Therapeutic Plasma Exchange and Immunoadsorption: Indications and Implementation

11

Ammon Handisurya, Christof Aigner, Benjamin Schairer, and Kurt Derfler

11.1 Introduction

The term apheresis comprises a variety of extracorporeal treatment modalities, which enable the removal of pathogenic components with or without replacement fluid. The following chapter will focus on plasma exchange and immunoadsorption, which was initially reported as an option to treat Waldenström's macroglobulinemia by Solomon and Fahey (1963).

11.1.1 Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) is based on a rather simple mechanism: plasma is separated from corpuscular blood elements and, thereafter, discarded and replaced by substitution fluids, e.g., plasma or human albumin 5%. By this rather unspecific procedure, circulating immunoglobulins (antibodies and autoantibodies) and immune complexes are removed from circulation. However, the concomitant loss of other plasma proteins like coagulation factors, fibrinogen, electrolytes, or

A. Handisurya (✉)
Apheresis Unit, Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria

1st Medical Department,
Hanusch Hospital, Vienna, Austria
e-mail: ammon.handisurya@wgkk.at

C. Aigner · B. Schairer · K. Derfler
Apheresis Unit, Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
e-mail: christof.aigner@meduniwien.ac.at; benjamin.schairer@meduniwien.ac.at; kurt.derfler@meduniwien.ac.at

S. A. Abutalib et al. (eds.), *Best Practices of Apheresis in Hematopoietic Cell Transplantation*, Advances and Controversies in Hematopoietic Transplantation and Cell Therapy, https://doi.org/10.1007/978-3-319-55131-9_11

protein-bound drugs as well as the diminish of return effect limits the plasma volume processed during a single treatment (Zöllner et al. 2014; Chirnside et al. 1981). In general, the continuous substitution of plasma by an isovolemic, iso-osmotic, and iso-oncotic fluid is mandatory during TPE, and the 1.0–1.5 times estimated plasma volume is usually processed during a single treatment (Fig. 11.1, Table 11.1) (Schwartz et al. 2016).

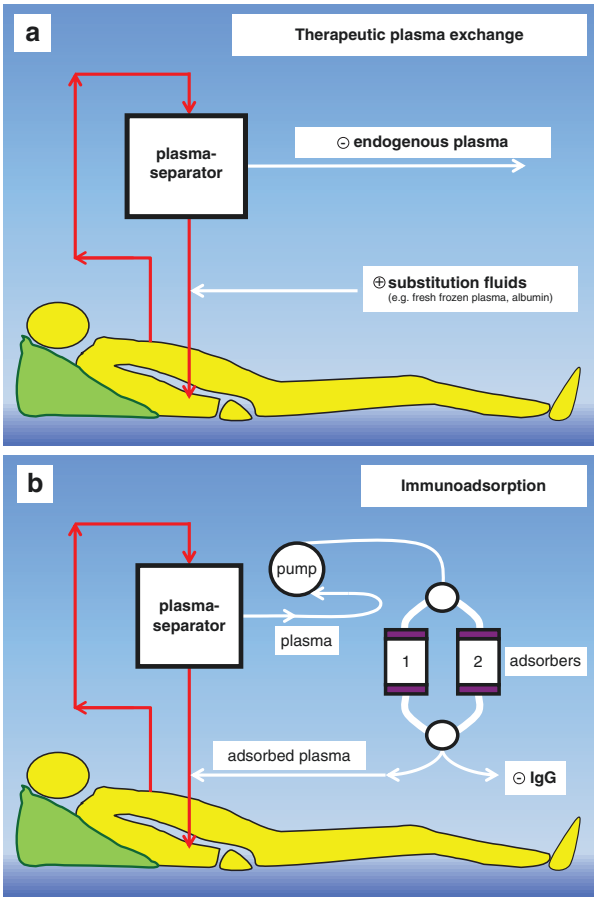

Fig. 11.1 Schematic presentation of therapeutic plasma exchange (**a**) and immunoadsorption (**b**)

Table 11.1 Recommended treatment volume in therapeutic plasma exchange and immunoadsorption

Apheresis modality	Recommended treatment volume [L]
Immunoadsorption	2.5–3.0 times estimated plasma volume
Therapeutic plasma exchange	1.0–1.5 times estimated plasma volume
Estimated plasma volume [mL, simplified formula] = 70 × body weight [kg] × (1-HCT (in decimal number))	

11.1.2 Immunoadsorption

Immunoadsorption (IA) has first gained clinical acceptance as therapeutic option to remove atherogenic lipoproteins in patients with familial hypercholesterolemia. Based on the experience derived from hyperlipidemic subjects, IA was subsequently also employed to remove immunoglobulins, immune complexes, and circulating alloantibodies (i.e., antibodies directed against antigens from a genetically distinct member of the same species) in a wide variety of different autoimmune diseases. During IA, plasma is separated from blood cells but, in contrast to TPE, thereafter, loaded in two reusable adsorber columns, where specifically immunoglobulins are adsorbed and, consecutively, removed. From immunoglobulins depleted endogenous plasma is then retransferred to the patient together with the previously separated blood cells. Thus, IA does not require any substitution fluid, and also the processed treatment volume is theoretically unlimited as IA, in contrast to TPE, does not usually cause losses of electrolytes or plasma proteins other than immunoglobulins. Due to antibody kinetics, 2.5–3.0 times estimated plasma volume is usually processed during a single IA treatment (Table 11.1). Of note, IA is not FDA cleared in the USA.

