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Review Article

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Therapeutic Apheresis in Pediatrics with Neurological and Hematological Diseases

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Abstract

The advantages of therapeutic apheresis (TA) with hollow fiber membranes are a complete separation of the corpuscular components from the plasma and due to increased blood flow rate higher efficacy [1]. The use of therapeutic apheresis in pediatric patients, which increasing more and more, has always been restricted by technical difficulties and the low incidence of diseases requiring this kind of treatment. The development of new, more sophisticated membranes and new adsorption technologies allow the most selective separation of plasma components. TA has been successfully introduced in a variety of autoantibody-mediated diseases [2]. The updated information on immunology and molecular biology of different neurological and hematological diseases are discussed in relation to the rationale for apheresis therapy and its place in combination with other modern treatments. The different diseases can be treated by various apheresis methods. Pathogenetical aspects are demonstrated in these diseases, in which they are clarified. TA has been shown to effectively remove the autoantibodies from blood and lead to rapid clinical improvement. For the neurological and hematological diseases, which can be treated with TA, the guidelines of the Apheresis Application Committee (AAC) of the American Society for Apheresis (ASFA) are cited [3, 4].

Keywords: Therapeutic Apheresis, Therapeutic Plasma Exchange, Immunoadsorption, Neurologic, Hematologic, Hemostasiological Diseases

Introduction

During the mid-1970, new process for plasmapheresis became available which used membrane modules instead of centrifuges. 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 solution [2]. Membrane techniques are simple and safe to apply and can be competitive to other plasma separation and treatment technologies [5]. The advantages of membranes plasmapheresis include its simplicity to use with blood pumps and no observed white blood cell or platelet loss, compared with centrifuges.

As early as 1980, physicians adapted the single-needle technique to plasmapheresis and simplified the system in the process. They used a double head pump in combination with a hollow fiber module, a pressure balancing system, and a bi-lancing pump [6]. Over a period of more than 25 years, this system was used in more than 20.000 treatments. In addition, two level detectors were added to the system; therefore, the system could work on a semi-automatic principle [7].

The demand for treatments of children and adolescents was increasing more and more. The problem was to win the industry to minimize the hollow fibers, the tubes, the circulating extracorporeal blood volume and the machines. In 1984, a small double head pump was developed which works according to this principle. It is especially useful in newborns and premature infants where blood volume is limited [8]. Both hemofiltration and plasmapheresis treatments may be carried with the small, double-head pump (220 x 255 x 95 mm). Plasmapheresis treatment requires a supplementary heater and bi-lancing pump. A special system of tubes for the blood and filtrate line, hemofilters, and plasma membrane separators are also available. The double-head pump works according to the principle of pressure-pressure and volume control. A combined air and level detector, as well as a volumetric control, safeguards this unit. The discontinuous mode of operation of both pumps causes a permanent change in flow and pressure. In this process, the second pump controls the pressure of the venous back flow. The procedure avoids high pressures in the hollow fiber membranes that would otherwise be required for the blood reflux. The main advantages of the double-pump system are that a relatively large volume flows through the plasma separator without the maximum pressure exceeding the safety limit, and the average pressure in the membrane separator can be adjusted to individual requirements [8]. The developed system has proved particularly suitable for newborns and small children. Thin pediatric venous catheters (18 – 20 gauges) could be used to place in the umbilical vein (premature infants) or in the femoral vein (newborns and smaller infants).

Methods, Patients

The use of TA procedures in pediatric patients has always been restricted by technical difficulties and the low incidence of disease requiring this kind of treatment [9]. Since the availability of smaller membrane plasma separators, TPE has been increasingly used implemented in pediatric diseases.

TA includes the following methods, which are mentioned here [10]:

- Therapeutic plasma exchange (TPE) in which the whole blood is passed 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.
- Whole blood adsorption (hemoperfusion, HP): 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, HELP), 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, the 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) and exposed to ultraviolet A light and then reinfused to the patient during the same treatment.
- In addition, other adsorption methods which are mentioned elsewhere [10].

This review is to highlight the disease processes commonly treated with TA in children, and to address the technical considerations pertinent to the provision of safe and effective in pediatric setting. Especially younger and smaller children will have lower total blood volumes and more difficult vascular access.

The total blood volume based on a child´s age and weight, and varied between 70 mL/kg for adolescents and 85 mL/kg for normal sized new-borns and infants [11]. The calculated total blood volume affects decisions regarding the need to prime the extracorporeal circuit, especially because in the apheresis circuit the volume is fixed for the duration of the circuit. The extracorporeal circuit needs to be primed with a solution that will help maintain intravascular integrity such as red cell diluted with saline or 5% albumin to a hematocrit value near 40%, or a 5% albumin-electrolyte solution in children who are more stable hemodynamically [12].

The vascular access in small children, stiffer and more durable central venous catheters are favoured to withstand the negative pressure generated by machine inlet flows, which generally exceed 20 – 40 mL/min, thin pediatric venous catheters of 18 gauges are used in these patients. In older children and adolescents with good peripheral extremity vasculature, standard wide-bore 20-gauge or more intravenous catheter access can be sufficient. Anticoagulation therapy can be administered via heparin (with goal activated clotting time, ACT, of 180 – 220 s) or anticoagulant citrate dextrose formula A. The most common adverse sequelae of citrate anticoagulation are metabolic alkalosis and hypocalcemia. In these cases, calcium infusions are necessary [12].

Other problems can be multiple psychosocial factors that may play a larger role in performing TA on a child than an adult. In pediatric patients of all ages, undergoing treatments can cause a great deal of anxiety for both the child and any parents or adult caregivers. In these cases, taking advantage of clinical staff with prior pediatric experience, or child life specialists are useful. In recent years, guidelines have been written for implementing TA with regard to the special situation of pediatric patients.

Pediatric Diseases

Neurological disorders constitute the largest group of indications for TA [13]. Severe central nervous system (CNS) involvement is associated with poor prognosis, and high mortality rate. High dose steroid and cyclophosphamide (oral or intravenous) are the first choice of drugs in the treatment; TA, intravenous immune globulin (IVIG), thalidomide, intratechal treatment may be valuable in treatment resistant, and serious cases. Table 1 shows the most of the pediatric neurological diseases that have been treated with TPE.

