpura

The immune thrombocytopenia are a heterogeneous group of bleeding disorders with similar hemostatic manifestations with different pathogenic etiologies (103). Idiopathic thrombocytopenic purpura (ITP) caused by autoantibodies are accompanied by hemorrhagic diathesis in severely progressing cases, and is the most common autoimmune hematologic disorder. In most part, the etiology is unknown. An important role plays the spleen, since it not only produces a large part of the antibodies directed against thrombocytes, but also breaks down the damaged thrombocytes. The antibodies can pass through the placenta barrier and affect also the fetus (111). With steroid alone, in more than 60 % of the patients, part or full remission can be reached. Cytostatics and splenectomy are further therapy strategies (103). Therapy-resistant, acute, and chronic cases have also been successfully treated with high doses of IVIG of 400 mg/kg BW/day. Auto- or alloantibodies to platelet antigens are the cause for ITP, and fixed antibodies may trigger complement activation (112). The opsonized platelets are destroyed in the macrophage-phagocytic system mediated by the

FC receptors FcγRI-III and complement receptors CR1 and CR3. In the spleen occurs the most platelet destruction, but also in liver and bone marrow, therefore, splenectomy is therapeutically very effective. The platelet membrane glycoproteins GP-IIb/IIIa and Ib/IX are the main antigenic determinants (112,113).

The formation of antibodies against neoantigens expressed after adherence of the drug to the RBC membrane is a further mechanism leading to platelet destruction in drug-induced ITP (114). In acquired autoimmune a deficiency of a metalloprotease, ADAMTS13, was shown in many cases of ITP (8). Alloimmunization is the cause of neonatal alloimmune thrombocytopenia, platelet transfusion refractoriness, and post-transplant purpura. In the human platelet antigen (HPA) system the alloantigens are classified (115). Neonatal immune thrombocytopenia is the platelet counterpart of hemolytic disease in newborns. The mother, HPA-a-negative, is sensitized to HPA-1-positive platelets of the fetus. Alloimmunization (IgM ab > IgG ab) against platelets induced by fetomaternal hemorrhage occurs during an HPA-incompatible pregnancy or after an HPA-incompatible platelet transfusion (112,116). Type II immune complexes, in heparin-induced thrombocytopenia, 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 (103).

After a viral illness or immunization follows abrupt onset ITP in childhood. In most of the children no treatment is necessary, and in 80 – 85 % of the cases, the disorder improves within 6 months. In 15 – 20 % of the children develop a chronic ITP, in some cases resembles the more typical adult disease. The 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 time (103). Mainly women of childhood age (female: male 3 : 1) affects this form of ITP. Childhood ITP has an incidence of between 4.0 and 5.3 per 100,000 children (114).

The blood count, clinic symptoms, autoimmune profile, and other investigations, and on other causes of thrombocytopenia using the history, physical examination lead to the diagnosis of ITP (103). Platelet associated IgG (PAIg) is elevated in both immune and non-immune thrombocytopenia and therefore not important for diagnosis. Following eradication therapy in patient's refractory to therapy, some patients have shown

improvement in platelet counts by the presence of *H. pylori*.

High dose of IgG and anti-D is successful in ITP, therefore is TA reduced to second-line or third-line treatment in these patients. The first-line therapy is high dose corticosteroids, high dose IVIG, intravenous anti-D, cyclosporine A, and Dapsone and splenectomy. If these therapies failed, patients must be treated with interferon- $\alpha$  (IFN $\alpha$ ), rituximab, campath-1H, mycophenolate mofetil and TA (103). Therapeutic apheresis is indicated in patients with chronic ITP, if the application of IgG is not possible due to allergic reactions, Rh-negative status, or splenectomy.

