Chapter 4

Plasma Exchange in Clinical Practice

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Additional information is available at the end of the chapter

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Abstract

Plasma exchange (PEX) is a treatment method with increasing range of indications. However, due to the small number of randomized trials, its effectiveness is still under debate in certain conditions. The aim of our chapter is to present the major principles of PEX, discuss safety issues and reveal current data for treatment effectiveness of the method. Novel indications for PEX will also be discussed.

Keywords: plasma exchange, indications, contraindications, safety

1. Introduction

Plasma exchange (PEX) is an invasive therapeutic method, separating plasma from blood cells. Thus, pathogenic antibodies or other large molecules are removed and plasma is replaced by human albumin and/or fresh frozen plasma (FFP). The method was first developed in the first half of the twentieth century. Over the years a significant improvement in the PEX technique, patient safety and broadening of indications were observed. Selective techniques were also introduced into practice, leading to selective removal of proteins and reduction of protein loss during the standard procedure, especially fibrinogen. Thus, improved effectiveness and patient safety was achieved.

2. Plasma exchange: basic principles

Generally, in PEX, blood is pumped out of the patient's circulation and is transferred to the filter, separating plasma from blood cells. Afterwards, blood cells are pumped into the patient's vein. Patient's plasma is substituted by human albumin and/or FFP.

2.1. Vascular access

In most of the cases, central venous catheters are used in PEX, especially in acute conditions. They can be placed in internal jugular, femoral and subclavian veins. However, if life-long treatment is needed (e.g., LDL apheresis), arteriovenous fistula creation may be required. In addition, as the blood flow is low (90–150 ml/min), large peripheral veins can be used (cubital veins). Single-vein access is also possible but in cases where centrifugal separation of plasma is used.

2.2. Separation techniques

Plasma is separated from blood cells via two major methods—centrifugal and hollow-fiber membrane separator. In addition, more selective methods were developed.

2.2.1. Centrifugal separation

The separator is a disposable rotating centrifugal bowl. Blood runs into the bowl and centrifugal force separates blood cells from plasma. Blood cells are pumped back into patient's circulation, whereas plasma is separated in sterile bags. The process can occur simultaneously or intermittently. There is no upper limit for the size of the molecules removed by centrifugal PEX. Usually the blood flow ranges between 90 and 150 ml/min. A major disadvantage of centrifugal PEX is platelet count reduction, which may reach up to 50% [1].

2.2.2. Membrane PEX

In this type of PEX, highly permeable hollow fiber membrane filters are used. The fibers have pores with diameter ranging from 0.2 to 0.5 μm. As blood runs through the fibers plasma is separated from the blood cells, which are returned in patient's circulation. All immunoglobulins are effectively cleared by this method. However, its effectiveness is poorer in immune complexes and cryoglobulins. The risk for platelet count reduction is small. Yet, there is a risk for hemolysis, especially if faster blood flow is used (normal values for the method are 90–200 ml/min). Synthetic membranes are used; plasma filters should not be reused [1].

2.2.3. Selective separation techniques

The abovementioned plasma separation techniques remove plasma from whole blood, thus causing loss of normal proteins, especially coagulation factors and albumin. In order to reduce protein loss, selective PEX techniques were introduced into practice.

2.2.3.1. Double cascade PEX

Cascade filtration is a semi-selective separation technique, in which after initial separation of plasma from blood cells, additional filtration of plasma is performed with different diameters of fiber pores, so that target protein fractions are filtered and the rest are pumped back in circulation. This technique showed up to 70% reduction in albumin loss after the procedure [2].

2.2.3.2. Cryofiltration

The method is used to remove cryoglobulins in several immune diseases. After plasma is initially filtrated, it is cooled to 4°C. This causes precipitation of cryoglobulins and they do not pass the second membrane. Afterwards, the cooled plasma is warmed to body temperature again and is returned to the patient.

2.2.3.3. Thermofiltration

Similar to cryofiltration, plasma is firstly separated from whole blood. Before the selective filtration, the filtrate is warmed up to 40°C, causing aggregation of VLDL and LDL molecules. Then second filtration is performed and the filtrate is introduced back into patient's blood. The method is not widely used due to the fact that little is known about the changes in large molecules after being exposed to higher temperatures [2].

2.2.3.4. Unselective adsorption

Unselective adsorption uses charcoal or ion exchange raisins to remove exogenous or endogenic toxins from blood (hemoperfusion) or from filtered plasma (plasmaperfusion). These methods are most commonly indicated in exogenous intoxications. There are reports that hemoperfusion was effective in sepsis, septic shock and disseminated intravascular coagulopathy [3]. Currently, plasmaperfusion is gaining ground over hemoperfusion due to its improved effectiveness and improved safety profile.

2.2.3.5. Selective adsorption

In selective adsorption the initial filtrate runs through prearranged immunosorbents. Thus, specific antibodies can be selectively removed, whereas albumin and clotting factors are returned to the patient. There are two types of selective adsorption—*immunoadsorbtion (IA)* and *selective plasma adsorption*. In IA, either the plasma runs through column bearing antigens directed against certain antibodies or antibodies against certain plasma constituents. In selective plasma adsorption, plasma components are removed by binding to ligands other than antibodies and antigens (e.g. heparin and dextransulfate in LDL adsorption).

Different immunoadsorbtion (IA) techniques exist, but protein A-based IA is the most commonly used one. Protein A is a *Staphylococcus aureus*-derived molecule that binds to the Fc-region of immunoglobulin G (IgG). The principle of the procedure is similar to the previous selective methods—plasma is firstly separated from blood and then the filtrate runs through protein A—containing filters. Thus, immunoglobulins (IgG) and immune complexes are removed and the filtrate is pumped back into circulation. The method is well tolerated and is used in the following situations: acute antibody-mediated rejection, presensitized kidney transplant (KT) candidates, systemic lupus erythematosus (SLE), Guillain-Barrè syndrome, Goodpasture syndrome, myasthenia gravis, hemolytic uremic syndrome (HUS) and so on.