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) (Guillain-Barre Syndrome)

AIDP is an auto aggressive disorder that develops subsequent to infectious diseases and because of other noxae [2]. It is an acute polyradiculitis, which mostly affects the distal and proximal muscles of the extremities, as well as the trunk muscles and can progress with severe ascending paralysis, ending in respiratory paralysis [14]. Most patients with AIDP have inflammatory, predominantly demyelinating polyneuropathy. This acute progressive disease, leading to rising paralysis, usually reaches its height within one to two weeks; 25 percent of all patients require artificial ventilation. AIDP occurs in one out of 50,000 persons each year in the industrial nations, regardless of gender or age [2].

The pathophysiologic mechanism has not been established completely, but in many cases, an antecedent infection by campylobacter jejuni leads to the production of antibodies (abs) directed against certain epitopes of the bacterium that also destroy the myelin sheath of the peripheral nerve. This phenomenon has been described as molecular mimicry [15]. The spectrum of organisms responsible for infections can trigger GBS ranges from Eppstein-Barr virus to mycoplasma, herpes zoster, and mumps virus, borrelia to the HIV viruses [16].

In recent years, the triggering causes have been described as being: 1) antibodies against peripheral nerves, in particular against myelin; 2) circulating immune complexes; 3) complement activation in the cerebrospinal fluid and in serum; 4) other inflammatory mediators and cytokines; and 5) a disorder in cell-related immunity [2, 17].

Spontaneous recovery normally occurs between the 2nd and 4th week of illness, and, in 75 percent of the patients, it can even occur after several months of illness. Due to remaining damage and relapses, lethality is between 5 and 25 percent after one year. The rationale for TA is based on the humeral and cellular immune dysfunction in this disease [18].

Intra-venous immunoglobulin (IVIG) has also been shown to be effective in the treatment of AIDP. In a recent large international randomized study of TPE, IVIG, and combined treatments in AIDP, all three modalities were effective [19]. While no significant statistical differences were noted between the groups, TPE was noted to be better than IVIG, and the combination was better than either of the treatments alone [20, 21].

In recent years, researchers have applied a combination therapy of TPE or IA following by IgG (0.4g/kg BW for 5 days) [2]. Haupt

et al. reported results which suggesting that such a combination treatment of AIDP may be superior to plasma exchange alone [22]. Accordingly, with TPE treatment in GBS, it was possible to reduce the costs by between 30 to 40 percent in America, due to the shorter periods of inpatient treatment and shorter duration of artificial respiration [2].

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Chronic inflammatory demyelinating polyradiculoneuropathy is an uncommon progressive or relapsing paralysing disease caused by inflammation of the peripheral nerves [3]. Neurologic symptoms are decreased sensation, diminished or absent reflexes, elevated cerebrospinal fluid level, and evidence of demyelination [4]. CIDP is an acquired disorder of the peripheral nervous system has probably an autoimmune pathogenesis. The nature of the responsible auto-antigens is unclear in most patients. The frequency of such antibodies is significantly greater in CIDP patients than in normal control subjects [23].

Recent clinical trials have confirmed the short-term efficacy of IVIG, prednisone and TPE. In the absence of better evidence about long-term efficacy, corticosteroids or IVIG are usually favoured because of convenience. Benefit following introduction of azathioprine, cyclophosphamide, cyclosporine, other immunosuppressive agents, and interferon-β and –α and rituximab has been reported but randomized trials are needed to confirm these benefits [23, 24].

Therefore Hughes et al. recommended in 2006 that the principle treatments are [25]:

- intravenous immunoglobulin or corticosteroids should be considered in sensory and motor CIPD,
- IVIG should be considered as the initial treatment in pure motor CIDP,
- if IVIG and corticosteroids are ineffective TPE should be considered,
- if the response is inadequate or the maintenance doses of the initial treatment are high,
- combination treatments or adding an immunosuppressant or immunomodulatory drugs could be considered,
- symptomatic treatment and multidisciplinary management should be considered.

In the guidelines on the use of TA in clinical practice-evidence-based approach from the AAC of the ASFA, the AIDP and CIPD have the category I with the recommendation grade (RG) 1A (Table 1) [3, 4]. The main etiology of AIDP is autoimmune antibody-mediated damage to the peripheral nerve myelin. Several controlled trials comparing TPE to supportive care alone indicate TPE treatment can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones [3]. The Cochrane Neuromuscular Disease Group review of TPE in AIDP found that

Table 1: TA in pediatric diseases (neurological 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 undertaken (3, 4)).

Apheresis Application Committee of ASFA,2013, 2016 (3, 4)					
Neurological diseases	**TA modality**	**Category**	**RG**	**Exchange volume (TPV)**	**Replacem. fluid**
Acute inflammatory demyelinating polyneuropathy (AIDP); Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD)	TPE, IA-Protein, Peptid-GAM®, Tryptophan	I I	1A 1B		5% HA-ES NS
Miller-Fisher syndrome (MFS)	TPE	III	2C		
Myasthenia gravis (moderate, severe) Pre-thymectomy	TPE	I I	1A 1C		
Lambert-Eaton myasthenic syndrome	TPE	II	2C		
Multiple sclerosis (MS) • acute MS • chronic MS • chronic progressive MS	TPE, IA	 II III III	 1A, 1B 1B 2B	1-1.5 TPV	5% HA-ES
Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS); Sydenham´s corea (SC)	TPE	I I	1B 1B		
Phytanic acid storage disease (Refsum´s disease)	TPE, Lipoprotein apheresis	II II	2C 2C		NS
Chronic focal encephalitis (Rasmussen encephalitis)	TPE, IA-Protein	III III	2C 2C		5% HA-ES NS
Acute disseminated encephalitis (ADEM)	TPE	II	2C		5% HA

Peptid-GAM®: synthetic peptid-goat-antimouse, Tryptophan: adsorber with Covalently bound tryptophan, ES: electrolyte solution, NS: no substitution

TPE is most effective when initiated within 7 days of disease onset.

Miller-Fisher syndrome (MFS) is characterized by the acute onset of ophthalmoplegia, ataxia, and areflexia. It is considered a variant form of Guillain-Barré syndrome. Because MFS is classified as a variant form of GBS and has a close association with the presence of the anti-GQ1b antibody, one would expect the efficacy of treatment with TPE or IVIG to have been proved. Anecdotal reports of the response of patients with MFS to TPE would be consistent with a pathogenic role for the anti-GQ1b antibody (Table 1). However, there are some MFS patients without this antibody, and the ultimate proof that anti-GQ1b antibody mediates MFS has not been demonstrated [26]. Further controlled studies are necessary.

