CHAPTER 190

Therapeutic Apheresis in Critically Ill Patients: Indications, Modalities and Techniques, Clinical Results

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OBJECTIVES

This chapter will:

1. Identify pathophysiologic considerations for the application of therapeutic apheresis.
2. Describe the role and application of apheresis in critical care medicine.
3. List advantages and drawbacks of selective apheresis systems compared with plasma exchange.
4. Identify accepted indications for apheresis treatment.

Therapeutic apheresis (TA) has been established more than 50 years by introducing therapeutic plasma exchange (TPE),[1] a procedure that has been used already in an experimental setting more than 100 years ago.[2] Since then, TPE has been applied in a wide variety of disease states in nephrology, but also numerous other indications.[3] Over the past decades, apheresis techniques have been developed further, providing a variety of different techniques with improved selectivity and effectiveness over TPE.[4,5] However, whereas TPE can be performed almost everywhere around the world, the worldwide distribution and availability of selective apheresis system is very inhomogeneous. This has regulatory as well as economic implications.

There are two major reasons for the nephrologist to be involved in the therapy of patients in critical care medicine: (1) probably most commonly, because of highly acute and rapidly progressing kidney disease and (2) because of the close interaction with other disciplines seeking the support of nephrologists with respect to the application of TA in their patients. Therefore almost all acute and also a number of chronic diseases with potential indications for TA therapy out of both areas may progress and lead to the necessity of intensive care in individual patients. Furthermore, therapy of intensive care patients also may undergo critical review with respect to additional available options.[4] Here, the fear of side effects arising from pharmacologic interventions and, mainly immunosuppressive, therapy may lead to the decision for apheresis. The same is true for patients with intolerance to certain medications and for pregnant women, in whom most available medications have contraindications and endanger the unborn child. In contrast, sepsis representing the most prominent and also devastating condition leading to the admission to the intensive care unit (ICU) is currently not the dominant indication for TA.[3,6,7]

This chapter subsequently summarizes indications that may be treated in primarily nephrologic critical care settings as well as indications beyond the field of nephrology, which may be presented to the attending nephrologist to provide therapeutic support by TA.

PATHOPHYSIOLOGIC ASPECTS OF APHERESIS IN CRITICAL CARE MEDICINE

General Aspects

Whenever TA comes into play, the underlying disease condition and the way apheresis may interfere with the ongoing disease should be given further consideration. This then may lead to the decision for a more or less selective procedure. Although TPE will lead to the unselective removal of all plasma components, the more advanced immunoadsorption (IA) techniques lead to a more selective removal of target molecules.[8–10] On the other hand, TPE provides the chance of an isovolumetric replacement of the patient's plasma and intact plasma components, and this may exert beneficial effects for treated patients.[11,12] Despite recent efforts to aim at several newer targets such as viruses and bacteria as well as chemokines,[13,14] apheresis is used predominantly to target the antibody-mediated immune response and therefore is applied in a wide variety of autoimmune disorders.[3]

Modulation of the Immune Response by Apheresis

As mentioned earlier, a higher selectivity has certain advantages but drawbacks with respect to its modulatory effect. Clearly, the removal of pathogenically relevant (auto) antibodies is one major aim of TA. This then affects not only the subsequent activation of complement and immune cells but also the neutralizing and opsonizing functions of immunoglobulins (Ig) and thereby downregulates the antibody-mediated immune response.[15] Thereby the humoral as well as the cellular immune response is modulated. By the same mechanisms, TA also affects/compromises the patient's host defense. Although, for instance, plasma separation filters also induce complement activation, adsorptive surfaces seem to decrease complement activation in human plasma.[16,17] All TA systems will, to a higher or lesser extent, modulate the humoral immune response, although only TPE may exert additional effects via the substitution of functional human plasma components. In turn this could inhibit but also drive the immune response under certain conditions such as a genetically dysregulated complement cascade.[11] Effectiveness of TA in diseases without known pathophysiologically relevant autoantibodies (aab) suggests that TA does not modulate ongoing disease exclusively on the level of antibody removal[10,18] but may be a signal that the precise pathophysiology, including potentially relevant aab, is still unknown. Clearly, TA has also modulatory effects on the chemokine levels.[19–22] However, direct beneficial effects have not been identified and cannot be titrated.