11.2 Methods

11.2.1 Vascular Access

In theory, all types of vascular access including native peripheral veins are eligible for apheresis (Fig. 11.2). Due to the significantly lower risk of infectious complications, a peripheral vascular access should be favored over central venous catheters. Insufficient peripheral veins and high need for an immediate initiation of apheresis, however, often necessitate central venous catheters. In a chronic setting, when apheresis treatments over a longer period of time are anticipated, a conversion to peripheral venous access including the surgical creation of a hemodialysis fistula should be considered. At our center, 95% of all chronic apheresis treatments (n = approx. 2800/year) are performed via native peripheral veins using 16–18 gauge dialysis cannulas, one at each arm (for withdrawal and return of blood).

11.2.2 Anticoagulation

Due to the extracorporeal circuit, anticoagulation is compulsory to prevent clotting of blood. While the sole use of citrate, anticoagulant citrate dextrose, formula A (ACD-A, Baxter®, Munich, Germany), may be sufficient in TPE, IA is usually performed using citrate in combination with heparin administered as an initial bolus of 1000–4000 IE followed by a continuous infusion of approximately 20 units/min (max. total dose 6000 IE/treatment). The combination of two anticoagulants during IA, where reusable IA adsorbers are employed, improves the quality of the separated plasma and ensures a higher reduction of eliminated immunoglobulins per IA over a longer period of time. The ratio of citrate to whole blood flow is kept at 1:20 to 1:30.

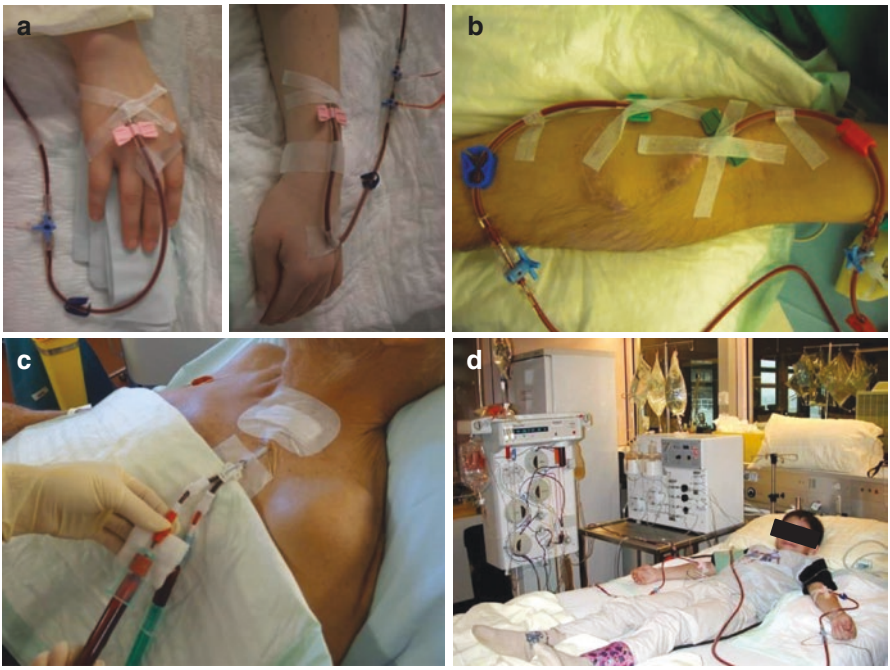

Fig. 11.2 Eligible types of vascular access: (**a**) native peripheral veins (venovenous access), (**b**) arteriovenous fistula, (**c**) central venous catheter, (**d**) example of a venovenous treatment in a 6 years old boy

11.2.3 Devices

For initial plasma separation, necessary for both TPE and IA, blood is drawn via above mentioned 16–18 gauge dialysis cannula at a flow rate of 70–100 mL/min assuring a plasma flow rate of 25–50 mL/min. IgG-plasmapheresis is routinely performed using an automated double-needle, continuous-flow operation system, consisting of a plasma separator and, for IA, the additionally connected adsorption-desorption-automate (ADASORB; Medicap, Ulrichstein, Germany), to which the two IA adsorber columns are attached. The ADASORB regulates the loading of the two IA adsorbers in alternate cycles with (1) plasma for adsorption of immunoglobulins or (2) regeneration solutions for desorption, i.e., elimination of adsorbed immunoglobulins. Of note, none of the IA device is FDA cleared in the USA.

Three different IA adsorber columns are used at our department (>24,000 treatments within 24 years):

1. Ig-Therasorb® (Miltenyi Biotec, Bergisch Gladbach, Germany): Each adsorber column contains 150 mL Sepharose coupled with polyclonal sheep antibodies to human IgG heavy and light chains and has an immunoglobulin-binding capacity of approximately 4.0 g.

2. Immunosorba® and LIGASORB® (Fresenius Medical Care, Bad Homburg, Germany): Reusable protein A-based adsorber columns, which remove IgG-subclasses 1,2,4 and to a smaller degree IgG-3 (Süfke et al. 2017; Koefoed-Nielsen et al. 2017). The removal rate of IgG-3, however, is comparable when high plasma volumes are processed.
3. Globaffin® and Coraffin® (Fresenius Medical Care, Bad Homburg, Germany): More recently developed reusable broadband adsorbers based on synthetic peptides (GAM®) covalently coupled to Sepharose CL-4B (Stummvoll et al. 2017; Dandel et al. 2015).