Myasthenia Gravis (MG)

MG is a disease caused by autoantibodies, which are directed against acetylcholine receptors of the skeletal muscles. The acetylcholine receptor antibodies (Ach-R-ab) belong to a heterogenous group of polyclonal abs, which are directed against various sections of the post-synaptic receptor molecule. Due to blockage of the receptors, normal nerve transmission from motor nerves to striated muscle is interrupted. This disease primarily affects the muscles of the eyes, oesophagus, and respiratory muscles, as well as the extremities.

The therapies are thymectomy and administration of cholinesterase-blocking substances [27]. In cases with severe progression, immunosuppressives are also given to suppress autoantibody synthesis. TPE has been implemented with good results, especially in the case of severe, previously therapy-resistant progression [28]. The rapid elimination of autoantibodies achieved with TPE results in an improvement in clinical symptoms within hours to days. With the rapid improvement in the symptoms of their patients through TPE. Immunosuppressive drugs target autoantibody production but can take months to have an effect. IVIG and TPE have a more rapid effect than immunosuppressive therapy [29].

The rationale for TA is to remove circulating autoantibodies. In acute attacks, TPE is the first-line therapy (Table 1). The seropositve and seronegative patients respond to TPE. TPE is especially used in myasthenic crisis, perioperatively for thymectomy, or as an adjunct to other therapies to maintain optimal clinical status [3]. TPE works rapidly; clinical effect can be seen within 24 hours but may take a week. The benefits will likely subside in 2 – 4 weeks, if immunosuppressive therapies are not initiated to keep antibody levels from reforming. A combination of TPE and immunosuppressives seems to be successful but randomized trials are necessary. Eculizumab, a human monoclonal antibody (HMA), is used in studies of patients with refractory MG and showed good results, but further studies are necessary [29, 30].

Lambert-Eaten myasthenic syndrome is a rare, but reasonably well understood, antibody-mediated autoimmune disease that is caused by serum autoantibodies and results in muscle weakness and autonomic dysfunction [31]. Like MG, Lambert-Eaton syndrome is based on a disorder of the transmission of neuromuscular excitation. In these cases, no acetylcholine is released. There are only case series, which have suggested some benefit by TPE.

The rationale is similar to that in myasthenia gravis; that is, patient strength should be improved by the removal of the pathogenic antibody to the voltage-gated calcium channel. In most cases, patients are treated long-term with a combination of corticosteroids and immunosuppressive therapy has failed has TPE been attempted (Table 1) [32].

Multiple Sclerosis (MS)

Multiple sclerosis is a replasing, remitting chronic demyelinating disease of the CNS and is the most common cause of neurologic disability in young adults [33]. It has been estimated that some 120,000 to 140,000 patients are affected by MS alone in Germany. Worldwide, there are more than one million afflicted with the disease, and in the United States, there are more than 300,000 patients. MS is also diagnosed in children and adolescents. Estimates suggest that 8,000-10,000 children (up to 18 years old) in the USA have MS, and another 10,000-15,000 have experienced at least one symptom suggestive of MS.

The definition of MS as an autoimmune disease is based on the following characteristics [20]:

- HLA association and genetic predisposition: T cell subset and cytokine correlation with disease activity,
- clinical responses to immunosuppression and immune activators,
- analogies with experimental autoimmune encephalomyelitis,
- cerebrospinal fluid oligoclonal IgG bands,
- CNS pathology using immunocytochemistry techniques,
- evidence of intrathecal synthesis of tumor necrosis factor beta in MS, and the level of TNF alpha in cerebro-spinal fluid may correlate with the severity and progression of disease and reflect histologic disease activity in MS,
- increased levels of gamma interferon correlate with the disease worsening.

MS is an autoimmune disease the pathogenesis is not clearly understood. TPE may be benefit MS patients by removing an antibody, such as antimyelin antibody, or by modulating immune response. There have been four immunopathologic patterns of demyelination in early MS lesions. The characteristics of demyelination for each pattern are [3]: T cell/macrophage-associated, antibody/complement-associated, distal oligodendrogliopathy, and oligodendrocyte degeneration.

The rationale for treating MS patients with plasma exchange derives from the presence of these circulating antimyelin antibodies, non-antibody demyelinating factors, aquaporin-4-specific serum autoantibodies, and neuroelectric blocking factors (Table 1) [34]. TPE removes antibodies and other humoral factors from the circulation safely and effectively. TPE has also been shown to increase the number and percentage of suppressor T cells and decrease the helper T cells in MS patients, thus effectively decreasing the ratio of elevated helper/inducer to suppressor/cytotoxic cell [35]. This point is important, because T cells play a pivotal role in the pathogenesis of MS [2]. Children should be treated with corticosteroids. If corticosteroids alone do not bring enough improvement, other treatments, including IVIG, Interferon ß 1a, and TPE, are available to treat-to-treat MS attacks. For drug removal in MS with natalizumab who develop progressive multifocal leukoencephalopathy (PML), TPE may also be used. PML is a severe opportunistic brain infection caused by virus, which is a known complication of natalizumab therapy [3].

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS); Sydenham´s chorea (SC)

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and Sydenham´s chorea is post infectious neuropsychiatric disorders. Both have neuropsychiatric symptoms, which typically follow Group-A beta-hemolytic streptococcus (GABHS) infection. Streptococcal antigens induce antineural antibodies by an abnormal immune response if this pathogenesis is postulated [3]. GABHS infection has been associated with childhood-onset neuropsychiatric. The onsets of PANDAS are acute and dramatic which present with emotional/mood lability, attention deficit, deterioration of handwriting, separation anxiety, tactile/sensory defensiveness, enuresis, cognitive deficits, and motor hyperactivity.

SC is the main common acquired chorea of childhood. The major clinical manifestations are chorea, hypotonia, and emotional lability. The duration of SC is several months with a recurrence rate of about 20 percent [3]. The mean ages of onset for PANDAS and SC are 6.8 years and 8.4 years old, respectively. SC is diagnosed exclusively by clinical presentations and a history of rheumatic fever. Choreatic movements are rapid, and affect the face, trunk, and extremitites. PANDAS are temporally associated with GABHS; it is not associated with rheumatic fever. Laboratory tests show elevated or increasing streptococcal antibody titers, but an elevated titer does not necessarily indicate a recent streptococcal infection. The presence of streptococcal infection in PANDAS is associated with at least two episodes of neuropsychiatric symptoms as well as negative throat culture or stable titers during times of remission.