The AAC of the ASFA has given the category II with RG 1C for IA in refractory cases of ITP and the category IV with RG 1C for TPE (3, 12) (Table 1). Therapeutic apheresis removes antiplatelet antibodies to prevent bleeding by keeping the platelet count above a critical level. A minimum of over 50,000 platelets/ $\mu$ L is the goal of therapy with TA. The measurement of free antiplatelet autoantibodies is useful for determining whether TA is indicated (103). Vaccine-induced ITPs, which are associated with high titers of IgG class antibodies against platelet chemokine platelet factor, are reported (117-119). It is not possible to reliably conclude which form of therapy should be given preference, because only a few studies are yet available. The initial treatments in ITP are corticosteroids, IVIG and iv anti-Rh D. If no improvement is observed within one or two weeks with thrombocytes  $> 80,000 \mu$ L, then TA should be commenced immediately. Therapeutic apheresis is recommended with 1 – 1.5 TVP a day for 4 days, and two to four treatment sessions of TA per month can also have a positive effect in chronic cases. Prior to surgery in acute resp. chronic uncontrollable bleeding, TA is also recommended (103). Immunoabsorption with Protein-A was also successfully introduced in the treatment of ITP (120,121).

If ITP persists or recurs, splenectomy is recommended in adults but is deferred to prevent overwhelming post-splenectomy infection or allow for spontaneous remission (3). In patients with refractory ITP with life threatening bleeding or in whom splenectomy is contraindicated, TPE and IA with Protein-A is indicated. The use of protein-A columns is contraindicated when the patient is on angiotensin converting enzyme (ACE) inhibitors, has a history of hypercoagulability or thromboembolic events. The frequency is once a week or every 2 – 3 weeks. However, there are no clear guidelines concerning treatment schedule and duration. When

the patient shows improvement in platelet count  $> 50 \times 10^9/L$  or no improvement after 6 treatments, IA treatment is generally discontinued.

New treatment options for thrombocytopenia, especially ITP, HMA and thrombopoietin agents, has been developed, and combination of different diagnosis and therapeutic approaches are the main strategy for different cases (103). Besides rituximab, other monoclonal antibodies targeted against CD40, CD38 and the immune-proteasome decrease antibody production by inhibition of the neonatal Fc receptor (122). Thrombopoietin is the major physiology regulator of the platelet (123). Thrombopoietin is produced in the liver at a constant rate and cleared from the circulation by TPO receptors on circulating platelets thereby providing an effective feedback system regulating platelet production by bone marrow megakaryocytes. Other new second-line drugs for ITP are the TPO-RAs. Avatrombopag, eltrombopag and romiplostim are the most used for platelet response. They have high efficacy and safety as second-line treatments in short term for adult patients with persistent ITP, they stimulate the platelet and megakaryocyte production (124,125). Further larger multi-center studies are necessary to find the most effective therapy in thrombocytopenia.

## Post-Transfusion Purpura

When donor B lymphocytes and dendritic cells migrated as passenger cells to the recipient's system occurs post-transfusion purpura (PTP), where the cells undergo clonal expansion after "homing in" on, and producing alloantibodies to the incompatible HPA allele (103). The PTP is a rare bleeding disorder caused by alloantibody specific to platelet antigens. The most of the affected patients, the antibody against human platelet alloantigen HPA-1a is responsible. Most of affected patients are multiparous women who presumably have been previously sensitized during pregnancy (126). The primary cause for alloimmunization in PTP have been rarely implicated blood transfusions. The thrombocytopenia is usually severe and resolves spontaneously within several weeks. Patients may develop severe if not fatal bleeding during the course of the disease. The diagnosis is confirmed by demonstrating antibodies to platelet antigens.

The treatment is corticosteroids, high IVIG (0.4 g/kg BW/day for 2-5 day or 1 g/kg BE/day for 2 days) and TPE. Immunoglobulins possibly act by Fc receptor blockade of reticuloendothelial system (3). First, patients given high dose of corticosteroids. The TPE is only indicated if IVIG is not effective and

severe thrombocytopenia persists. The AAC of the ASFA has given the PTP the category III with RG 2C based on limited available data (3,12) (Table 1). The treated volume, replacement fluid and the frequency of TPE are the same as such in ITP, and TPE can be discontinued when platelet count starts increasing ( $> 20 \times 10^9/L$ ) and non-cutaneous bleedings stops. If PTP is diagnosed or suspected, patients should be treated with TPE as soon as possible. Recombinant factor VIIa may be considered in a bleeding patient when HPA-1a negative platelets are not available. If TPE remove HPA-1a alloantibodies, a decrease of antibody titer, removal of any unattached HPA-1a antigen, and an increase in platelet count and cessation of bleeding is reached. The TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG therapy is not effective (3).