Procedure-Related Considerations

Apart from pathophysiology, a number of treatment-specific considerations should be made before the initiation of treatment. Of course, the risk of the procedure, especially under ICU conditions, versus the potential benefit has to be weighed. This includes the patient's comorbidities, which may be influenced by the extracorporeal treatment.[23] With respect to the ICU setting, especially TPE also will remove all pharmacologic compounds either solubilized in plasma or bound to albumin.[8] For TPE, adequate substitution has to be performed during each treatment, whereas IA does not, or only to a very limited extent, interfere with or remove medications and/or albumin. The only exemptions are antibody therapies including intravenous immunoglobulins (IvIg).

Technical aspects include the use of either systemic (heparin) or regional (citrate) anticoagulation.[24,25] Procedures with a longer duration frequently apply a combination of both. Although citrate will expose patients to a much lower risk for bleeding complications, it may be problematic in patients with reduced liver function and a lacking capacity to metabolize the infused citrate solution.[26–28] The same problem may arise from substitution of larger volumes of human plasma, because plasma products contain a relevant amount of citrate. For TPE, volume substitution has to be adjusted to the specific needs of treated patients. Citrate solution will cause additional volume load in treated patients, whereas the effective removal of Ig by immunoadsorption will cause a reduction of colloid-osmotic pressure and a drift of fluid into the third space, which finally may harm respiratory-compromised patients.

With respect to the vascular access, the ICU setting and general management predisposes patients to the placement of central venous catheters. However, it is necessary to make a careful decision in this direction, because central catheters are a frequent cause of complications, inside and outside the ICU.[29,30] Whenever technically feasible, peripheral venous access will be the better choice.

Frequently, specific therapeutic plans cannot, or only to a limited extent, be taken from existing literature. Nevertheless, a therapeutic strategy and readouts for treatment effectiveness, and thereby prolongation or interruption of TA, must be developed. This may relate to the removal of target molecules or the clinical course of disease. Clinically, a number of patients show a delayed improvement of symptoms, making such treatment decisions even more complicated.[31]

Finally, all TA systems have to be placed close to the patient and require a defined amount of space in sometimes relatively narrow ICU settings. Therefore decisions about the placement of these systems in addition to the frequently already well-equipped ICU have to be made. On the other hand, logistic considerations also may drive the decision

that patients should undergo apheresis in an ICU setting instead of under the standard fashion of care. This is another reason why nephrologists face a continuum with respect to the severity of disease that may be treated in critical care nephrology.

MODALITIES AND TECHNIQUES

Therapeutic Plasma Exchange

The fundamental basis of TPE is the separation of patient's plasma from cellular blood components.[8,32] For many years, this could be achieved only in extracorporeal circuits equipped with plasma filters, necessitating a relatively high and constant blood flow that could be provided only via central venous catheters or arteriovenous fistulas. The introduction of centrifugal plasma separation systems overcame this limitation, today enabling TPE procedures using peripheral venous access. Modern centrifugal systems provide high effectivity using a blood flow of approximately 50 to 80 mL/min and can adapt to changes in blood flow during treatment.

Because separated plasma will be discarded after treatment, isovolumetric substitution of iso-oncotic fluid is necessary to keep up the colloid-osmotic pressure. This can be achieved by using either a combination of human albumin and crystalloids or fresh frozen plasma from healthy donors. Both variants provide the risk for a number of adverse events, including hypotension and allergic reactions.[8,33,34] As a major limitation, one TPE procedure can process/replace only a bit less than one time the complete plasma volume of the individual patient in a single session. On the other hand, the complete removal of plasma components may offer the advantage to target additional, disease-relevant pathogenetic (so-called pleiotropic) mechanisms such as altered chemokine signaling and circulating miRNAs. Table 190.1 summarizes potential risks and benefits arising from TPE.