The treatments for PANDAS include antibiotics and cognitive behavioral therapy. Severe form of SC is treated with diazepam, valproic acid, carbamazepine, or haloperidol [3]. If these fail, corticosteroids may be tried. While children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis, the efficacy of penicillin prohylaxis in preventing symptom exacerbations in children with PANDAS remains doubtful. In severe symptomatic or refractory patients with PANDAS or SC, IVIG (1 g/kg/day for 2 days) or TPE has been shown to reduce symptom severity or shorten the course. TPE is indicated in severe extreme cases after the conservative therapy have been exhausted; or as first line therapy in situations of life threatening functional impairment [36]. The frequency is daily or every other day for 5 or six procedures over 7 to 14 days. There are no data on any benefit of repeated treatment. In the guidelines on the use of TPE from the AAC of the ASFA PANDAS or SC have the category I with RG 1B (Table 1) [3, 4].

Phytanic Acid Storage Disease (Refsum´s Disease)

Refsum´s disease, also called heredopathia atactica polyneuritiformis, is a rare recessive autosomal inherited metabolic disease, based on an isolated lack of the enzyme, which results in phytanic acid (PA) being stored in the body and causing corresponding symptoms [37]. The clinical symptoms include retinitis pigmentosa, anosmia, deafness, chronic sensory-motor neuropathy, ataxia and the accumulation of PA in blood and body tissues [38, 39]. Removal of the phytanic acid through TPE and a phytanic acid-reduced diet can achieve a significant improvement in the disease [40]. Dietary restriction is the first and important therapy step in Refsum disease. The average daily intake of phytanic acid is 50 – 100 mg/day, and ideally, this should be reduced to 10 – 20 mg/day. PA is almost exclusively of exogenous origin and levels of PA > 800 µmol/L is not uncommon. Poorly metabolized PA, pristanic acid (PrA), and picolenic acid (PiA) accumulate in fatty issues, myelitis sheaths, heart, kidneys and retina, leading to retinitis pigmentosa, peripheral dissociative polyneuropathy, cerebellar ataxia ("sailors walk"), renal, cardiac and liver impairment 65 percent of plasma PA and PrA is localized within VLDL, LDL, HDL lipoprotein particles. Dietary restriction of PA is mostly not sufficient to prevent acute attacks and stabilize the progressive course [40]. Clinical improvement is given achieved when the phytanic acid is reduced to below 500 mg/l by TPE. Latest experience with black cumin oil (nigella sativa) in a dose of 3 g/day shows a support and regression of some malnutrition effects in PA restricted dietary and a supportive effect to membrane differential filtration [41].

In the guidelines of the AAC of the ASFA the Refsum´s disease has the category II with the RG 2C (Table 1) [3, 4]. TPE can reduce the elevated plasma levels of PA. This can avoid acute attacks or exacerbation of the disease as well as for maintenance therapy. The normal plasma PA level in humans is < 33 µmol/L. Symptomatic levels of Refsum´s disease range from 700 to 8,000µmol/L. PA is also bound to plasma lipoproteins and triglycerides therefore lipoprotein apheresis has been used to successfully treat these patients [3].

The approaches to therapeutic apheresis for Refsum´s´disease vary; a typical course consists of 1-2 plasma exchange treatments per week for several weeks to months [3]. In some cases, maintenance TPE continue with decreasing frequency over subsequent weeks to months. Therapeutic strategy is ultimately determined by monitoring the patient´s PA level, clinical signs and symptoms, and the need to control or prevent exacerbations of the disease [42].

Chronic focal encephalitis (Rasmussen Disease)

The Rasmussen disease, is chronic focal encephalitis, and characterized by intractable focal seizures and slowly progressive neurological deterioration [3]. Onset is typically in childhood, mean age 6.8 ± 5.1 years, but a similar syndrome has been described in adults, too. The etiology of this disease is unknown, but antecedent infection with Eppstein-Barr virus, herpes simplex, enterovirus, or cytomegalovirus has been implicated. Cytomegalo-virus genome has been found in resected cortical tissue of three adult patients with Rasmussen´s encephalitis. Cerebrospinal fluid analysis in most cases is normal. Mild lymphocytic pleocytosis and elevated protein may be found. The important symptom of Rasmussen´s encephalitis is epilepsy uncontrollable with anticonvulsant drugs, progressive hemiparesis, and progressive unilateral cerebral atrophy. There is progressive loss of function in the affected cerebral hemisphere [3].

Anticonvulsants are necessary but are not always effective in controlling the disease nor do they stop its progression. Subtotal, functional complete hemispherectomy can markedly reduce seizure activity in a majority of patients but results in permanent contralateral hemiplegia corticosteroids and IVIG given for up to two years in a tapering schedule to diminish epilepsia and other symptoms [3].

Patients with Rasmussen encephalitis and antibodies against neural molecules, and autoantibodies can be produced in the CNS after cytotoxic T cell-mediated neuronal damage [4]. The Rasmussen encephalitis has the category III with RG 2C in the AAC of the ASFA and the rationale for therapeutic apheresis is as follows [3]:

Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine wether TPE is effective in postponing surgical therapy. An initial course of TPE may be followed by 2 days of IVIG 1 g/kg/day. Monthly IA of 1.5 – 2 TPV per treatment has been reported effective in one patient [3]. Confirmation of anti-GluR3 antibodies may support the use of TA in patients with Rasmussen´s encephalitis (Table 1). The frequency of TPE is every other day. After initial 5 – 6 TPE over 10 – 12 days, subsequent courses of TPE (with or without IVIG) may be performed at 2 – 3 month intervals as empirically needed. Immunosuppressive medications may increase the interval between courses.

Acute disseminated encephalomyopathy (ADEM)

ADEM is an acute inflammatory monophasic demyelinating disease that effects the brain and spinal cord, which typically occurs after a febrile (often presumed to be viral) prodrome or vaccination [3]. Typical presentation for the multifocal neurological deficits is ataxia, weakness, dysarthria, and dysphagia accompanied by change in mental status. Most commonly, it is a monophasic illness that lasts from 2 to 4 weeks. Children and young adults are most affected. The differentiation of ADEM from the first attack of multiple sclerosis has prognostic and therapeutic implications. The features of ADEM, which can help to distinguish it from MS, are florid polysymptomatic presentation, lack of oligoclonal band in CSF, predominance of MRI lesions in the subcortical region with relative sparing of the periventricular area, and complete or partial resolution of MRI lesions during convalescence.