11.3 Indications for Therapeutic Plasma Exchange and Immunoadsorption

Several indications for both plasmapheresis modalities have been established in numerous autoimmune diseases and in the peri-transplant setting (Schwartz et al. 2016). However, TPE and IA most commonly do not represent first-line therapy but are rather initiated when conventional treatment either fails or elicits inadequately delayed effects in a clinically critical condition (Schwartz et al. 2016; Süfke et al. 2017; Koefoed-Nielsen et al. 2017; Stummvoll et al. 2017; Dandel et al. 2015; Clark et al. 2016; Azoulay et al. 2017; Rock et al. 2017; Raval et al. 2017).

A summary of the indications according to the American Society for Apheresis (Schwartz et al. 2016) is shown in Table 11.2. The system used for categorization and grading is given in an abbreviated version (Schwartz et al. 2016) in Table 11.3.

Here we will focus on three hematological entities with, in part, imminent treatment character.

Table 11.2 Hematological and hemostasiological indications for plasmapheresis according the Writing Committee of the American Society for Apheresis

Disease	Indication	Modality	Category	Grade
Amyloidosis, systemic		TPE	IV	2C
Aplastic anemia		TPE	III	2C
Pure red cell aplasia		TPE	III	2C
Autoimmune hemolytic anemia	– Warm antibody, severe	TPE	III	2C
	– Cold agglutinin disease, severe	TPE	II	2C
Catastrophic antiphospholipid syndrome		TPE	II	2C
Coagulation factor inhibitors	– Alloantibody	TPE	IV	2C
	– Autoantibody	TPE	III	2C
	– Alloantibody	IA	III	2B
	– Autoantibody	IA	III	1C
Cryoglobulinemia	– Symptomatic, severe	TPE	II	2A
	– Symptomatic, severe	IA	II	2B

(continued)

Table 11.2 (continued)

Disease	Indication	Modality	Category	Grade
Erythropoietic porphyria, liver disease		TPE	III	2C
Hematopoietic stem cell transplantation	– Major HPC, marrow	TPE	II	1B
	– Major HPC, apheresis	TPE	II	2B
	– HLA desensitization	TPE	III	2C
Hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, macrophage activation syndrome		TPE	III	2C
Heparin-induced thrombocytopenia and thrombosis	– Pre-cardiopulmonary bypass	TPE	III	2C
	– Thrombosis	TPE	III	2C
Hyperviscosity in monoclonal gammopathies	– Symptomatic	TPE	I	1B
	– Prophylaxis for rituximab	TPE	I	1C
Immune thrombocytopenia	– Refractory	TPE	III	2C
	– Refractory	IA	III	2C
Multiple myeloma	– Cast nephropathy	TPE	II	2B
	– Paraproteinemic demyelinating neuropathies	TPE	III	2C
Paraneoplastic neurological syndromes		TPE	III	2C
		IA	III	2C
Posttransfusion purpura		TPE	III	2C
Red cell alloimmunization in pregnancy	– Prior to IUT availability	TPE	III	2C
Thrombotic microangiopathy	– Coagulation-mediated THBD mutation	TPE	III	2C
	– Complement-mediated complement factor gene mutations	TPE	III	2C
	– Complement-mediated factor H autoantibodies	TPE	I	2C
	– Complement-mediated MCP mutations	TPE	III	1C
	– Drug-associated ticlopidine	TPE	I	2B
	– Drug-associated clopidogrel	TPE	III	2B
	– Drug-associated calcineurin inhibitors	TPE	III	2C
	– Drug-associated gemcitabine	TPE	IV	2C
	– Drug-associated quinine	TPE	IV	2C

Table 11.2 (continued)

Disease	Indication	Modality	Category	Grade
	– Hematopoietic stem cell transplantation associated	TPE	III	2C
	– Shiga toxin-mediated severe neurological symptoms	TPE/IA	III	2C
	– Thrombotic thrombocytopenic purpura	TPE	I	1A

Table 11.3 Categorization and grading system of the Writing Committee of the American Society for Apheresis

Category	*Description*
I	Apheresis as first-line therapy, either stand-alone or with other modes of treatment
II	Apheresis as second-line therapy, either stand-alone or with other modes of treatment
III	Optimum role of apheresis not established, individualized decision making
IV	Published evidence for ineffectiveness or harmfulness of apheresis
Grade	*Description*
1A	Strong recommendation, high-quality evidence
1B	Strong recommendation, moderate evidence
1C	Strong recommendation, low- to very low-quality evidence
2A	Weak recommendation, high-quality evidence
2B	Weak recommendation, moderate evidence
2C	Weak recommendation, low- to very low-quality evidence

11.3.1 Thrombotic Microangiopathy

Thrombotic microangiopathies (TMAs), which may be categorized in inherited and acquired forms (Table 11.4), are a combination of symptoms characterized by acute and chronic thrombotic occlusion of arterioles and arteries (Caprioli et al. 2003; George and Nester 2014). The classical clinical and laboratory signs indicating TMA are Coombs negative, mechanical hemolysis, and thrombocytopenia. Acute kidney injury or neurological symptoms may also be present.