TABLE 190.1

Comparison of Therapeutic Plasma Exchange and Immunoadsorption

	TPE	IA
Selectivity	Unselective	Advanced selectivity, depending on column
Removal of Ig	Moderate	High
Substitute	Iso-oncotic, isovolumetric (FFP; albumin with crystalloids)	Not necessary
Risk of transmission of blood-borne disease	Yes	No
Anticoagulation	Citrate or heparin	Citrate or heparin or combined
Removal of pharmacologic agents in plasma	Relevant	Not relevant
Removal of pharmacologic agents bound to albumin	Relevant	Not relevant
Reduction of colloid-osmotic pressure	No	Yes
Risk of allergic reactions	High	Low
Replacement of functional plasma components	All	None
Duration of single treatment	Short	Long
Compromised coagulation	Yes	Yes
Limitation of processed plasma volume	Less than 1×	No

FFP, Fresh frozen plasma; *IA,* immunoadsorption; *Ig,* immunoglobulin; *TPE,* therapeutic plasma exchange.

Immunoadsorption

In contrast to TPE, IA allows the selective removal of distinct plasma components for therapeutic purposes. The first reported IA was published by Hosokawa et al. in 1989.[35] Similarly to TPE, IA is based on an initial plasma separation step that can be performed using either membrane or centrifugal plasma separation. The only exemption is the CytoSorb column, which can be used in hemoperfusion systems.[14] For all other IA columns, a second extracorporeal circuit leads to the processing of the separated plasma by loading the specific IA columns.[4,36] Depending on the system, this can be either a single-use column or two separated multiuse columns that can be regenerated during the IA procedure. Because of the intermittent regeneration process, regenerating systems theoretically offer a virtually unlimited adsorption capacity. In clinical settings, regenerating systems are able to process the patient's plasma volume several times during a single treatment session (commonly two or three times), thereby offering superior effectivity with respect to the adsorption of target molecules compared with single-use IA systems and TPE.[10] In contrast, the necessity of plasma separation in addition to the intermittent loading and regeneration cycles of adsorber columns take more time, thereby prolonging the overall treatment procedure. This is compensated by the higher selectivity,[9] the widely lacking removal of other plasmatic components or drugs and rendering substitution of plasma or albumin unnecessary. A comparison of TPE and IA procedures is provided in Table 190.1. Table 190.2 summarizes currently available IA columns and target molecules.

Lipoprotein Apheresis

Lipoprotein apheresis (LA) systems provide a dominant higher selectivity toward lipoproteins. LA cannot be performed only using plasma separation based but also with hemoperfusion (whole-blood) systems. Although hemoperfusion systems offer high effectivity and short treatments, the direct contact of blood cells with negatively charged surfaces bears the risk of unwanted side effects such as the bradykinin-release syndrome (especially in presence of angiotensin-converting enzyme inhibitors).[37,38] Plasma separation–based systems can process plasma by subsequent heparin-induced precipitation, adsorption, and plasma filtration, reflecting a double-filtration plasmapheresis procedure.[39–41] Although all systems target disease-causing, elevated lipoproteins, mainly heparin-induced extracorporeal low-density lipoprotein (LDL) apheresis and double-column

TABLE 190.2

Available Immunoadsorption Columns (End of 2016)

BRAND NAME	ADSORBER LIGANDS	TARGET MOLECULE(S)	REGENERATING COLUMNS
Therasorb-Ig pro and –Ig flex	Sheep-Ig directed against human Ig	Human Ig	Yes
CytoSorb (hemoperfusion system)	Biopolymer	Hydrophobic molecules up to 55 kD	No
Globaffin	Synthetic peptide ligand Gam 146	Human Ig	Yes
Glycosorb-ABO	Synthetic carbohydrates	Human anti-A/-B	No
IgEnio	Single-chain ab fragments against human IgE	Human IgE	No
Immunosorba	Staphylococcal protein A (protein A column)	Human Ig	Yes
Immusorba and PH	Tryptophane (TR) or Phenylalanine (PH)	Human Ig	No
LIGASORB	Recombinant protein A	Human Ig	No
PentraSorb CRP	Fully synthetic CRP ligands	C-reactive protein	Yes
Selesorb	Dextran sulfate on cellulose beads	Human Ig	Yes
Therasorb-IgE	Sheep-Ig directed against human IgE	Human IgE	Yes
Therasorb-Ig omni	Two recombinant antibody fragments against constant regions of κ and λ light chains	Human Ig	Yes
Therasorb-LDL	Sheep anti-apoB antibodies	Human apo-B	Yes