Corticosteroids are the first-line therapy, which hasten recovery and result in clinical improvement in up to 60 percent of patients. IVIG is for patients who do not respond to corticosteroids [3]. TPE is used and has a clearly defined role in other neurological conditions that are presumed to be immunologically mediated. TPE removes presumed offending antibodies as well as through immunomodulation. The category II for TPE with the RG 2C after the AAC of the ASFA is assigned on paucity of data (Table 1). The frequency is every other day between 3 to 6 treatments.

Other Neurological Diseases

Brashear et al. found autoantibodies to GABAergic neurons in the **Stiff-Man syndrome** that were removed by TPE, and the patient improved [43]. Other neurological diseases, such as cryoglobulinemic polyneuropathy, central nervous system systemic lupus, acquired neuromyotonia, polymyositis/dermatomyositis, polyneuropathy in paraproteinemia, neuropathy by hyperlipidemia, and encephalopathy in metabolic/hematologic diseases such as thyrotoxicosis, hepatic coma, and M. Moschcowitz are diseases that involve more organ systems and are mentioned elsewhere. Extensive blood and plasma exchange for the treatment of the coagulopathy have been successfully implemented in children with meningococcemia [44]. Other TA methods like immunoadsorption or lymphocytapheresis have been applied in ataxic neuropathy and idiopathic hypertrophic cranial pachymeningitis, Fabry disease, acute transverse myelitis and subacute sclerotic panencephalitis with success [45, 46]. In the neurological diseases mentioned above, TA can be regarded as a support therapy to the current treatment strategies.

Hematological Diseases

TPE is indicated in the management of various hematological diseases. For most of these diseases, clear pathogenetic mechanisms of the disease are understood, and there are well-defined criteria with regard to the therapy. Optimal medical management of immunohematological disorders requires the use of TA, serological immunomodulation, and classical pharmacological immunosuppression with steroids, cytotoxic agents, and antimetabolites were overall therapy is individually taylored to the needs of the patient. Variables such as severity of disease, degree of organ system damage before intervention, age and the existents of co-morbid conditions make controlled trials difficult if not impossible. In some rare hematological diseases, it is impossible to recruit a large number of cases to perform a controlled clinical trial. Therefore, for most of these diseases only small series of cases are available for analysis.

TA in hematological diseases often requires on one site TPE 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 DIC, sepsis. 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. The TA method chosen depends on the pathophysiological origin of a given disease. Additionally, 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 complement components that determine the best TA and drug therapies. Table 2 shows selected hematological and hemostasiological diseases in which TA has been implemented.

Rhesus Disease, Hemolytic Disease in Newborns (HDN)

Rh disease or incompatibility during pregnancy is an indication for TPE [47]. Although it has been common practice for years to carry out anti-D gamma globulin prophylaxis in Rh-negative women after the birth of a Rh-positive child, increased anti-D antibodies still occur in up to three percent of subsequent pregnancies. This can lead to life-threatening M. hemolyticus neonatorum for the fetus. Newborn babies rapidly develop anemia and hyperbilirubinemia with kernikterus. Exchange transfusion is the therapy of choice. Recently, TPE has also become possible [8]. Through the detection of anti-D antibodies in the mother and examination of the amniotic fluid for bilirubin and anti-D antibodies, the diagnosis can be quickly made. Intrauterine exchange transfusions involve a high risk, but it can be a life saving procedure. The earlier Rh incompatibility manifested itself in pregnancy, the poorer the prognosis. If it occurs prior to the 26th week of pregnancy, more than 93 percent of fetuses die by the 31st week. If Rh incompatibility manifests itself after the 26th week, the mother receives TPE treatment, and the child intrauterine or postpartal exchange transfusion 71 percent of these children can survive were as without treatment most die [47].

Hemolytic disease in newborns presents as icterus neonatorum or hydrops fetalis. Both 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 [48]. The anti-RhD antibodies, which belong all to IgG subclasses, are able to transverse the placental barrier into the fetal circulation. The antibodies destroy fetal red blood cells by a non-complement-dependent mechanism. Hemolytic disease in newborns usually occurs during the second pregnancy with a RhD-positive fetus. In

severe fetal hemolysis in a sensitized mother, intravascular fetal transfusion with RhD-negative erythrocytes compatible with the mother´s serum is indicated. After birth, the new born may receive a neonatal exchange transfusion, TPE, and/or phototherapy, depending on severity of HDN [49].

The widespread use of fetal intravascular transfusion and the advent of IVIG therapy have now reduced the former significance of this disease. Combined with IVIG, TA 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 [2]. TPE/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 [49]. Maternal TPE was performed in 2.4 percent of the cases with a response rate of 100 percent. 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 Rhesus incompatibility. The physician must be aware that anti-D antibodies can also increase with TPE.

In 2006, Bing et al. reported successfully treating 44 pregnant women with Rh incompatibility using a combination of anti-D immunoglobulin and TPE, and intrauterine transfusion [50]. 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, and delivery) can improve the perinal 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. Administration 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) [3]. Amniocentesis provides samples for fetal genotype, amniotic fluid spectral analysis, and fetal lung maturity. The measurement of fetal hematocrit allows, if needed, an intrauterine transfusion (IUT), which cannot occur until 20 weeks' gestational age. The fetus is transfused with RBCs negative for the antigen against which maternal antibody is directed. Fetal mortality related to IUT is 1 – 2 percent. IUT can repeated, approximately every 1 – 2 weeks, until the fetus is ready for delivery.

Table 2: TA in hematological and hemostasiological diseases in pediatrics

Apheresis Applications Committee of ASFA 2013, 2016 (3, 4)					
Hematological and hemostasiological diseases	**TA modality**	**Category**	**RG**	**Exchange volume (TPV)**	**Replacement fluid**
Rhesus incompatibility (HDN), Red cell alloimmunization in pregnancy	TPE	II II	2C 2C	1-1.5 TPV	5% HA-ES
Autoimmune hemolytic anemia -warm autoimmune hemolytic disease (WAIHA) -cold agglutinin disease	TPE	III II	2C 2C		
Sickle cell anemia - acute stroke - acute chest syndrome - prophylaxis for primary or secondary stroke; prevention of transfusion iron overload - multi-organ failure Babesios - severe - high risk population	RBC-exchange	I II III III I II	1C 1C 1C 2C 1B 2C	1-2 total RBC	RBC
Aplastic anemia (AA) Pure red cell aplasia	TPE	III II	2C 1B	1-1.5 TPV	5% HA-ES
ABO incompatible hematopoietic Progenitor cell transplantation Graft-versus-host disease (GVHD) - skin (acute) - skin (chronic) - non skin (acute/chronic)	TPE ECP	II II II III	1B-2B 1C 1B 2B	270 ml	FFP