Other adsorbents can carry antibodies against proteins to be removed too. Polyvinyl-alcohol gel, bound to tryptophan, is used for removal of anti-acetylcholine-receptor antibodies in myasthenia gravis; phenylalanine-bound polyvinyl-alcohol gel for selective removal of anti-DNA antibodies; and cardiolipin antibodies in SLE [2].

2.3. Anticoagulation

Practically in all PEX procedures, anticoagulation is needed. In centrifugal PEX, usually citrate anticoagulation is used, whereas in membrane PEX, heparin is the anticoagulant of choice [1]. Citrate has advantages in patients with high bleeding risk, as it has no influence on systemic coagulation, but it is associated with increased incidence of hypocalcaemia. The usual dose of heparin is bolus dose 2000–5000 IU, followed by infusion of 500–2000 IU per hour. Anticoagulants are administered pre-filter. Low-molecular weight heparins (LMWH) can be used too. They are associated with lower incidence of side effects and more selective prevention of clotting. In our institution low-molecular weight heparins are used in doses, 0.01 ml/kg body weight or generally 0.8–1.0 ml LMWH per procedure.

2.4. Substitution fluids

PEX requires large volumes of replacement fluids. A single procedure was found to reduce plasma macromolecule levels by 60% [4]. The use of crystalloids is ineffective, as they are not capable of preserving the intravascular oncotic pressure. Gelatin-based plasma expanders have limited practical importance, as they have shorter half life compared to albumin-based fluids. Therefore, the most widely used substitution fluid is human albumin. Replacement volume reaches 50 ml/kg, 4–5% human albumin per procedure. The major disadvantage of albumin replacement is the lack of coagulation factors. Therefore fresh frozen plasma (FFP) can be applied after PEX. In certain diseases, the replacement fluid should consist of FFP only— for example, HUS, thrombotic thrombocytopenia purpura (TTP) and so on. Other indications for FFP use are reduction of plasma fibrinogen level below 1.25 g/l, increase of prothrombin time more than 2 s above normal values and increased risk of bleeding (pulmonary hemorrhage, 48 h after biopsy/surgery) [1]. FFP should be used with caution, as its application is associated with hypotension, citrate-associated paraesthesia, urticaria, anaphylaxis and blood-borne infections.

2.5. Treatment volume: frequency of PEX

2.5.1. Treatment volume

A formula for determining the needed volume of single PEX was suggested by A.A. Kaplan [5]:

$$Volume\ PEX\ =\ \left[0.065 * body\ weight(kg)\right] * (1 - Hct) \tag{1}$$

where *kg: kilograms and Hct: hematocrit*.

An easier way to assess the needed PEX volume is 30–50 ml/kg body weight.

2.5.2. Frequency of PEX

PEX is usually performed daily or every other day. The duration of treatment is 10–14 procedures, but it can be guided by clinical outcomes and laboratory results (auto-antibody titers, platelet count, etc).

2.6. PEX: mechanism of action

PEX and IA have beneficial effects on different diseases due to the following mechanisms [2]:

- Elimination of pathological constituents—alloantibodies/autoantibodies, paraproteins, circulating immune complexes, toxins and so on.
- Substitution of plasma proteins: clotting factors, hormone carrier proteins, immunoglobulins and so on.
- Modifying immune cells' functions: deblocking of reticuloendothelial system and modifying lymphocyte response.

2.6.1. Immunosuppressive treatment in PEX

Despite the mentioned beneficial effects, PEX is not effective in immune disease when used alone, as it influences pre-existing pathological molecules and has no influence on their formation. It was established that the procedure causes rapid decrease in antibody titers, which is followed by increased antibody production and B-cell proliferation [6]. In addition, the combination PEX and immunosuppressive therapy has better results compared to using plasma exchange and immunosuppression alone.

Several combinations have been suggested. Initially, steroids of 1–2 mg/kg for 2–3 weeks or cyclophosphamide of 2–3 mg/kg for 2–3 weeks, followed by azathioprine of 1–2 mg/kg for several months after cyclophosphamide treatment, were suggested. Later, cyclophosphamide pulses and PEX were found superior to oral intake and PEX [7]. Over the last years new immunosuppressive agents have been introduced as concomitant therapy in PEX—cyclosporine A, tacrolimus and mycophenolic acid [8]. In addition, biological agents are more widely used—monoclonal antibodies (e.g., rituximab) and intravenous immunoglobulin (IVIG). Rituximab is usually applied, 375 mg/m^2/weekly, for 2–4 weeks. IVIG is applied, 100 mg/kg, after each PEX [9, 10].

2.6.2. Additional medications

Calcium gluconate and potassium chloride can be infused to counterbalance PEX-associated hypocalcaemia and hypokalemia.

3. Contraindications to plasma exchange: complications

3.1. Contraindications to PEX

The major contraindications to PEX are hemodynamically unstable patients, sepsis, history for allergy to human albumin or FFP.

3.2. Complications

Generally, the procedure is safe, and though the incidence of all complications peaks to 40%, the risk for life-threatening adverse events (defined as death, hypotension-requiring vasopressor agent, arrhythmias, medical intervention and hemolysis) is low, ranging between 0.025 and 4.75% [11, 12]. There are three groups of complications in PEX, which are summarized in **Table 1**.