Inherited TMAs: Complement-mediated TMA results from an impaired regulation of the alternative complement pathway caused by mutations in complement regulatory proteins or in complement protein C3. The most frequent mutations occur in complement factor (CF) H, CFI, and CD46, followed by mutations in C3, CFB, and the factor H-related proteins 1–5. Notably, CD46 is a membrane-bound protein, whereas all other are circulating factors. Previously, mutations in 40–60%

Table 11.4 Syndromes of TMA (modified after (George and Nester 2014))

Name	Cause	Clinical features	Initial management
Inherited disorders			
ADAMTS13 deficiency-mediated TMA (TTP)	Mutations in *ADAMTS13*	Neurological symptoms	PI
Complement-mediated TMA	Mutations in *CFH*, *CFI*, *CFB*, *MCP*, and *C3*, leading to uncontrolled AP activation	AKI or CKD, optional: involvement of other organs	PI, TPE, complement inhibition
Metabolism-mediated TMA	Homozygous mutations in *MMACHC*	Often in children <1 year; sometimes in adolescents and adults	Vitamin B12, betaine, folic acid
Coagulation-mediated TMA	Homozygous and compound heterozygous mutations in *DGKE*, *THBD*; (PLG)	Typically AKI in children <1 year	PI
Acquired disorders			
ADAMTS13 deficiency-mediated TMA (TTP)	Autoantibodies directed against ADAMTS13	Neurological symptoms, uncommon in children	TPE, immunosuppression
Shiga toxin-mediated TMA (STEC-HUS)	Infection with toxin-producing strains of *E. coli* or *Shigella*	Most common in small children. Usually sporadic, but large outbreaks may occur	Supportive treatment
Drug-mediated TMA	Immune reactions (i.e., in quinine) or dose-dependent toxicity (i.e., in tacrolimus)	Immune: sudden onset, often with anuric AKI	Removal of drug, supportive treatment
		Dose: gradual onset of AKI over weeks	TPE
Complement-mediated TMA	Autoantibodies directed against CFH. Association with deletion in *CFHR*	AKI in children and adults.	TPE, immunosuppression, complement inhibition

ADAMTS13 a disintegrin and metalloproteinase with a thrombospondin motif 13, *TTP* thrombotic thrombocytopenic purpura, *PI* plasma infusions, *TMA* thrombotic microangiopathy, *CFH*, *CFI*, *CFB* complement factor H, I, B, *MCP* membrane cofactor protein, *C3* complement protein 3, *THBD* thrombomodulin, *AP* alternative pathway, *AKI* acute kidney injury, *CKD* chronic kidney disease, *TPE* therapeutic plasma exchange, *MMACHC* methylmalonic aciduria and homocystinuria type C protein, *DGKE* diacylglycerol kinase epsilon, *PLG* plasminogen, *CFHR* complement factor H-related protein

of patients with a disease penetrance of 50% among the carriers were reported (Noris et al. 2010; Fremeaux-Bacchi et al. 2013; Bu et al. 2016).

The coagulation-mediated TMA is caused by mutations in diacylglycerol kinase epsilon (DGKE) and thrombomodulin (THBD). In case of DGKE mutations, patients do not show any abnormalities in extended complement component workup,

while patients with THBD might show signs of systemic complement dysregulation (Lemaire et al. 2013; Delvaeye et al. 2009).

Some syndromes associated with TMA can be attributed to metabolic dysregulation. Cobalamin C disease is a rare autosomal inherited disease caused by mutations in the methylmalonic aciduria and homocystinuria type C protein *(MMACHC)* gene and usually manifests in the first year of life with developmental delays and muscular hypotonia (Cornec-Le Gall et al. 2014).

Acquired TMAs: Secondary causes of TMA are manifold and include drug reactions, systemic diseases, and infections (Campistol et al. 2013). Drug-associated TMAs can be attributed to dose-dependent adverse drug reactions or immune-mediated reactions, e.g., quinine. The therapy for drug-induced TMA is the discontinuation or the dose reduction of the causal agent. However, in case of ticlopidine-associated TMA, ADAMTS13 levels are often diminished and inhibitors can be detected (Reese et al. 2015). In this case, TPE can be considered, as recommended by the American Society of Apheresis (Schwartz et al. 2016).

In acquired complement-mediated TMA, complement dysregulation is caused by autoantibodies against CFH (Józsi et al. 2008). In 90% of these cases, a homozygous deletion in *CFHR1* and *CFHR3* can be diagnosed. Treatment of these cases often requires immunosuppression. Anticomplement therapy is the definite therapy (Sana et al. 2014).

Shiga toxin-mediated TMA (formerly called classic HUS) results from acute infection with certain members of the *E. coli* family after ingestion of contaminated food or water. Symptoms are bloody diarrhea, followed by hemolytic anemia, thrombocytopenia, and acute kidney injury. Children under the age of 1 year are most commonly affected. Treatment of choice is supportive treatment (Campistol et al. 2013).

Thrombotic Thrombocytopenic Purpura: ADAMTS13 deficiency-mediated TMA, or formerly called thrombotic thrombocytopenic purpura (TTP), is diagnosed by the detection of decreased levels of ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin motif 13, which cleaves von Willebrand factor (vWF) into small multimers. vWF is essential for homeostasis as it induces platelet aggregation and thrombus formation on damaged endothelium. Severe ADAMTS13 deficiency (<5–10% of normal enzyme activity) is diagnostic of TTP in the right clinical scenario. In contrast to the other forms of TMA, TTP predominantly affects the central nervous system, and renal involvement is not typical (George and Nester 2014). Acquired TTP is more common than the hereditary form, which is caused by mutations in the ADAMTS13 gene and is commonly associated with a neonatal onset. Acquired TTP is caused by autoantibodies against ADAMTS13, which inhibit the enzyme function. The autoantibodies tend to disappear during remission, which suggests a transient immune reaction. Recently, a monoclonal antibody against vWF, caplacizumab, has shown promising results in the treatment of acquired TTP in a phase 2 trial (Peyvandi et al. 2016).