Erythrocytosis Polycythemia Vera (PV)	Erythro- cyt-apheresis	III I	1C 1B	RBC	5% HA-ES
Idiopathic thrombocytopenic purpura(ITP)	TPE, IA	IV II	1C 1C	1-1.5 TPV	NS
Thrombotic thrombocytopenic purpura (TTP) Post-transfusion purpura (PTP)	TPE	I III	1A 2C		5% HA-ES
Thrombocytosis -symptomatic -prophylactic or secondary	Thrombocyt- apheresis	II III	2C 2C		FFP
Hyperleukocytosis -leukostasis -prophylaxis	Leukocyt apheresis	I III	1B 2C		NS
Coagulation factor inhibitors -alloantibody	TPE, IA	IV III	2C 2B		FFP NS
-autoantibody	TPE, IA	III III	2C 1C		FFP NS

ECP: extracorporeal photopheresis, RBC: red blood cell, FFP: fresh frozen plasma, ES: elec-trolyte solution, NS: no substitution

The AAC of the ASFA has given the HDN the category II with RG 2C (Table 2): The rationale for therapeutic apheresis is that TPE removes the maternal red cell alloantibody that is responsible for HDN [3, 4]. Therefore, TPE can decrease the maternal antibody titer and, in turn, the amount transferred to the fetus, thereby protecting it from HDN. Survival in severe cases of HDN with the use of TPE and/or IVIG prior to IUT is about 70 percent. 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. Typically, IUT can be performed after the fetus reaches 20 weeks of gestation [50, 51].

TPE can safely be performed during pregnancy [2]. 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 [2]. The frequency of TPE is every other day [3]. TPE should be considered early in pregnancy (from 7th to 20th week) and continued until IUT can safely be administered, about 20th week of gestation. One approach is use TPE for the first week (three procedures) followed by IVIG at 1g/kg weekly [52].

Hemolytic Anemia

The etiologies of hemolysis often are categorized as acquired or hereditary. Common acquired causes of hemolytic anemia are autoimmunity, microangiopathy, and infections. Immune-mediated hemolysis, caused by anti-erythrocyte antibodies, can be secondary to malignancies, autoimmune disorders, drugs, and transfusion reactions. Microangiopathic hemolytic anemia occurs when the red cell membrane is damaged in circulation, leading to intravascular hemolysis and the appearance of shistocytes. Infectious agents such as malaria and babesiosis invade red blood cells [53]. 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 antibiosis and supportive care for infections, surgical debridement and antibiotics for Colstridia Welchii, stopping the offending drugs in the case of G6PD deficiency. In the case of 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 justified.

Autoimmune Hemolytic Anemia (AIHA)

Autoimmune hemolytic diseases are characterized by reduced erythrocyte in vivo survival time and by the presents of warm or cold agglutinizing antibodies against the autologous erythrocytes. Differentiation between the following antibodies is made based on their serological features [53, 54]:

- Thermo-type (warm agglutination) autoantibodies. This group consists mostly of IgG and its various subclasses. Optimum antibody binding activitis is reached at body temperature (37 ° C).
- Cryo-type (cold agglutination) autoantibodies. These belong to the group of IgM antibodies and display their strongest reaction to antigen-bearing cells at low temperatures (0 - 10° C). They become of clinical importance when a temperature of 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 Comb's test), and elevated serum LDH (54). 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 destruction mediated by macrophage-phagocytic system [54]. 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 reason for the formation of the autoantibodies 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 macrophages of the liver (extravascular hemolysis) [55].

Although most cases of autoimmune hemolysis are idiopathic, potential causes should always be sought. Lymphoproliferative disorders (e.g., chronic lymphocyte leukemia, non-Hodgkin's lymphoma) may produce warm or cold autoantibodies. A number of commonly prescribed drugs can induce production of both types of antibodies. Warm AIHA (WAIHA) also 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 [54]. Along with conventional therapy with corticosteroids and cytostatics or even splenoctomy, TA is increasingly being implemented with success [56].

The AAC of the ASFA has given the AIHA the category III with the RG 2C for the warm autoimmune hemolytic anemia and for the cold agglutinin disease the category II with the RG 2C (Table 2) [3, 4]. The symptoms are fatigue and justice. 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 [3]. Cold autoantibodies with high thermal amplitude could be active with-in in vivo temperature ranges (i.e., 30 – 37° C), and in these cases the thermal amplitude most accurately predicts the severity of the disease [56].

First-line therapy for WAIHA includes prednisone at 1 – 2 mg/kg/day, until response becomes evident [3]. Prednisone suppresses antibody production and down-regulates Fc-receptor-mediated red cell destruction in the spleen. Second-line therapies are splenectomy, IVIG, rituximab, danazol, and immunomodulatory agents (e.g., Cyclophosphamide, azathioprine, cyclosporine A) and TA.

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 [57]. TPE can remove pathogenic immune complexes, activated complements, and autoantibodies [3]. TPE 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 to the RBC and thus not efficiently removed when plasma is removed. 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 the hemodialysis is controlled and the need for transfusions is limited [3].

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 β-chain of hemoglobin [58]. Membrane abnormalities from sickling and oxidative damage caused by hemoglobin S, along with impaired deformability of sickle cell, leads to splenic trapping and removal cells. Some degree of intravascular hemolysis occurs as well. Hemoglobin electropheresis reveals a predominance of hemoglobin S (Hb S). Sickle cells are observed on the peripheral smear. Hb S polymerizes upon deoxygenation, causing red blood cells to become rigid and deformed sickled RBCs [3]. 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 multiogran failure. Infection is the most common cause of death in children, primarily due to autosplenectomy. Overall mortality rate for SCD is 2.6 percent (0.5 deaths/100 person years) with the peak at 1 – 3 years of age [3].

The main therapies include penicillin prohylaxis, folic acid, pneumococcal and Haemophilus influenza vaccinations, analgesis for painful episodes, and antibiotics for infections [3]. RBC 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 percent is indicated to prevent first/primary stroke and Hb S < 30 – 50 percent to prevent secondary/recurrent stroke and to treat chronic debilitating pain, pulmonary hypertension, and anemia with chronic

renal failure [3]. However, in acute ischemic stroke or acute life- 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 [59].