As the most serious complication, death has incidence of up to 0.05%, though most of the patients were with severe pre-existing conditions [2]. However, the complication rate varies across registries, as mortality was 0% in the Swedish apheresis data base, encompassing more than 20,000 procedures. Yet the same trend was observed—overall complications' rate reached 4.3%, of which just 0.9% were serious adverse events [13].The highest risk for complications was detected in unstable patients, hypotension, active bleeding, bronchial

Vascular access-associated	Hematoma
	Infection/sepsis
	Pneumothorax
Substitution therapy-associated	Anaphylaxis to FFP
	Death, due to anaphylaxis
	Coagulopathy
	Blood-borne infections
	Hypocalcaemia
	Hypokalemia
Other	Hypotension
	Dyspnea
	Low platelet count
	Hemolysis
	Drug and vitamin removal
	Death, due to cardiac arrest, pulmonary edema and pulmonary embolism
	Anaphylactoid reactions, hypotension, flushing due to ACE inhibitors and the use of dextran sulfate systems for LDL apheresis

FFP: fresh frozen plasma, ACE inhibitors: angiotensin-converting enzyme inhibitors, LDL: low-density lipoprotein.

Table 1. Complications in plasma exchange.

obstruction and anemia [14]. In addition, the complications are significantly more in PEX with FFP substitution, compared to human albumin only.

Similar results were observed in our institution. In 51 PEX procedures no life-threatening complications were detected. Two episodes of hypotension were established, not requiring vasopressor agents. Two patients developed paraesthesia. Laboratory results prior and after PEX remained stable (hemoglobin level, white blood cell count, platelet count and potassium and calcium levels). An expected drop in fibrinogen, immunoglobulin A and G levels, was detected, without bleeding or infection episodes, associated with the procedure [15].

In conclusion, though the procedure is relatively safe, due to the risk for serious complications, it should be performed by experienced personnel.

3.3. Indicators to monitor during PEX treatment

3.3.1. Clinical indicators

The basic clinical parameters should be monitored prior to and after the procedure—blood pressure, heart rate and body temperature. Clinical assessment can be performed at shorter intervals of time during the procedure in unstable patients.

3.3.2. Laboratory indicators

Full blood count, plasma calcium, plasma potassium, fibrinogen levels and prothrombin time should be evaluated after each procedure. Other laboratory tests can be performed prior to and after PEX treatment, including antibody titers.

4. Plasma exchange: clinical indications

4.1. Clinical indications: classification

PEX was prescribed with different volume, duration, frequency, number of performed procedures and different concomitant (immunosuppressive) therapy over the years. This is the reason for the relatively small number of randomized controlled trials (RCTs) concerning plasma exchange.

In order to evaluate the present data for the effectiveness of PEX in the treatment of different diseases, the American Society for Apheresis (ASFA) has classified the indications into four categories, according to the possible beneficial effect of PEX [16, 17]:

- *ASFA category 1: Disorders for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment*.
- *ASFA category 2: Disorders for which apheresis is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment*.

- *ASFA category 3: Optimum role of apheresis therapy is not established. Decision-making should be individualized.*
- *ASFA category 4: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.*

4.2. Clinical indications: renal diseases

4.2.1. Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is a glomerular disease, associated with crescent formation in over 50% of the glomeruli, necrotic changes and rapid deterioration of kidney function. Kidney findings can be coupled with pulmonary hemorrhage, thus defining the Goodpasture's syndrome. RPGN can be detected also in systemic lupus erythematosus (SLE), IgA nephropathy, post-infectious glomerular disease and systemic vasculitis [anti-neutrophil cytoplasmic antibodies (ANCA)-associated RPGN].

4.2.1.1. Anti-glomerular basement membrane disease

Anti-glomerular basement membrane (anti-GBM) disease or Goodpasture's syndrome encompasses diseases with antibodies against the glomerular basement membrane. A term within this definition is Goodpasture's disease, indicating disease associated with antibodies against the α3 chain of collagen type 4, present in alveoli and glomeruli. Goodpasture's syndrome can present with renal and pulmonary involvement—rapidly progressing renal failure, hemoptysis and pulmonary failure. PEX and immunosuppression (steroids, cyclophosphamide) are the cornerstones of anti-GBM disease. Alveolar involvement is associated with high mortality; therefore, the presence of pulmonary hemorrhage is absolute indication for PEX (ASFA category 1) [16, 17]. Dialysis-independent patients with anti-GBM disease also fall in this category. In dialysis-dependent cases without alveolar hemorrhage, the effectiveness of the method is reduced and is classified as ASFA category 3. Treatment should be performed daily/every other day for at least 14 days. Though ant-GBM antibody titers can be evaluated, the best way to assess effectiveness of the treatment is clinical outcomes [16].

4.2.1.2. ANCA-associated glomerular disease

The major representatives of this group are Wegener's granulomatosis with polyangiitis, microscopic polyangiitis and Churg-Strauss syndrome. They are characterized with RPGN, systemic involvement, minimal or no immune deposits in the vascular wall and usually have elevated ANCA titers (ANCA/+/positive), though 10% of the cases are ANCA /−/negative. Treatment of ANCA/+/and ANCA/−/is similar and is based on immunosuppression and PEX. Immunosuppressive treatment includes high-dose steroids and cyclophosphamide. Rituximab can substitute cyclophosphamide too [18]. PEX is performed daily/every other day for 6–9 procedures. In cases of rapidly progressing kidney failure daily procedures are recommended. PEX is indicated in patients with pulmonary hemorrhage and on dialysis (ASFA category 1), whereas for dialysis-independent patients the effectiveness is significantly lower, therefore, categorized by ASFA as category 3 [16, 17].

4.2.2. Infection-associated glomerular disease

Infection-associated glomerular disease consists of the following major subgroups of diseases:

- Bacterial infection-related diseases: Post-streptococcal glomerulonephritis (PSGN), infective endocarditis-related glomerulonephritis and shunt-associated glomerulonephritis
- Hepatitis C virus (HCV)-associated glomerular disease
- Hepatitis B virus (HBV)-related glomerular disease
- Human immunodeficiency virus (HIV)-related glomerular disease
- Protozoal infection-related glomerular disease

The cornerstone of infection-related glomerular disease is treatment of the underlying infection. However, in cases of histologically detected crescents, rapidly progressive GN, complicating PSGN or schistosomiasis-related glomerulonephritis immunosuppressive treatment can be considered. In HCV – related glomerulonephritis, associated with presenting with mixed cryoglobulinemia (IgG/IgM), presenting with nephrotic proteinuria/acute flare of cryoglobulinemia/rapid deterioration of kidney function, immunosuppressive treatment can be coupled with PEX [18]. PEX is effective in cryoglobulinemia and is categorized as ASFA category 1 and is superior to IA. Generally, 3–8 procedures are required. Immunosuppression with rituximab was superior to other immunosuppressive agents [16].