## Thrombocytosis

A circulating platelet count  $\geq 500 \times 10^9/l$ , phenomenon to acute bleeding, hemolysis, infection, inflammation, asplenia, cancer, or iron deficiency is defined as thrombocytosis (3). 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 conservative therapy includes low dose aspirin, indicated for thromboprophylaxis in patients with ET, or PoV who do not have a bleeding tendency. To maintain a normal Hct in PoV, phlebotomy is required. Before general anesthesia and surgery, the platelet count should be normalized. A platelet lowering agent, hydroxyurea is preferred. Anagrelide and interferon alpha are further treatments. Thromboembolic complications are treated acutely with unfractionated or low molecular heparin followed by transition to therapeutic warfarin (127).

The therapeutic mechanisms are not well defined, and a rapid cytoreduction is believe to ameliorate prothombosis factors associated with the dysfunctional platelets (3). The AAC of the ASFA has given the category II with the RG 2C for symptomatic thrombocytosis and the category III with RG 2C for prophylactic or secondary thrombocytosis for thrombocytapheresis based on conflicting and limited data in the literature (3,12) (Table 1). The rationale for thrombocytapheresis is undefined and the efficacy unproven. The frequency is daily and a replacement is not

necessary. Thrombocytapheresis is indicated in chronic treatment, too. A normalization of the platelet count, and maintenance of a normal count until cytoreductive therapy takes effect, is the goal. More than one procedure may be required to achieve a normal count by very high pre-treatment counts. The goal is the normalization of the platelet count and maintenance of a normal count until cytoreductive therapy takes effect (103). Thrombocytapheresis provides an immediate symptomatic relief and is an efficient useful emergency lifesaving procedure in patients with thrombocytosis (127-129).

A newer treatment possibility is the application of JAK inhibitor, mostly ruxolitinib, in essential thrombocythemia, myelodysplastic syndrome, myelofibrosis (130). Ruxolitinib decreased the expression of cytokines and growth factors required for hematopoiesis by inhibiting JAK1/2 pathways (131).

## 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 complication (16). The earliest complications and death are directly attributed to hyperleukocytosis and its resultant microcirculatory dysfunction, known as leukostasis, where the sludging of leukemic blasts in capillary vessels and adhesive interactions give rise to deleterious effects (132,133). The involvement of any organ system may rise the symptoms, however, intraparenchymal brain hemorrhage and respiratory failure account for the majority of deaths. A rapid destruction of leukemic cells in response to chemotherapy also causes metabolic disturbances, the so-called tumor lysis syndrome.

The hyperleukocytosis is defined as a circulating white blood cell (WBC) or leukemic blast cell count  $> 100 \times 10^9/L$  (3). The hyperleukocytosis causes complications, which are organ to tissue dysfunction directly attribute to the high burden of circulation leukemic myeloid or lymphoid blast cells in the absence of infection, thromboembolism, or other underlying etiology. In acute myeloid leukemia (AML) when the WBC is  $> 100 \times 10^9/L$  and in acute lymphoblastic leukemia (ALL) when WBC is  $> 400 \times 10^9/L$ , leukostasis is observed (12). In the central nervous system manifestations are confusion, somnolence, delirium, coma, and parenchymal hemorrhage with focal neurologic deficits. Dyspnea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure, radiographic findings of interstitial and/or alveolar infiltrations are the pulmonary symptoms (3).

The main treatment is induction chemotherapy. Hydroxyurea may be a useful temporizing cytoreductive agent (3). The tumor lysis syndrome and hyperuricemia, which can follow hyperleukocytosis, are treated with intravenous electrolyte fluids, alopurinol or rasburicase balkanization of the urine, and dialysis. Red blood cell transfusion is generally indicated prior to cytoreduction.

Leukocytapheresis is widely used following anecdotal case reports describing striking clinical improvements with prompt leukoreduction, and it appears to be effective on early mortality and overall survival. and in clinical manifestation, leukocytapheresis is effective on overall and possible early mortality (134,135).