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 RG 1C for primary and secondary stroke prophylaxis and for prevention of transfusion iron load for erythrocytapheresis [3]. For multi-organ failure, there is the category III with the RG 2C for RBC exchange (Table 2).

The replacement fluid is HbS negative leukoreduced RBCs, and, if available, antigen matched for E, C, and Kell [3]. The frequency in acute situations is one procedure, and in chronic situations at required intervals to maintain the desired Hb S level < 30 – 50 percent. 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 level < 30 – 50 percent [59].

Babesiosis

is another haemolytic anemia, which is a protozal disease transmitted from an animal reservoir to humans by the bites of hardtacks, or, more rarely, by transfusion [3]. 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 [3]. In clinical apparent cases, 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, AKI, DIC, congestive heart failure, and pulmonary disease. Specific diagnosis is made through examination of a Giemsa-stained blood smear, DNA amplication using polymerase chain reaction, or detection of specific antibody. The first line therapy includes a combination of antibiotics, most quinine sulfate and clindamycin. 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 2) [3, 4].

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 the blood stream and replacing them with noninfected RBC. Because babesia organism do not have an exo-erythrocyte phase, removal of RBC-associated parasites is potentially curative. Second, the hemolytic process produces vasoactive compounds, including a variety of cytokines and thromboplastin, which can promote renal failure and DIC. RBC exchange may help to curtail the production of these substances. The greatest advantage of RBC exchange over antibiotic therapy is its rapid therapeutic effectiveness [3]. The frequency is a single procedure but it can be repeated. The specific level to which parasitemia must be reduced to elicit the maximum therapeutic effect is not clear. Treatment is usually discontinued after achieving < 5 percent residual parasitemia.

Aplastic Anemia (AA)

Until now, only some cases of aplastic anemia that have been treated with TPE have been published [2]. 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 (PRCA) the category II with RG 1B (Table 2) [3, 4]. 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 [3, 60, 61]. 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 [62]. 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 [3]. 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 report-

ed including high-dose erythropoietin (EPO), TPE, IA, rituximab, donor lymphocyte infusions, discontinuation of cyclosporine, and antithymocyte globulin. The optimal treatment is currently not well defined [3].

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 (Table 2) [3, 4]. 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 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 ≤ 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 [3].

Graft-Versus-Host Disease (GVHD)

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) (Table 2) [3, 4]. The GVHD after allogenic 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 [3].

The rationale of extracorporeal photopheresis 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 [3]. For cGVHD, ECP improves skin or oral manifestations in 60-80 percent 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. ECP does not induce general immunosuppression the greatest benefit may be in facilitating a rapid corticosteroid taper [3].

The treated volume is a mononuclear cell product of approximately 270 ml consisting of mononuclear cells, plasma and saline [3]. 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. ECP 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 extracorporeal photopheresis in graft-versus-host disease are reported elsewhere [63, 64].

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 [65-67]. 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 [3]. This finding 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 [68]. PoV is associated with a point mutation of an auto-inhibitory Janus kinase 2 (JAK2) protein kinase domains [69,70]. The activation on this domain results in erythropoiesis losing its dependence on erythropoietin signaling and becoming virually autonomous [71].

Erythropoietin is primarily produced in the renal cortex, accounting for 90 percent of this circulating protein. Secondary sites of production consist of liver, spleen, lung, testis, brain, and erythroprogenitor cells. Erythropoietin stimulation results in the production of 2×10^{11} red blood cells per day [72]. 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 [73].

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 (Table 2) [3].

PoV 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 [3, 74].

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 [3].

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 [4].

Idiopathic Thrombocytopenic Purpura (ITP)

Thrombocytopenia is an inherited or acquired disease that results in a reduction of circulating thrombocytes. This condition may be asymptomatic or manifests itself in hemorrhagic diathesis with petechial bleeding. The immune thrombocytopenias are a heterogenous group of bleeding disorders with similar hemostatic manifestations but different pathogenic etiologies.

ITP 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 [75]. In more than 60 percent of the patients, part or full remission can be reached with steroid therapy. Splenectomy and cytostatics are further therapeutic measures. In recent years, in addition to being treated with TPE, therapy-resistant, acute, and chronic cases have also been successfully treated with high doses of intravenous immunoglobulin of 400 mg/kg BW/day [76]. The pathophysiological mechanism in ITP is the binding of auto- or alloantibodies to platelet antigens. Fixed antibodies may trigger complement activation [74]. 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-Iib/IIIa and Ib/IX [77].

Another 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 [78]. Recently, acquired autoimmune deficiency of a plasma metalloprotease named ADAMTSJB was shown in many cases of ITP [79]. 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 [80]. 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 [81].

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 [82]. 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 [83].

The diagnosis of ITP based principally on the exclusion of other causes of thrombocytopenia using the history, physical examination, blood count, peripheral blood film, autoimmune profile and other investigations [82]. Platelet associated IgG (PAIg) is elevated in both immune and non-immune thrombocytopenia and therefore has no role in the diagnosis of uncomplicated ITP. It is worth determining the presence of H. pylori in-patient's refractory to therapy since some patients have shown improvement in platelet counts following eradication therapy. The first-line therapy comprises oral corticosteroids and IVIG.

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), anti-rituximab, campath-1H, mycophenolate mofetil and TA [82, 83]. TA can induce remissions in approximately 80 percent of patients with ITP. TA 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 50,000platelets/ul. The measurement of free antiplatelet autoantibodies is a useful test for determining whether TPE is indicated and if so, to assess its efficacy [82].

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 (Table 2) [3]. 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/ul), 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 [2]. Immunoadsorption with Protein-A was introduced successfully in the treatment of ITP [84, 85].

If thrombocytopenia persists or recurs, splenectomy is recommended in adults but is deferred to prevent overwhelming postsplenectomy infection or allow for spontaneous remission [3]. TPE and IA with Protein-A columns may be considered in patients with refractory ITP, with life threatening bleeding or in whom splenectomy is contraindicated. IgG antibodies and IgG-containing circulating immune complexes can be selectively removed by IA with Protein-A. The use of this column is contraindicated when the patient is on ACE inhibitors, has a history of hypercoagulability or thromboembolic events. 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 x 10^9/L or no improvement after about 6 treatments [3]. The column with Protein-A is no longer in the US but may be available in other countries.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is a rare disease of unclear genesis that carries a poor prognosis. It is probably a polyetiological complex, with the kidneys and brain as target organs [86]. 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 path mechanism of TTP [87]. Deficiency of von Willebrand factor (vWF) cleaving protease ADAMT 13 has been demonstrated to be the proximate cause of a subset of TTP.