4.2.3. Membranoproliferative glomerulonephritis

In cases of membranoproliferative glomerulonephritis (MPGN), an underlying disease (SLE, HCV or HBV infection, monoclonal gammopathies and rheumatologic disorders) should be ruled out. Idiopathic MPGN is treated with immunosuppressive agents. PEX is rarely indicated, except for HCV-associated MPGN, complicated with cryoglobulinemia (Section 4.2.2). In all other cases of MPGN the use of PEX is under debate due to the small number of studies and the controversial results [19].

4.2.4. Minimal change disease and focal segmental glomerular sclerosis

Minimal change disease (MCD) and focal segmental glomerular sclerosis (FSGS) are disorders presenting with nephrotic syndrome. Several pathogenic mechanisms for increased protein loss in urine have been suggested, including the presence of permeability factors, increasing the permeability of glomerular basement membrane (GBM) for proteins. Several molecules were considered for permeability factors (e.g., cardiotrophin-like cytokine 1), but currently no definite molecules proved to increase GBM permeability. Due to the similar pathogenesis and podocyte involvement, MCD and FSGS are considered by most of the researchers as different steps in the progression of a single glomerular disease. Both MCD and FSGS have primary and secondary forms. The treatment of the secondary forms is based on the treatment of the underlying disease, whereas primary forms are treated with steroids or cyclophosphamide, mycophenolate mofetil and calcineurin inhibitors [18]. Plasma exchange is not effective in FSGS and MCD in native kidneys.

LDL apheresis was found to have beneficial effects in steroid-resistant FSGS cases [20]. Long-term efficacy of low-density lipoprotein apheresis for focal and segmental glomerulosclerosis is present. However, the data for this selective method in FSGS are insufficient and this modality is not widely available. PEX is indicated in recurrent FSGS after kidney transplantation (ASFA category 1), despite the inconsistent data for the efficacy in preserving graft function. At least nine procedures should be performed in recurrent FSGS, though the PEX can be prolonged for several months after improvement in proteinuria, by performing weekly or monthly procedures. In addition, pre-transplant PEX was found to reduce the incidence of recurrent FSGS [16, 17].

4.2.5. Membranous nephropathy

Membranous nephropathy (MN) is a glomerular disease, presenting with nephrotic syndrome. It has idiopathic and secondary forms (neoplasia, SLE, viral diseases). In primary MN auto-antibodies against the M-type phospholipase A2 receptor were detected, possibly involved in the pathogenesis of the disease [21]. Treatment of MN is based on angiotensin-convertase enzyme (ACE) inhibitors, steroids, combined with cyclophosphamide or calcineurin inhibitors. Current guidelines do not suggest the use of PEX, though currently there are reports for successful treatment of MN with PEX and rituximab/IVIG [9].

4.2.6. IgA nephropathy: Henoch-Schönlein purpura

IgA nephropathy (IgAN) is characterized by mesangial proliferation and deposits of immunoglobulin A in the mesangium. Henoch-Schönlein purpura (HSP) is a small vessel vasculitis, involving intestines, skin, joints and the kidney. Histologically the renal findings in HSP are similar to IgAN. A rare presentation of the disease is acute kidney injury due to crescentic glomerular involvement. Small studies indicate beneficial effects of PEX in crescentic IgAN [22]. However, guidelines do not support plasma exchange in IgAN or HSP (ASFA category 3), even in the presence of crescents or severe extra-renal manifestations of HSP, due to the scarce data supporting plasmapheresis in these cases [16, 18].

4.2.7. Lupus nephropathy

PEX was found to have no significant effect on patients with lupus nephropathy (LN) in the randomized controlled trial [23] (AFSA category 4). A recent meta-analysis also established no significant effect of PEX in the treatment of proliferative LN [24]. In addition, IA was not superior to PEX in LN [16, 17]. PEX and IA are used in other presentations of SLE (the issue will be discussed in a different section).

4.2.8. Systemic amyloidosis

Plasma exchange is ineffective in systemic amyloidosis and falls into ASFA category 4, both for AA and for AL sub-forms [16]. However, β2 microglobulin adsorption was partially effective in β2 amyloidosis [17].

4.2.9. Kidney transplantation

PEX is used in three major directions—pre-transplantation treatment of sensitized/AB0 incompatible patients, antibody removal in rejection and recurrent disease after KT.

4.2.9.1. HLA-sensitized patients and AB0 incompatible KT

Desensitization protocols are used in candidates for KT in order to increase the donor pool in organ transplantation. Treatment of patients with HLA antibodies and positive cross-match reaction proved to be effective with excellent results for the 1-year graft survival. Different protocols exist, yet PEX or IA are the cornerstones of HLA desensitization protocols, accompanied by immunosuppressive treatment with IVIG or rituximab or both [25, 26]. Currently, bortezomib is being introduced in the immunosuppressive regimen. However, HLA desensitization was not effective in deceased donors [16]. The treatment should aim for negative cross-match prior to KT. Despite the good short-term results, in the long term, there is increased incidence of rejection and poorer graft survival.

In AB0-incompatible KT, again protocols using PEX/IA, combined with IVIG/or/and rituximab, are used (ASFA category 1) [16, 17]. The procedures are performed prior to and after KT. The treatment aim is reduction of anti-AB0 antibody titers from 1:4 to 1:32. Currently, short- and long-term graft survival is similar to AB0-compatible transplantation [27].