Treatment strategies depend on the underlying cause of TMA. Of note, some form of therapy is, however, required even before the final diagnosis, i.e., the type of TMA, is established. Consensus guidelines recommend the emergent initiation of

TPE or, if TPE is unavailable, of plasma infusions after (preliminary) diagnosis of TMA. The effectiveness of TPE depends on the form of TMA and, in inherited complement-mediated TMA, on the underlying mutation. The rationale of TPE in TMA is to supplement functioning complement (regulatory) proteins such as CFH, CFI, and CFB while removing dysfunctional complement (regulatory) proteins and other potential disease-causing factors. If mutations of membrane-bound proteins, i.e., CD46, are present, TPE does not positively influence patient outcomes (Bresin et al. 2013). In contrast, TPE in combination with immunosuppressive agents remains a standard treatment approach in case of autoantibody-mediated TMA as underlying circulating autoantibodies are effectively removed (Sana et al. 2014). Alternatively, anticomplement agents should be considered, especially in cases with limited response to TPE (Legendre et al. 2013).

11.3.2 Acquired Coagulation Inhibitors

Coagulation inhibitors may occur spontaneously in seriously ill patients with previously normal coagulation and lead to varying degrees of hemorrhagic diathesis. In most cases, these autoantibodies are directed against factor VIII (so-called acquired hemophilia A) and far less frequent against coagulation factors II, IIa, or V (inhibitors of other coagulation factors are extremely rare) (Cugno et al. 2014; Franchini and Mannucci 2013).

Treatment of bleeding complications caused by acquired coagulation inhibitors against factor VIII comprises (1) the control over active bleeding by administration of desmopressin and substitution of factor concentrates and (2) the elimination of the inhibitor (Franchini and Mannucci 2013; Kruse-Jarres et al. 2017). The choice of factor concentrates is determined by the severity of bleeding and the titer of the coagulation inhibitor, usually measured in Bethesda units (BU). While high doses of human factor VIII concentrates may be sufficient in cases with low factor VIII inhibitor titer (<5 BU), activated prothrombin complex concentrates, recombinant porcine factor VIII, or recombinant human factor VIIa are necessary in those subjects with a titer >5 BU. As most of these factor concentrates are rather expensive, the expenses may exceed 90.000€/day. Further, even after diagnosis of the acquired coagulation inhibitor, this state represents a life-threatening condition as the response to conservative pharmaceutical immunosuppressive treatment used to eliminate the inhibitor, i.e., corticosteroids, cyclophosphamide, and rituximab, is often delayed, and the administration of the mentioned factor concentrates is insufficient to control the bleeding especially in postsurgical setting (Kruse-Jarres et al. 2017; Goldmann et al. 2015).

IA has been demonstrated to provide a rapid reduction of circulating inhibitors (Jansen et al. 2001). The mean reduction of acquired anti-factor VIII autoantibodies by a single IA session, desorbing about 2.5-fold the calculated plasma volume, was 71.9 ± 19.4% (range 50.0–97.1%). The level of total serum IgG was reduced

by 68.7 ± 10.1%, of total serum IgA by 55.7 ± 12.7%, and of total serum IgM level by 48.6 ± 11.1% per IA session (Jansen et al. 2001). In mean 8.1 ± 5.1 IA treatments, concomitant to the substitution of human factor VIII, had to be performed until sufficient response without further bleedings was achieved (Jansen et al. 2001). These findings were corroborated by data of Goldmann et al. (2015) suggesting an IA-based protocol including immunosuppressive treatment to be considered as first-line therapy or even as salvage strategy. As IA was able to significantly reduce or even avoid substitution of coagulation factors, a dramatic reduction in the treatment costs of these patients might be achieved (Freedman et al. 2003).

11.3.3 Prolonged Red Cell Aplasia After Major ABO-Incompatible Allogenic Hematopoietic Cell Transplantation

Allogenic hematopoietic cell transplantation (HCT) is widely used to treat patients with malignant and nonmalignant hematological and autoimmune diseases. While compatibility in the major human leucocyte antigens (HLA) system is essential for short- and long-term outcome after transplantation, ABO-incompatible (ABO-I) HCT is regarded feasible and affects approximately 30–50% of all HCT patients (Worel 2016). A complication following major ABO incompatibility is pure red cell aplasia (PRCA), which is associated with higher peri-transplant and long-term mortality due to iron overload related to poly-transfusion (Worel 2016). The underlying mechanism of PRCA is not fully understood, but the persistence of memory B lymphocytes of the recipient, which continuously produce hemagglutinins against the ABO antigens on donor erythrocytes, or the persistence of preformed host isohemagglutinins, which suppress the donor erythropoiesis, is held responsible for this complication of ABO-I HCT (Worel 2016; Rabitsch et al. 2003a, b). Only limited experience on the prevention of PRCA is available. Some investigators reported a beneficial effect of pretransplant TPE, but further studies are clearly warranted (Worel 2016; Dellacasa et al. 2015).