Recent studies show a defective function of perforin in these two conditions. Perforin is a protein found in the cytoplasmatic granules of both T cytotoxic lymphocytes and natural killer cells [2]. 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 (DIC) 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 [88]. 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 [88]. The mainstay of treatment for TTP is TPE but the role of splenectomy is still undefined. TPE 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 [89].

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 (Table 2) [3, 4]. TPE 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. Corticosteroids are often used as an adjunct at 1 mg/kg/day. Other adjuncts include rituximab, vincristine, and splenectomy [87]. 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 [3].

TPE with plasma replacement has significantly improvement 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 [3]. Transfusion of RBC, when necessary, may be given emergently during TPE. TPE is performed daily until the platelet count is above 150 x 10^9/L and LDH near normal for 2 – 3 consecutive days. Persistence of shistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment [3].

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 [90]. 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 [91]. 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 [3]. 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. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG therapy is not effective [3].

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 2) [3, 4]. The treated volume, replacement fluid, and the frequency of TPE are the same such in ITP and TTP. TPE can be discontinued when platelet count starts increasing (> 20 x 10^9/L) and non-cutaneous bleedings stops.

Thrombocytosis

The thrombocytosis is defined as a circulating platelet count 500 x 10^9/L, and most commonly, phenomenon related to acute bleeding, hemolysis, infection, inflammation, asplenia, cancer, or iron deficiency [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 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 [92].
Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believe to ameliorate prothrombosis factors associated with the dysfunctional platelets [3]. 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 prophylatic or secondary thrombocytosis based on conflicting and limited data available in the literature (Table 2). 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 [3]. Therapeutic thrombocytapheresis provides an immediate symptomatic relief and is an efficient useful emergency lifesaving procedure in patients with thrombocytosis [93, 94].

Hyperleukocytosis

The many early complications and death are directly attributed to hyperleukocytosis and its resultant microcirculatory dysfunction, a phenomenon known as leukostasis, where the sludging of leukemic blasts in capillary vessels and their adhesive interactions give rise to deleterious effects [95]. 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 x 10^9/L (3). 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 x 10^9/L and in acute lymphoblastic leukemic (ALL) when the WBC is > 400 x 10^9/L [4]. 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 [3].

The important treatment is with 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 fluids, electrolyte

replacement, allopurinol or rasburicase, alkalinisation 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 2). Leukocytapheresis has been widely used following anecdotal case reports describing striking clinical improvements with prompt leukoreduction.

Among children and adults with ALL, clinical leukostasis occurs in < 10 percent of those with WBC counts < 400 x 10^9/L [3]. 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 reacumulation of circulating blasts [96, 97].

A single leukocytapheresis can reduce the WBC count by 30 – 60 % [3]. For AML patients with leukostasis complications, discontinue when the blast cell count is < 50 – 100 x10^9/L and clinical manifestations are resolved. For prophylaxis of asymptomatic ALL patients, discontinue treatment when the blast cell count is < 400 x 10^9/L. For ALL patients with leukostasis complications, discontinue treatment when the blast cell count is < 400 x 10^9/L and clinical manifestation are resolved. However, multicentre studies are necessary to better define the role of leukocytapheresis [98].

Coagulation factor inhibitions, Disseminated Intravascular Coagulation (DIC)

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

Major alterations in the coagulation process, offer various theoretical approaches for TPE. There are three stages in the pathomechanism of consumption coagulopathy reaction: hypercoaguable state, intravascular formation of clots, and consumption coagulopathy with reactive hyperfibrinolysis. 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 [99].

The process of consumption coagulopathy can be interrupted in the hypercoagulemic stage by eliminating or reducing the levels of active pro-coagulation factors example heparin, depletion of factors II, VII, IX and X with coumadin or TPE. TPE interrupts the pathogenetic 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.

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 [100]. More and more case reports are presented of successful treatments of DIC with HMA (e.g., eculizumab) [101].

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 [102]. 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.

F VIII inhibitors are the most common pathogenic antibodies directed against the blood coagulation factors. They develop in approximately 30 percent of patients with severe and moderately severe hemophilia an in response to infusions of F VIII [103]. 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 FV III. The risk of inhibitor development in patients with mild hemophilia increases with the amount of exposure F VIII [104].

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. TPE 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 hemophilics who are unresponsive to Factor VIII and as hematologic preparation to normalize these inhibitors prior to major surgery [105].

TPE is indicated in severely bleeding patients classified as immunological high responders [106]. TPE 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 IA with anti-immunoglobulin columns may be safer and more effective [107]. 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.

IA is being increasingly applied in the treatment of F VIII inhibitors. Several types of IA methods have been used, although reports are mainly anecdotal, 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 2) [3]. Multimodal therapy including corticosteroids, rituximab, and emicizumab are reported in the last years [108- 110].

Acquired Factor VIII (F VIII) Antibodies in Non-Hemophiliac 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.

F 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 patient. Approximately 50 percent of acquired hemophilia A patients have underlying conditions, including autoimmune disorders, malignancy, and pregnancy [111]. 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 VIIa or porcine F VIII concentrates can be used to treat patients with high-titer inhibitors. Recombinant F VIIa is effective in controlling most bleeding episodes. There have been no reports of inhibitory antibodies developing to the product [111].

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 and IA is in its rapid removal of antibodies and absence of excessive antibody formation. A disadvantage is an increased risk of bleeding with TPE treatment, if anticoagulation becomes necessary. With IA, a selective elimination of acquired factor VIII antibodies is available [112].

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 2) [3, 4]. Factor deficiency can be either congenital or acquired; the majority of acquired deficiencies result from autoantibodies. 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 [3]. For coagulation factor inhibitors, the extracorporeal removal by immunoadsorption is more effective than TPE [113]. 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

Hyper viscosity 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 [114, 115].

Discussion

In recent years, guidelines have been written for implementing TPE with regard to the special situation of pediatric patients [116-118]. 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. TPE in children requires selected modifications due to the child 's smaller size, blood volume, and development age. Special considerations must be given to instrumentation, volume calculations, access, and complications, as well as to the psychosocial aspects of child development [119, 120].

In addition to indication 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 the same are subject to the same requirements as for adults. 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 lumen 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 [120].

The use of TA is regarded to be an extreme therapeutic measure in children. 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%) [120].

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