4.2.9.2. Antibody-mediated rejection

Antibody-mediated rejection (AbMR) is associated with histologically detected graft injury, positive C4d staining and the presence of circulating donor-specific antibodies. Both IA and PEX are used in the treatment of acute AbMR, in association with IVIG, 100–200 mg/kg, after each procedure [28]. Treatment should be accompanied with anti-T cell treatment with thymoglobulin. Rituximab can be added to the immunosuppressive protocol [29]. Usually 5–6 procedures are performed.

Unfortunately, PEX in chronic AbMR is not as effective as in acute AbMR due to the irreversible changes in the graft [29].

4.2.9.3. Posttransplant recurrent glomerulonephritis

PEX/IA is the part of the first-line treatment in recurrent FSGS (Section 4.2.4). Recurrent anti-GBM disease is also an indication for aggressive plasma exchange. In recurrent ANCA-associated glomerulonephritis, similar treatment to native kidneys should be initiated [30]. In MPGN, PEX can also be considered, though the data are scarce. Currently, there are no data to support the use of PEX in recurrent IgAN and membranous nephropathy. PEX also had controversial results in recurrent LN after KT [30].

4.3. Clinical indications: hematology

4.3.1. Thrombotic microangiopathies

Thrombotic microangiopathies (TMAs) are acute syndromes, characterized by hemolytic anemia, thrombocytopenia and organ involvement due to microvascular thrombosis. It consists of two clinical aspects, having similar pathogenesis— hemolytic-uremic syndrome (HUS), presenting in children with predominant renal involvement, and thrombotic thrombocytopenic purpura (TTP), mainly in adults with severe neurologic presentation. The etiology encompasses the presence of autoantibodies, drugs, systemic diseases and pregnancy. The diagnosis should be made as early as possible, so that adequate treatment can be initiated.

4.3.1.1. PEX treatment in HUS

Plasma exchange was found effective mainly in atypical HUS, especially in the presence of complement factor gene mutations (ASFA category II) and the presence of factor H autoantibody (ASFA category I). Treatment should be started as early as possible, with treatment volumes of 50 ml/kg, daily procedures for at least 5 days and with subsequent reduction of the PEX procedures per week. Substitution should be performed with FFP only. The decision to stop treatment should be taken based on the patient's response and condition. In addition to PEX, treatment with rituximab and eculizumab can be added to the therapy [16].

4.3.1.2. PEX treatment in TTP

TTP is a potentially fatal disease and PEX has significantly improved survival in these patients. Therefore it is the first-line treatment in TTP. PEX is initiated at similar doses and daily procedures should be performed until platelet count rises above 150×10^9/l for three consecutive days. Supplementation should be made with FFP/cryoprecipitate poor plasma. Afterwards, procedures can be performed less frequently, though no data exist. Additionally, steroids and rituximab can be used in the treatment.

4.3.1.3. PEX in drug-related TMA

TMA is associated with the use of several drug classes—calcineurin inhibitors, medications reducing platelet aggregation (ticlopidine, clopidogrel) and so on. Of these, PEX proved to be an effective option in ticlopidine-associated TMA. In all other medications, PEX was not associated with clear improvement in patient outcomes [16, 17].

4.3.2. Multiple myeloma

Multiple myeloma has a wide spectrum of renal involvement, spanning from myeloma cast nephropathy, AL amyloidosis to cryoglobulinemia and membranoproliferative glomerulonephritis. Chemotherapy is the crucial part of the treatment. AL amyloidosis is not significantly influenced by PEX [16]. The effect of PEX in myeloma cast nephropathy was also evaluated in the past. However, the results so far are conflicting. Therefore, the use of PEX in everyday practice is not recommended [31].

4.3.3. Waldenström macroglobulinemia

Increased serum levels of plasma proteins increase serum viscosity, leading to small vessel damage, especially small veins. Clinically, hyperviscosity presents with retinopathy and neurological symptoms (headache, somnolence, coma and seizures). Hyperviscosity syndrome is usually detected in Waldenström macroglobulinemia and multiple myeloma. Generally, the treatment of the diseases is chemotherapy. PEX is applied in cases of symptoms associated with hyperviscosity. Generally, when substitution volume is 50 ml/kg, human albumin is used. Symptoms are relieved after 1–3 procedures; after that PEX can be discontinued or prophylactic procedures monthly can be performed [16, 17].

4.3.4. Autoimmune hemolytic anemia

Autoimmune hemolytic anemia (AIHA) is a disorder in which autoantibodies cause either intravascular or extravascular destruction of red blood cells (RBCs). AIHA is categorized in two major groups—warm AIHA (antibodies reacting at body temperature) and cold agglutinin disease (CAD, hemolysis occurring at temperatures between 0 and 5°C). The first-line treatment for warm AIHA is prednisolone; rituximab is used as the second-line agent. In CAD the primary goal is avoidance of exposure to the cold; in severe cases rituximab is the drug of choice. The results for PEX treatment in warm AIHA are conflicting; therefore, its use is limited to severe cases of fulminant AIHA. In CAD, PEX has shown no effect in terms of improvement of long-term outcomes. Due to the risk of agglutination at room temperature for CAD, the procedure should be performed at higher temperatures for both extracorporeal circuit and room temperature.

4.3.5. Aplastic anemia

Aplastic anemia (AA) and pure red cell aplasia (PRCA) are rare hematopoietic stem cell disorders. In AA there is pluripotent progenitor cell involvement, causing pancytopenia and hypocellular bone marrow. In PRCA only erythroid progenitors are affected, leading to normochromic, normocytic anemia, reticulocytopenia, severe reduction in marrow erythroid precursors and normal myelo- and lymphopoiesis, as well as platelet production. The diseases can be idiopathic, as well as secondary, due to infection, neoplasia, chemicals and drugs. As the pathogenesis of the conditions is mostly immunological (the presence of autoantibodies was established), immunosuppressive agents are usually used as first-line treatment. PEX can also be considered in immunosuppression-resistant cases. PEX is performed until hematopoiesis/erythropoiesis recovers [16].