Apart from supportive measures including erythropoietin-stimulating agents and transfusion of RBCs, treatment options consist of immunosuppressive treatment with corticosteroids, antithymocyte globulin, rituximab, or apheresis modalities like TPE and IA. In two case series, we reported on, in total, eight patients with PRCA after ABO-I HCT, who were treated with IA (Rabitsch et al. 2003a, b). To achieve maximal elimination of preformed and potentially reproduced circulating isohemagglutinins, the 2.5–3.0-fold of the estimated plasma volume was desorbed during each IA, and five IA treatments per week were performed initially. In the second larger case series (Rabitsch et al. 2003b), all five patients became transfusion independent after a median of 17 IA treatments (range 9–25). Of note, three of the included HCT recipients have been ineffectively treated with TPE before.

Despite the missing prospective, multicenter study, IA seems to be a promising therapeutic method for rapid, efficient, and safe elimination of persisting isohemagglutinins in patients with PRCA after ABO-I HCT.

11.4 Complications of Therapeutic Plasma Exchange and Immunoadsorption

Both forms of apheresis are usually well tolerated and associated with a low rate of adverse events. However, monitoring of vital signs during the treatment as well as routine laboratory tests, such as complete blood count, electrolytes, and coagulation markers, including fibrinogen is mandatory.

TPE-related side effects are mainly caused by the choice of the substitution fluid. For example, albumin 5% does not compensate for the loss of fibrinogen and coagulations factors caused by the removal of endogenous plasma (Chirnside et al. 1981), and plasma may cause anaphylactic and/or other transfusion-reacted reactions. Of note, fibrinogen loss may be significant even after only one TPE session, which may result in significant bleeding complications as was shown by Zoellner et al. (Fig. 11.3) (Zöllner et al. 2014). Thus, the combination of human albumin 5% and plasma or the exclusive use of plasma, especially in patients with hemorrhagic diathesis, is recommended.

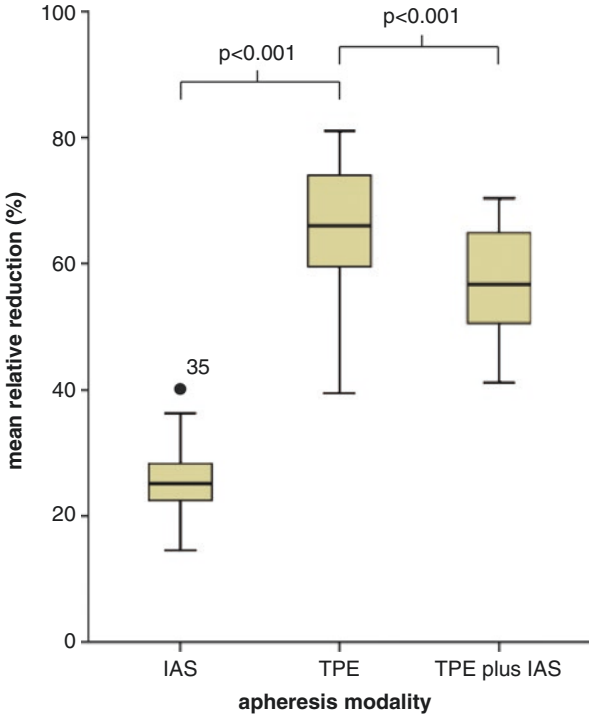

Fig. 11.3 Mean relative reduction (%) of plasma fibrinogen in relation to apheresis modality (adapted from (Zöllner et al. 2014))

Due to the unspecific removal of total IgG and also IgM, the rate of infectious complications may be increased irrespective of the apheresis modality, especially if concomitant immunosuppressive medication is needed (Stummvoll et al. 2012). Infection complications related to central venous catheters are well established and are not discussed in this chapter.

In addition, iron loss is frequent, and anemia requiring iron substitution develops in approximately 25% of subjects undergoing chronic apheresis.

Patients on ACE inhibitors may have facial flushing or hypotension. This reaction has been observed in patients taking an ACE inhibitor who undergo treatments involving an extracorporeal circuit, including IA, LDL apheresis, and TPE procedures. The hypotheses explaining this reaction involve the generation and accumulation of excess bradykinin (a potent vasodilator). One hypothesis suggested the reaction might be due to activation of the contact pathway in the extracorporeal circuit, which generates bradykinin. Others postulated that these reactions are secondary to the presence of prekallikrein activator in the albumin, which is activated to bradykinin. However, the relationship between hypotension during apheresis procedure and prekallikrein activator in the albumin has never been confirmed by actual measurements. Some experts prefer ACE inhibitor therapy to be discontinued 24–48 h prior to the start of apheresis procedures, if possible. If the procedure must be done, the decision of how to proceed is based on the emergent nature of the procedure and the risks/benefits for the individual patient.

A major issue is the effect of apheresis, especially of TPE, on drug levels. Literature on the elimination of specific drugs by TPE is scarce. In general, substances with high plasma protein affinity and low distribution volume are more susceptible to the removal by TPE (Cheng et al. 2017; Ibrahim et al. 2007). However, several other factors may also account for TPE-related changes in pharmacokinetics, including drug distribution or drug half-life (Cheng et al. 2017; Ibrahim et al. 2007). For example, plasma levels of rituximab, a chimeric anti-CD20 monoclonal antibody employed in several hematological and autoimmune diseases, are decreased by approximately 50%, if TPE is performed within 72 h after rituximab infusion (Puisset et al. 2013). In contrast, calcineurin inhibitors cyclosporine A and tacrolimus levels, used, e.g., for prophylaxis of graft-vs-host disease after HCT, are hardly altered by TPE (Ibrahim et al. 2007).