The AAC of the ASFA has given the leukocytapheresis the category I with the RG 1B, and the category III with the RG 2C for prophylaxis (3,12) (Table 1). In children and adults with ALL, clinical leukostasis occurs in < 10 % of those with WBC counts > 400 x 10<sup>9</sup>/L (12). No advantage over aggressive induction chemotherapy and supportive care offers prophylactic leukocytapheresis. Because of the limited and conflicting data, the category III indication for prophylaxis of hyperleukocytosis was assigned. Severe end-organ failure or hemorrhage may not improve, however, in patients with extensive and/or severe preexisting tissue damage. If in persistently symptomatic patients until clinical manifestations resolve or a maximum benefit is achieved, leukocytapheresis should be repeated. Concurrent chemotherapy is also required in order to prevent rapid reacumulation of circulating blasts (136,137).

The WBC count can be reduced of 30 – 60 % by only a single leukocytapheresis (3). When the blast cell count is > 50–100 x 10<sup>9</sup>/L and clinical manifestations are resolved, the leukocytapheresis is discontinued for patients with AML, and when the blast count is < 400 x 10<sup>9</sup>/L in ALL patients with leukostasis complications and clinical manifestations are resolved, the treatment is discontinued (138). In patients with clinical leukostasis significant improvements in 30-day mortality was achieved with leukocytapheresis (139). Leukocytapheresis is safe and the best treatment option in symptomatic hyperleukocytosis (140-142).

### **Coagulation Factor Inhibition, Disseminated Intravascular Coagulation**

Disseminated intravascular coagulation may complicate a variety of underlying diseases

processes, including sepsis, trauma, cancer, or obstetrical calamities, such as placenta abruption. The platelet count is invariable low or rapid decreasing in patients with DIC. The mortality rate of sepsis-associated DIC is high (143).

Three stages in the pathomechanism of consumption coagulopathy reaction are hypercoagulable state; intravascular formation of clots, and consumption coagulopathy with reactive hyperfibrinolysis, which offer various theoretical approaches for TA (143). If the blood flow is interrupted to tissue, the tissue in the affected areas dies and releases tissue thromboplastin. Factor VII is activated by tissue thromboplastin and the extrinsic pathway leading to focal clotting and with sufficient thromboplastin disseminated intravascular clotting with activation of both the extrinsic and intrinsic systems. More tissue dies due to clotting in capillary beds. Pro-coagulant factors such as protein and S and antithrombin III, and plasminogen are used up. Uncontrolled bleeding and extensive blood clotting are 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 (144).

By elimination or reducing the levels of active pro-coagulation factors example heparin, depletion of factors II, VII, IX and X with Coumadin or TPE, the process of consumption coagulopathy can be interrupted in the hypercoagulemic stage. With TPE the pathogenetic chain reaction in the second stage, in which intravascular clot formation occurs, pro-coagulant, anticoagulant, and depletes and failure of clearing function of the reticuloendothelial system can be interrupted (145). High molecule fibrin split products, in the third stage, can be eliminated by TPE, and the coagulation status normalized through the substitution of clotting factors and normal levels of anti-coagulant with FFP (8). More reports represented the successful treatment of DIC and multi-organ failure with TPE and/or HMAs (e.g., eculizumab) (146).

### **Hemophilia A**

Hemophilia is a defect of the endogenous coagulation system, either inherited or acquired. Diseases which result from reduction, lack or malformation of the factors VIII, IX XI, XII, or prekallikrein are included. Hemophilia A is longest-known hemorrhagic diathesis. Five to 20 % of hemophiliacs develop antibodies against factor VIII (F VIII) administered during the course of treatment. Factor VIII antibodies belong to the IgG

immunoglobulin group (147). These antibodies are directed against the patient's own F VIII and can lead to an acquired F VIII deficiency, and also occur spontaneously in older patients or after pregnancy. Hemophiliacs may become sensitized to concentrates of their deficient coagulation factors, in about 15 % of hemophilic patients. There are low and high responders. The activity of the inhibitor can be measured in Bethesda units (BM) or Malmö inhibitor (MIU).

Factor VIII inhibitors are the important pathogenic antibodies directed against the blood coagulation factors, and are developed in approximately 30 % of patients with severe and moderately severe hemophilia in response to infusions of F VIII (148). Within the first year usually, the patients develop inhibitors, however, the mechanisms underlying the 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 recombination's in the F VIII gene that are predicted to cause a complete lack of endogenous F VIII. With the amount of exposure F VIII, the risk of inhibitor development in patients with mild hemophilia increases (149). Patients often present large ecchymosis, extensive muscle hemorrhages, gastrointestinal bleeding, or even intracerebral bleeding, with a high mortality because of bleeding complications and treatment complications such as infections (150).