4.3.6. Hematopoietic stem cell transplantation

PEX is used in the case of AB0-incompatible hematopoietic stem cell transplantation (HSCT) and in HLA desensitization protocols. There are two types of AB0-incompatible HSCT—major and minor ones. In major AB0-incompatible HSCT, natural isoagglutinins in the recipient against the donor's A and/or B blood group antigens are present. They cause acute hemolysis of the RBCs present in infused hematopoietic progenitor cell (HPC) products. In minor AB0-incompatible HSCT, isoagglutinins cause hemolysis only if the antibodies are in high titers (above 1:128). In major AB0-incompatible HSCT, PEX and IA are used to reduce the titers of natural isoagglutinins. Procedures are performed daily, substitution volume is usually 50 ml/kg, and substitution fluid includes albumin and donor- and recipient-compatible FFP. The reduction of isoagglutinin titers below 1:16 is aimed prior to HSCT.

In HLA-sensitized patients there is reduced graft survival after HSCT. Reports indicate that successful procedure after desensitization is performed. PEX is used to remove donor-specific antibodies and is coupled with immunosuppression (IVIG, rituximab, bortezomib). However, the data considering the use of PEX in desensitization protocols are scarce. PEX usually is used every other day, aiming at negative cross-match test prior transplantation.

PEX is not recommended in graft versus host disease (GVHD). In these cases extracorporeal photopheresis (ECP) has a beneficial effect [17].

4.4. Clinical indications: neurology

4.4.1. Neurological diseases from ASFA category 1

In the following neurological conditions, PEX has beneficial effects and is considered as first-line treatment: Guillain-Barre Syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, Sydenham's chorea, N-methyl D-aspartate receptor antibody encephalitis and progressive multifocal leukoencephalopathy associated with natalizumab [16, 17]. The diseases are autoantibody mediated; therefore, PEX has a crucial role in removing the main pathogenic factor. In addition, immunosuppression is performed (steroids, calcineurin inhibitors, rituximab and IVIG). Generally, plasma exchange is performed 5–6 times for 10–14 days, or 2–3 procedures per week, where substitution volume is 50 ml/kg and albumin solutions are preferred. The procedure is performed until symptoms resolve, though maintenance PEX can also be considered.

4.4.2. Neurological diseases from ASFA category 2

The following diseases belong to this category: acute disseminated encephalomyelitis, acute neuromyelitis optica, Lambert-Eaton myasthenic syndrome, acute demyelinating multiple sclerosis and voltage gated potassium channel antibodies. The conditions are also autoimmune mediated, but the first-line treatments are immunosuppressive agents (steroids, IVIG and rituximab). PEX comes as a second-line treatment. Technically, the procedure is performed as the recommendations in Chapter 4.4.1.

4.4.3. Neurological diseases from ASFA category 3

Several neurological conditions fall into this category: chronic focal encephalitis, post-IVIG Guillain-Barre Syndrome, chronic progressive multiple sclerosis and paraneoplastic neurological syndromes. In these diseases, the most important part of the treatment is immunosuppression/anticancer treatment. There are conflicting results for the use of PEX/IA, in most of the cases aiming at slowing down the progression of the disease. Usually 3–6 PEX procedures every other day are performed. If IA is considered then 2–3 procedures/week must be conducted. Maintenance protocols have also been suggested [16].

4.4.4. Neurological diseases from ASFA category 4

In amyotrophic lateral sclerosis, dermatomyositis/polymyositis and inclusion body myositis, the use of PEX was not superior to conservative treatment alone; therefore, its use in clinical practice is currently not recommended.

4.5. Clinical indications: rheumatology

4.5.1. Systemic lupus erythematosus

SLE is an autoimmune disease, with involvement of several organs. It is an incurable, chronic, remitting and relapsing disease. Immunosuppressive agents are first-line treatments for SLE

(steroids, cyclophosphamide, azathioprine, biological agents, etc.). PEX was regarded as a treatment option due to the presence of pathogenic autoantibodies. However, the trials so far failed to establish improvement of the prognosis in mild SLE. In severe SLE (presence of TTP, cerebritis, alveolar hemorrhage and cryoglobulinemia), PEX coupled with immunosuppression demonstrated improvement in clinical outcomes. Therefore, severe SLE is classified as ASFA category 2. Lupus nephritis is not significantly influenced by PEX (ASFA category 4), except for the cases with LN and TTP [18]. Plasma exchange is performed daily/every other day; usually 3–6 procedures are sufficient in lupus cerebritis and alveolar hemorrhage.

4.5.2. Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a hypercoagulable state characterized by episodes of vascular thrombosis and the presence of antiphospholipid antibodies. It can be associated with SLE, though non-SLE APS is also present. Catastrophic APS is a rare disease, characterized by APS and multi-organ failure. The mainstay of the treatment is treatment of etiological factors and anticoagulation. The role of PEX is not clearly defined; it is suggested that it is involved in antibody and cytokine removal. In order to optimize the effect, substitution fluids should contain FFP as a source for proteins C and S; therefore, substitution with FFP and albumin is performed. The procedures are performed daily, there is no clear guideline in terms of duration and clinical response remains the most important indicator.

4.5.3. Scleroderma

Scleroderma is a progressive disease of unknown origin, with skin and visceral organ involvement. Currently, the cornerstone of the treatment is D-penicillamine. Immunosuppressive agents are used too. So far two therapeutic options have been evaluated—PEX and extracorporeal photopheresis (ECP). Despite several reports indicating beneficial effects of the procedures, the data are conflicting; therefore, the disease is categorized as ASFA category 3.

4.5.4. Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a vasculitis, involving medium-sized arteries, presenting with multi-organ involvement. The disease is idiopathic, or secondary, associated with infection [hepatitis B (HBV)]. In HBV-associated PAN the current treatment strategy includes steroids and antiviral agents. PEX is used as second ß line agent, and its beneficial effect is explained with removal of immune complexes. Idiopathic PAN is treated with steroids and cyclophosphamide. PEX in these cases is not recommended [17]. The usual substitution volume and albumin solutions are used. In HBV-associated PAN, 2–3 procedures per week are performed.