References

Azoulay E, Knoebl P, Garnacho-Montero J, Rusinova K, Galstian G, Eggimann P, Abroug F, Benoit D, von Bergwelt-Baildon M, Wendon J, Scully M (2017) Expert statements on the standard of care in critically ill adult patients with atypical hemolytic uremic syndrome. Chest 152(2):424–434

Bresin E, Rurali E, Caprioli J, Sanchez-Corral P, Fremeaux-Bacchi V, Rodriguez de Cordoba S, Pinto S, Goodship TH, Alberti M, Ribes D, Valoti E, Remuzzi G, Noris M (2013) European working party on complement genetics in renal diseases. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol 24(3):475–486

Bu F, Borsa NG, Jones MB, Takanami E, Nishimura C, Hauer JJ, Azaiez H, Black-Ziegelbein EA, Meyer NC, Kolbe DL, Li Y, Frees K, Schnieders MJ, Thomas C, Nester C, Smith RJ (2016) High-throughput genetic testing for thrombotic microangiopathies and C3 glomerulopathies. J Am Soc Nephrol 27(4):1245–1253

Campistol JM, Arias M, Ariceta G, Blasco M, Espinosa M, Grinyó JM, Praga M, Torra R, Vilalta R, Rodríguez de Córdoba S (2013) An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. Nefrologia 33(1):27–45

Caprioli J, Castelletti F, Bucchioni S, Bettinaglio P, Bresin E, Pianetti G, Gamba S, Brioschi S, Daina E, Remuzzi G, Noris M, International Registry of Recurrent and Familial HUS/TTP (2003) Complement factor H mutations and gene polymorphisms in haemolytic uraemic syndrome: the C-257T, the A2089G and the G2881T polymorphisms are strongly associated with the disease. Hum Mol Genet 12(24):3385–3395

Cheng CW, Hendrickson JE, Tormey CA, Sidhu D (2017) Therapeutic plasma exchange and its impact on drug levels: an ACLPS critical review. Am J Clin Pathol 148(3):190–198

Chirnside A, Urbaniak SJ, Prowse CV, Keller AJ (1981) Coagulation abnormalities following intensive plasma exchange on the cell separator. II. Effects on factors I, II, V, VII, VIII, IX, X and antithrombin III. Br J Haematol 48(4):627–634

Clark WF, Huang SS, Walsh MW, Farah M, Hildebrand AM, Sontrop JM (2016) Plasmapheresis for the treatment of kidney diseases. Kidney Int 90(5):974–984

Cornec-Le Gall E, Delmas Y, De Parscau L, Doucet L, Ogier H, Benoist JF, Fremeaux-Bacchi V, Le Meur Y (2014) Adult-onset eculizumab-resistant hemolytic uremic syndrome associated with cobalamin C deficiency. Am J Kidney Dis 63(1):119–123

Cugno M, Gualtierotti R, Tedeschi A, Meroni PL (2014) Autoantibodies to coagulation factors: from pathophysiology to diagnosis and therapy. Autoimmun Rev 13(1):40–48

Dandel M, Englert A, Wallukat G, Riese A, Knosalla C, Stein J, Hetzer R (2015) Immunoadsorption can improve cardiac function in transplant candidates with non-ischemic dilated cardiomyopathy associated with diabetes mellitus. Atheroscler Suppl 18:124–133

Dellacasa CM, D'Ardia S, Allione B, Aydin S, Tassi V, Francisci T, Pecoraro C, Busca A (2015) Efficacy of plasmapheresis for the treatment of pure red blood cell aplasia after allogeneic stem cell transplantation. Transfusion 55(12):2979–2982

Delvaeye M, Noris M, De Vriese A, Esmon CT, Esmon NL, Ferrell G, Del-Favero J, Plaisance S, Claes B, Lambrechts D, Zoja C, Remuzzi G, Conway EM (2009) Thrombomodulin mutations in atypical hemolytic-uremic syndrome. N Engl J Med 361(4):345–357

Franchini M, Mannucci PM (2013) Acquired haemophilia A: a 2013 update. Thromb Haemost 110(6):1114–1120

Freedman J, Rand ML, Russell O, Davis C, Cheatley PL, Blanchette V, Garvey MB (2003) Immunoadsorption may provide a cost-effective approach to management of patients with inhibitors to FVIII. Transfusion 43(11):1508–1513

Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaimé F, Dragon-Durey MA, Ngo S, Moulin B, Servais A, Provot F, Rostaing L, Burtey S, Niaudet P, Deschênes G, Lebranchu Y, Zuber J, Loirat C (2013) Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol 8(4):554–562

George JN, Nester CM (2014) Syndromes of thrombotic microangiopathy. N Engl J Med 371(7):654–666

Goldmann G, Marquardt N, Horneff S, Oldenburg J, Zeitler H (2015) Treatment of minor severe acquired haemophilia. Is there a rationale for immunoadsorption? Atheroscler Suppl 18:74–79

Ibrahim RB, Liu C, Cronin SM, Murphy BC, Cha R, Swerdlow P, Edwards DJ (2007) Drug removal by plasmapheresis: an evidence-based review. Pharmacotherapy 27(11):1529–1549

Jansen M, Schmaldienst S, Banyai S, Quehenberger P, Pabinger I, Derfler K, Hörl WH, Knöbl P (2001) Treatment of coagulation inhibitors with extracorporeal immunoadsorption (Ig-Therasorb). Br J Haematol 112(1):91–97

Józsi M, Licht C, Strobel S, Zipfel SL, Richter H, Heinen S, Zipfel PF, Skerka C (2008) Factor H autoantibodies in atypical hemolytic uremic syndrome correlate with CFHR1/CFHR3 deficiency. Blood 111(3):1512–1514