A rapid increase in antibodies after administration of F VIII display in many patients with antibody formation. The attempts to suppress the formation of antibodies in these patients through immunosuppression therapy have been for many patients unsuccessful. To reduce these antibodies, TPE is used prior to infusion of F VII. The combination of TPE and F VIII has been successful in stopping severe bleeding in hemophiliacs who are unresponsive to F VIII and as hematologic preparation to normalize these inhibitors prior to major surgery (8).

In severely bleeding patients classified as immunological high responders, TPE is indicated immediately (151). When plasma concentration of the inhibitors exceeds either 10 BM or 3 MIU, TPE can be considered, and should be implemented prior to high-dose administration of human F VIII concentrates. Immunoabsorption with anti-immunoglobulin columns may be safer and more effective (152). Another indication for TA is in cases where inhibitors occur after substitution to induce immune tolerance according to Malmö or similar protocols (16). Serial TPE and simultaneous

administration of F XIII/IX concentrates, high-dose IgG (0.4 g/kg BW/day), and cyclophosphamide is recommended. These treatments are successful in 80 %, and a chronic immunosuppression may be necessary in some patients.

Immunoabsorption is increasingly applied in the therapy of F VIII inhibitors, and several methods of IA may be clinically effective and cost-effective and should be considered early in the therapy of patients (Table 1) (3,152,153).

Other therapies including corticosteroids, HMA such as rituximab, or emicizumab are reported (154,155). New therapy concepts for hemophilia are the gene therapy with valoctocogene roxaparvovec. The durability of F VIII and bleeding reduction and the safety profile of valoctocogene roxaparvovec in a phase 3 study was shown (156). However, further larger multi-center studies are necessary.

## Acquired Factor VIII Antibodies in Non-Hemophilia Patients

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

Autoantibodies in non-hemophiliacs produce a condition often called acquired hemophilia A, and is the most common autoimmune bleeding disorders involving the coagulation system. Acquired hemophilia A patients are more likely to have a more severe bleeding diathesis than hemophilia A inhibitor patients. Approximately 50 % of acquired hemophilia A patients have underlying conditions, including autoimmune disorders, malignancy, and pregnancy (157). The rest of idiopathic cases most commonly occur in elderly patients of either sex.

On the inhibitor titer depends the treatment of bleeding episodes for patients with acquired hemophilia A or congenital hemophilia A with inhibitors. Low-titer inhibitors can be overwhelmed with F VIII by passing agents, prothrombin complex concentrates, or recombinant F VIIa or porcine F VIII concentrates can be used for the treatment of patients with high-titer inhibitors. Recombinant F VIIa is effective in controlling most bleeding episodes. There are no reports of inhibitory antibodies developing to the product (158).

Therapeutic apheresis is indicated in acute bleeding complications not only for the administration of



highly dosed concentrated F VIII, but also for the removal of circulating antibodies. Fresh frozen plasma for substitution also includes the administration of F VIII. The advantage of TPE or IA is the rapid removal of antibodies and absence of excessive antibody formation, and a disadvantage is an increased risk of bleeding with TPE treatment, if anticoagulation becomes necessary. A selective elimination of acquired F VIII antibodies is with IA available (159).

The AAC of the ASFA has given the coagulation factor inhibitors by hemophilia A and acquired factor antibodies in non-hemophilia patients the category III with RG 2B for IA and IV with RG 2C for TPE (Table 1) (3,12). Factor deficiency can be either congenital or acquired, the majority of acquired deficiencies result from autoantibodies. Congenital factor deficient patients can develop inhibitors, alloantibodies, to the factors. For inhibitor suppression, the treatment options include high dose corticosteroids, cyclophosphamide, cyclosporine A, rituximab, and high dose IVIG (3). Immunoabsorption is more effective than TPE for coagulation factor inhibitors (16). In TPE is the replacement fluid plasma in IA none, and the frequency as needed in TPE for congenital, rare factor deficiencies, and in IA for inhibitors daily. Efficizumab is introduced in the therapy of acquired hemophilia A. Efficizumab can facilitate hemostasis for acquired hemophilia A and are combined with safer, lower-intensity immunosuppressive therapies (160). A further therapy concept in acquired hemophilia A is the recombinant human activated F VII or the recombinant porcine F VIII. The recombinant F VII or F VIII are applied most in combination with emicizumab (160-162). However, more studies are necessary here.