4.6. Clinical indications: endocrinology and metabolic disease

4.6.1. Thyroid storm

Thyroid storm is an extreme manifestation of thyrotoxicosis. Conservative treatment is the first-line therapy and encompasses medications which stop the synthesis, release and

peripheral effects of the thyroid hormones. Once these first- and second-line choices fail to have effects, third-line treatment, such as PEX, is considered. PEX reduces serum levels of the hormones, as well as provides thyroglobulin, thus binding free thyroid hormones. Therefore, FFP and albumin should be considered for PEX in the thyroid storm. The procedures are performed daily until clinical improvement is established.

4.6.2. Diabetes mellitus type 1

Autoimmune destruction of the β cells of the pancreas is a key factor for the development of diabetes mellitus (DM) type 1. Therefore, PEX was evaluated as a possible treatment of DM type 1. Though several reports demonstrated improvement in clinical outcomes, the overall results are conflicting and PEX is not recommended in the treatment of the disease.

4.6.3. Familial hypercholesterolemia

Familial hypercholesterolemia (FH) is an autosomal dominant disorder, associated with mutations of hepatocyte apolipoprotein-B (apo-B) receptors, resulting in decreased hepatic LDL removal. It is characterized with elevated total cholesterol and LDL levels, early atherosclerosis and death from cardiovascular events (especially in homozygotes). Conservative treatment reduces LDL from 10 to 49%. In progressive diseases, interventional techniques including PEX and LDL apheresis are considered. Generally, the indications for LDL apheresis are failure of the conservative treatment (LDL reduction <50%) and progressive coronary artery disease. The results for LDL apheresis in homozygotes are excellent, and FH in these cases is classified in ASFA category 1. Apart from PEX, there are several selective LDL removal techniques:

- immunoadsorption
- electrostatic removal of apo-B lipoproteins by dextran sulfate columns
- heparin extracorporeal LDL precipitation (HELP) by precipitation of apo-B in the presence of heparin and low pH
- hemoperfusion-based direct adsorption of lipoprotein
- membrane differential filtration, filtering LDL from plasma.

Volumes in LDL apheresis vary; for PEX, standard volume of 50 ml/kg is suggested. The procedure is performed once per 1–2 weeks. The patients may require arteriovenous fistula for the treatment.

4.6.4. Fulminant Wilson disease

Wilson disease is an autosomal recessive genetic disorder, characterized by impaired biliary copper excretion and copper accumulation in the liver, brain, cornea and kidneys. Fulminant forms are associated with severe liver failure and multi-organ failure. The ultimate treatment is liver transplantation (LT), but PEX can be used as bridging therapy, due to the reduced donor pool. PEX is beneficial due to rapidly reducing copper levels, as well as providing coagulation factors via plasma infusion. The reports however are scarce. Due to the wider availability, PEX is usually preferred to molecular adsorbents recirculating system (MARS).

Substitution fluid should consist of FFP/FFP and albumin. The frequency is daily/every other day, until clinical and laboratory improvement is detected.

4.7. Clinical indications: cardiology and pulmonology

4.7.1. Lung allograft rejection

Different therapeutic apheresis modalities were evaluated after lung transplantation in the following conditions—bronchiolitis obliterans syndrome (BOS) and antibody-mediated rejection (AbMR). BOS is an increasing airflow obstruction, due to chronic rejection. AbMR after lung transplantation is an important cause for graft loss and diagnostic criteria are currently assessed. The first-line treatment for the two conditions is immunosuppression. In BOS ECP can be considered as second-line treatment. ECP probably decreases levels of effector T cells while at the same time expanding regulatory T cells, thus influencing the immune response. ECP had beneficial effects in several studies, in patients unresponsive to immunosuppression. In addition, it did not increase the risk for infection complications. Unfortunately, the data so far are scarce. Different approaches have been suggested, for example, 24 procedures for 6 months [16]. PEX is recommended as treatment of choice in resistant AbMR, though the results are inconclusive.

4.7.2. Cardiac allograft transplantation

There are two apheresis modalities used in cardiac transplantation. PEX is used in sensitized patients and in the treatment of antibody-mediated acute rejection, together with immunosuppressive agents [32]. PEX is crucial in desensitization protocols, whereas in AbMR, the results are still controversial. ECP is an option in cellular rejection and rejection prophylaxis [17]. The procedures are performed until improvement in laboratory, clinical and histological findings is achieved.

4.7.3. Idiopathic dilated cardiomyopathy

Idiopathic dilated cardiomyopathy (IDC) is characterized by cardiac enlargement and deteriorating heart function of unknown origin. External factors were detected, as well as autoantibodies against the myocardium. Current treatment encompasses conservative treatment (ACE inhibitors, diuretics, etc.). However, PEX and IA also were evaluated. IA showed improvement in clinical outcomes in adult patients. Small studies also demonstrated beneficial effects from PEX in ICD in adults and children [17, 33]. IA usually is performed daily/every other day for a total number of five procedures. Similar treatment protocol for PEX is suggested.

4.8. Clinical indications: dermatology

4.8.1. Pemphigus vulgaris

Pemphigus vulgaris (PV) is an autoimmune, potentially fatal disease, with mucocutaneous involvement. The cornerstone of the treatment is immunosuppressive agents and steroids. PEX and IA have been tested, aiming at reduction of the antibody titers. Clinical results,

however, are conflicting. Currently PEX/IA can be considered in severe cases of PV (ASFA category 3). PEX is performed daily/every other day, in cases of IA it is done three times per week, and then gradually tapered. Procedures are performed until clinical improvement is noted and a significant drop in autoantibody titer is achieved.