Koefoed-Nielsen P, Bistrup C, Christiansen M (2017) Protein a immunoadsorption may hamper the decision to transplant due to interference with CDC crossmatch results. J Clin Apher 32(3):163–169

Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, Tiede A, Kessler CM (2017) Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol 92(7):695–705

Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, Bingham C, Cohen DJ, Delmas Y, Douglas K, Eitner F, Feldkamp T, Fouque D, Furman RR, Gaber O, Herthelius M, Hourmant M, Karpman D, Lebranchu Y, Mariat C, Menne J, Moulin B, Nürnberger J, Ogawa M, Remuzzi G, Richard T, Sberro-Soussan R, Severino B, Sheerin NS, Trivelli A, Zimmerhackl LB, Goodship T, Loirat C (2013) Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 368(23):2169–2181

Lemaire M, Frémeaux-Bacchi V, Schaefer F, Choi M, Tang WH, Le Quintrec M, Fakhouri F, Taque S, Nobili F, Martinez F, Ji W, Overton JD, Mane SM, Nürnberg G, Altmüller J, Thiele H, Morin D, Deschenes G, Baudouin V, Llanas B, Collard L, Majid MA, Simkova E, Nürnberg P, Rioux-Leclerc N, Moeckel GW, Gubler MC, Hwa J, Loirat C, Lifton RP (2013) Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat Genet 45(5):531–536

Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, Daina E, Fenili C, Castelletti F, Sorosina A, Piras R, Donadelli R, Maranta R, van der Meer I, Conway EM, Zipfel PF, Goodship TH, Remuzzi G (2010) Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol 5(10):1844–1859

Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knöbl P, Wu H, Artoni A, Westwood JP, Mansouri Taleghani M, Jilma B, Callewaert F, Ulrichts H, Duby C, Tersago D, Investigators TITAN (2016) Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med 374(6):511–522

Puisset F, White-Koning M, Kamar N, Huart A, Haberer F, Blasco H, Le Guellec C, Lafont T, Grand A, Rostaing L, Chatelut E, Pourrat J (2013) Population pharmacokinetics of rituximab with or without plasmapheresis in kidney patients with antibody-mediated disease. Br J Clin Pharmacol 76(5):734–740

Rabitsch W, Knöbl P, Greinix H, Prinz E, Kalhs P, Hörl WH, Derfler K (2003a) Removal of persisting isohaemagglutinins with Ig-Therasorb immunoadsorption after major ABO-incompatible non-myeloablative allogeneic haematopoietic stem cell transplantation. Nephrol Dial Transplant 18(11):2405–2408

Rabitsch W, Knöbl P, Prinz E, Keil F, Greinix H, Kalhs P, Worel N, Jansen M, Hörl WH, Derfler K (2003b) Prolonged red cell aplasia after major ABO-incompatible allogeneic hematopoietic stem cell transplantation: removal of persisting isohemagglutinins with Ig-Therasorb immunoadsorption. Bone Marrow Transplant 32(10):1015–1019

Raval JS, Mazepa MA, Whinna HC, Park YA (2017) Monitoring therapeutic apheresis utilization: database versus registry. J Clin Apher 32(3):208–209

Reese JA, Bougie DW, Curtis BR, Terrell DR, Vesely SK, Aster RH, George JN (2015) Drug-induced thrombotic microangiopathy: experience of the Oklahoma registry and the BloodCenter of Wisconsin. Am J Hematol 90(5):406–410

Rock G; Members of the Canadian Apheresis Group (2017) The Canadian apheresis group registry. Transfus Apher Sci 56(1):86–88

Sana G, Dragon-Durey MA, Charbit M, Bouchireb K, Rousset-Rouvière C, Bérard E, Salomon R, Frémeaux-Bacchi V, Niaudet P, Boyer O (2014) Long-term remission of atypical HUS with anti-factor H antibodies after cyclophosphamide pulses. Pediatr Nephrol 29(1):75–83

Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, Dunbar NM, Witt V, Wu Y, Shaz BH (2016) Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the writing Committee of the American Society for apheresis: the seventh special issue. J Clin Apher 31(3):149–162

Solomon A, Fahey JL (1963) Plasmapheresis therapy in macroglobulinemia. Ann Intern Med 58:789–800

Stummvoll GH, Schmaldienst S, Smolen JS, Derfler K, Biesenbach P (2012) Lupus nephritis: prolonged immunoadsorption (IAS) reduces proteinuria and stabilizes global disease activity. Nephrol Dial Transplant 27(2):618–626

Stummvoll G, Aringer M, Handisurya A, Derfler K (2017) Immunoadsorption in autoimmune diseases affecting the kidney. Semin Nephrol 37(5):478–487

Süfke S, Lehnert H, Uhlenbusch-Körwer I, Gebauer F (2017) Safety aspects of immunoadsorption in IgG removal using a single-use, multiple-pass protein a immunoadsorber (LIGASORB): clinical investigation in healthy volunteers. Ther Apher Dial 21(4):405–413

Worel N (2016) ABO-mismatched allogeneic hematopoietic stem cell transplantation. Transfus Med Hemother 43(1):3–12

Zöllner S, Pablik E, Druml W, Derfler K, Rees A, Biesenbach P (2014) Fibrinogen reduction and bleeding complications in plasma exchange, immunoadsorption and a combination of the two. Blood Purif 38(2):160–166