CRP, C-reactive protein; *Ig,* Immunoglobulin.

plasmapheresis also can remove a number of other molecules such as fibrinogen, IgM, or albumin.[41] This also may be of additional therapeutic value (e.g., removal of IgM for kidney transplantation).[15]

Today, no clear data support the view that there is a clinically relevant difference regarding the efficacy of LDL removal. Available apheresis systems are summarized later in this chapter. From a lipidologic point of view, this therapy should be continued in intensive care patients unless the patient has comorbidities that necessitate or presume discontinuation.[42] This is of higher relevance in patients with more advanced cardiovascular disease.

AVAILABLE LIPOPROTEIN APHERESIS SYSTEMS

1. Dextran sulfate cellulose columns binding apo-B lipoproteins from plasma
2. Dextran sulfate cellulose columns binding apo-B lipoprotein from whole blood
3. Heparin-induced extracorporeal LDL precipitation (HELP)
4. Direct adsorption of lipoprotein using hemoperfusion binding apo-B lipoproteins from whole blood on polyacrylate-coated polyacrylamide beads
5. Membrane diafiltration to filter LDL from plasma (double filtration plasmapheresis)
6. Immunoadsorption using matrix-bound sheep anti-apo-B antibodies

INDICATIONS

Worldwide, most indications are targeted using TPE where the best evidence is present. This clearly is reflected by the latest guidelines of the American Society for Apheresis,[3] an organization based in a country where virtually no selective procedures (IA, very limited LA) are performed.

The following tables summarize nephrologic indications as well as indications from other specialties that may be treated under ICU conditions by nephrologists.

The following categorization was used:

A. First-line therapy
B. Second-line therapy
C. Based on individual decision

Nephrology and Rheumatology

Disease	Technique	Indication	Category
Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis	Therapeutic plasma exchange (TPE)	Dialysis-dependent acute kidney injury, diffuse alveolar hemorrhage	A
Antiglomerular basement membrane syndrome (Goodpasture syndrome)	TPE	Dialysis-dependent acute kidney injury, diffuse alveolar hemorrhage independent from necessity of dialysis	A
Cryoglobulinemia	TPE immunoadsorption (IA)	Systemic, severe systemic, severe	A B
Kidney transplantation, ABO-incompatibility	TPE, IA	Desensitization, living donation	A
		Humoral rejection, acute	A
Thrombotic thrombocytopenic purpura (TTP)	TPE		A
Thrombotic microangiopathy, not TTP	TPE	Complement-mediated	C
		Shiga-toxin induced	C
Catastrophic antiphospholipid syndrome	TPE	Severe	B
Scleroderma	TPE, IA	Severe, systemic	C

Hematology

Disease	Technique	Indication	Category
ABO-incompatibility (AIHI)	TPE	Severe complications	B
Acquired hemophilia	IA	Alloantibodies, Autoantibodies	C
Hematopoietic stem cell transplantation, ABO-incompatible	TPE	Major HPC, bone marrow	B

Hyperviscosity syndrome due to monoclonal gammopathy	TPE	Symptomatic, prophylaxis before rituximab therapy	A
Sickle cell crisis	Red blood cell exchange	Stroke, chest pain, others	A B C
Babesiosis	Red blood cell exchange	Severe	B
Aplastic anemia	TPE	Severe	C
Autoimmune hemolytic anemia; cold agglutinin disease, warm autoimmune hemolytic anemia	TPE	Severe	B