4.8.2. Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is a life-threatening skin disorder, characterized by widespread erythema, necrosis, epidermal detachment, erosion of mucous membranes and systemic clinical symptoms (fever, sepsis, multi-organ failure). The etiology of the condition encompasses medications, infections, solid organ transplantation and bone marrow transplantation. The major aspects of current treatment are etiologic treatment, supportive care, fluid resuscitation and treatment of infectious complications. Due to the marked heterogeneity of the reports considering PEX in TEN, currently it is considered as part of the treatment only in refractory cases. The procedure is performed daily/every other day, and up to five procedures are usually performed.

4.8.3. Psoriasis vulgaris

Psoriasis is a skin disease that is accompanied by systemic inflammation and is characterized by epidermal hyperproliferation and dermal inflammation. Different treatment modalities are used—from topical medications, ultraviolet light to systemic agents (immunosuppressive agents and biological formulations). PEX is not indicated in psoriasis (ASFA category 4). However, ECP was found to have beneficial effects in disseminated forms.

4.9. Clinical indications: gastroenterology

4.9.1. Acute liver failure (ALF)

Acute liver failure (ALF) can develop in the setting of healthy liver (fulminant hepatic failure) or on top of chronic liver disease. The condition is associated with high mortality; prognosis depends on etiology. Generally, conservative treatment is the cornerstone of treatment. In patients with ALF and poorer prognosis for improvement, liver support systems are used for bridging therapy to liver transplantation. Liver support systems generally are of two types—cell-based (currently experimental) and non-cell-based support systems— and include PEX, albumin dialysis, MARS and selective plasma exchange. Apheresis probably improves outcomes in ALF due to removal of toxins and inflammatory cytokines. Use of PEX had better clinical outcomes compared to patients not treated with PEX. PEX combined with MARS improved bilirubin clearance versus PEX only, though clinical outcomes were similar in both groups. A recent study demonstrated that high-volume PEX (treated volume reaching 15% of body weight) effectively improves survival, compared to standard medical care. Unfortunately, the technique is not available worldwide. The procedures (PEX or high-volume PEX) should be performed daily, until clinical and laboratory improvement is noted or liver transplantation is performed. Substitution fluid should include FFP and albumin.

4.9.2. Liver transplantation

PEX is increasingly being used in AB0-incompatible liver transplantation (LT). The most beneficial effect was detected in living donation; the procedure is coupled with immunosuppression (IVIG, rituximab). In AB0-incompatible LT in living donation, PEX is a first-line treatment prior to the operation. In deceased donation, PEX can also be applied in AB0 incompatibility. The reports are limited in number. In addition, the effectivity of PEX is reduced in the setting of cadaver transplantation and urgent LT. In these cases crossover LT can be considered. PEX had a beneficial effect in antibody-mediated rejection after LT. However, the reports are predominantly retrospective ones, and further evaluation of PEX effectivity in humoral rejection after LT is needed. Procedures are performed daily until negative cross-match test is achieved. No titers for natural agglutinins were suggested. In humoral rejection, clinical and laboratory parameters should be evaluated.

4.9.3. Inflammatory bowel disease

The cornerstone of inflammatory bowel disease (IBD) treatment is conservative treatment (immunosuppressive agents and biological agents). PEX is not indicated in IBD; however, cytapheresis techniques were evaluated. The results are still insufficient to incorporate these invasive methods in everyday practice.

4.10. Clinical indications: sepsis and poisoning

4.10.1. Sepsis

Sepsis, especially associated with multi-organ failure, is a condition with mortality peaking up to 70%. The mainstay of treatment is antibiotics, fluid resuscitation and so on. The possible beneficial effect of PEX is removal of inflammatory molecules and replenishing anticoagulant proteins. Selective techniques have been evaluated too. Despite the promising results from retrospective studies, prospective trials showed conflicting results of PEX use in improving clinical outcomes. The substitution volume is 50 ml/kg, and substitution fluid should be FFP [17]. The procedures should be performed in intensive care unit and are performed daily.

4.10.2. Exogenous intoxications

This category encompasses three conditions—drug overdose/poisoning, envenomation and mushroom poisoning. The mechanism of action of each agent is different; therefore, different treatment options are used. The basic treatment options currently are stabilization of airways, breathing, circulation, gastric lavage, oral charcoal administration and forced diuresis. More aggressive approaches include hemodialysis and hemoperfusion. PEX was evaluated in mushroom poisoning and demonstrated improvement in survival, especially if early initiation is performed. The reports concerning PEX in envenomation are anecdotal. Data for PEX in drug poisoning are insufficient too. Generally, PEX can be used in drug poisoning with molecules having high-protein binding. The usual substitution volume is recommended, substitution fluid is albumin, but FFP can also be considered, especially if coagulopathy is present. PEX is performed daily until clinical symptoms resolve.

4.11. Clinical indications: oncology

4.11.1. Hematological malignancies

The use of PEX in multiple myeloma and Waldenström disease has already been discussed. Generally, PEX is not used in other hematological malignancies. However, other techniques (e.g., ECP) are recommended in cutaneous T-cell lymphoma [17]. In addition, leucapheresis and plateletpheresis can be performed in life-threatening leukemia/myeloproliferative disorders [2].

4.11.2. Solid tumors

Several reports indicated improvement in clinical outcomes in solid tumors and metastatic cancer [2]. A possible explanation is that via PEX, inhibitory molecules are removed from plasma, thus improving immune response. Due to the heterogeneity of the studies and the conflicting results, no clear indications for PEX in these cases are defined. Further studies in this field are needed.

5. Conclusion

There are three major obstacles for the adequate evaluation of PEX effectiveness—the small number of patients enrolled, small number of randomized controlled trials and high cost of the procedure. However, with the advance of the technique and adequate collection of data on PEX use, these obstacles can gradually be overcome in the future. A more interesting perspective is the development of more selective techniques, as well as the use of magnetic separation and cell filtration. Thus, we can expect wider use of apheresis in medical practice in the future.

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