### Hyperviscosity Syndrome

Hyperviscosity syndrome caused by cryoglobulinemia, macroglobulinemia, multiple myeloma, or hypergammaglobulinemia, and the Waldenström's macroglobulinemia, hyperviscosity in monoclonal gammopathies, are a generally recognized indication for TA in adults, however in children these diseases are very rare or unknown (163,164).

### Closing Remarks

Since the mid-1970 the hollow fiber modules were introduced, and since the pathogenetic relevance of autoantibodies could be defined in various diseases, disease-specific adsorbers have developed, more and more immunologic and non-immunologic diseases were treated with TA. Besides the physical problems, which play an important role, also technical ones such as the apparatus required, and

above all vascular access (165, 166). In addition to indication for TA and early commencement of therapy, the following are important considerations, the selection of good vascular access, an adequate exchange volume, 40 ml/kg BW, and a lowest possible extracorporeal volume (167). The patients must be monitored during and between TPE sessions. Special attention is necessary to circulation, consciousness, coagulation status, and blood count. By using a large-bore catheter placed in a central vein, sterile procedure must be adhered, to prevent catheter infection or sepsis (168). The therapeutic apheresis appears to be beneficial during the acute phase of the disease (169).

After the AAC of the ASFA only some hematologic disorders got as first line therapy for TA, such as acute stroke of sickle cell anemia, severe babesiosis, factor H ab of HUS, polycythemia Vera, TTP, and the leukostasis of hyperleukocytosis. As second-line therapy for TA are HDN, red cell alloimmunization in pregnancy, cold agglutinin disease, acute chest syndrome in sickle cell anemia, high risk population in babesiosis, complement gene mutation of HUS, pure red cell aplasia, ABO incompatible hematopoietic progenitor cell transplantation, acute and chronic skin GVHD, ITP, and symptomatic thrombocytosis (Table 1). All other hematologic diseases have got the category III or IV from the AAC of the ASFA. The use of TA is regarded to be an extreme therapeutic measure in patients. Therapeutic apheresis must be done, if the need for such treatment is undebatable. The most frequently observed adverse effects are vascular relative access insufficiency, and mild hypotension, if a well-trained and experienced team performed the treatments.

Very expensive and still technically complicated are all mentioned TA methods. A reduction in costs is a valid demand in view of the scarce resources available in the healthcare system. 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. With extensive research and development required the industry justifies the high costs. All those involved in the health-care system must intensify their cooperation in this respect. However, medical processes are advancing and will not be stopped.

In recent years, more and more other modern therapeutic methods are used in the therapy of hematologic disorders with success. These new therapies are different HMAs, which are special

developed for different hematologic diseases. Other new therapy concepts are JAK 1 or JAK 2 inhibitors, and the gene therapy, and others.

Important is for all mentioned diseases the quotient relevant for cost-effectiveness assessment (cost of treatment – cost saved): (improvement in life quality). This must be discussed and calculated exactly by all involved persons. Every effort should be made to delay the progression of acute and chronic diseases. Therefore, TA is clearly an important tool in treatment of many complex conditions now and in future (170).

### **Conclusion**

Since the introduction of hollow fiber membranes, exceptional efforts in research, development, and clinical use have been undertaken in the apheresis

sector alone, for example, the introduction of selective separation techniques into clinical routine. More than 80 % of treated patients could be healed with TA. Therapeutic apheresis has been used successfully in the most of hematologic diseases, and is always combined with immunosuppressive therapy and/or human monoclonal antibodies and other medications. The most of the hematologic diseases like anemias, erythrocytosis, thrombopenia, hyperleukocytosis, and coagulation inhibitors has improved in the last years. In severe hematologic diseases, TA with immunosuppression, steroids, cytotoxic agents, and/or HMAs are indicated. However, for all treated hematologic diseases with TA, immunosuppression and/or HMAs, or other medications more multicenter studies with larger numbers of patients are necessary in future.

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