Neurology

Disease	Technique	Indication	Category
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)	TPE, IA		A
Chronic inflammatory demyelinating polyradiculoneuropathy	TPE (IA)		A
Multiple sclerosis	TPE, IA	Acute inflammatory CNS infection, steroid refractory	B
Myasthenia gravis	TPE, IA	Moderate to severe, acute myasthenic crisis	A
Autoimmune encephalitis	IA	Acute, pathogenic autoantibodies	C
Lambert-Eaton syndrome and other paraneoplastic neurologic syndromes	IA, TPE	Acute CNS affection	C
Sydenham syndrome	TPE		C
Pediatric **A**utoimmune **N**europsychiatric **D**isorders **A**ssociated with **S**treptococcal Infections (PANDAS)	TPE		C

CNS, Central nervous system.

Lipidology and Cardiology

Disease	Technique	Indication	Category
Familial hypercholesterolemia	LPA	Homozygous and heterozygous forms in presence of progressive cardiovascular disease	A
Hypertriglyceridemia	TPE, LPA	Acute pancreatitis	C
Cardiac transplantation	TPE	Desensitization, antibody-mediated rejection, recurrent rejection	B
Dilatative cardiomyopathy	IA (TPE)	NYHA II-IV	B

Hepatology

Disease	Technique	Indication	Category
Liver transplantation, ABO-incompatibility	TPE	Desensitization	A
Wilson disease	TPE	Fulminant	A
Acute liver failure	High-volume TPE	Transition to liver transplantation	A
	MARS (Molecular Adsorbent Recirculating System)		B

Others

Disease	Technique	Indication	Category
Voltage-gated potassium channel antibodies	TPE		B
Other disorders	IA, TPE	Acute course and presence of pathogenic autoantibodies	C
Thromboangiitis obliterans	IA	Severe, rescue before amputation	C
Cryoglobulinemia	TPE, Cryofiltration	Severe	B
Sepsis	TPE, CytoSorb		C

CLINICAL RESULTS

All indications mentioned earlier may be treated using TA procedures in the ICU; however, clinical results are heterogeneous. All indications within the "A" category are clear cut, and recommendations to use TA as the primary or as part of the primary approach are based on a relevant number of clinical trials, patients, and data verifying treatment efficacy, either alone or in combination with pharmacotherapy. In category "B" indications, pharmacologic therapy is of proven value as the first-line therapy. However, TA should be chosen after failure of the first-line treatment (e.g., in acute inflammatory CNS affection in multiple sclerosis after failure of corticosteroids).

In a larger number of disorders, mainly retrospective data suggest effectivity of TA, but controlled or randomized trials are lacking. The majority of indications have never been tested in randomized or even larger clinical trials. Frequently, TA was used only as a second-line or rescue therapy after the failure of other approaches. Nevertheless, existing data reflect

that this therapy may be beneficial, and the risk of treatment will outweigh the potential risk for the patients. In these cases, the decision in favor of apheresis always is made on an individual basis. Widely, the same is true with regard to IA. Because of the limited distribution/availability of IA, most data in TA have been generated using TPE, and subsequent smaller studies have shown comparable effectiveness using IA in lieu of TPE.[31,43–45] Whenever the molecular target is of high pathophysiologic relevance and can be adsorbed specifically by IA columns, IA has to be considered being the more effective approach as a consequence of its higher removal capacity. Table 190.1 outlines further aspects that may lead to the decision in favor of IA.

Clinical Results in Established Nephrologic Indications (Category A)

The following paragraphs summarize all established TA indications typically found in critical care nephrology. All other indications depicted in the tables in the previous section arise from a close interaction between nephrologists and other disciplines, in which treatment regimens including TA are part of specific therapy guidelines of the corresponding areas.

Granulomatosis With Polyangiitis and Microscopic Polyangiitis

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) represent the two most common types of systemic small-vessel vasculitis affecting the kidneys, and commonly also the lung, thereby presenting as pulmonary-renal syndrome. The presence of antinuclear cytoplasmic antibodies (ANCA) is common and of proven direct pathophysiologic relevance.[46,47] Established therapeutic interventions have drastic beneficial effects on the natural course of the disease.[48] In recent years, a number of multicenter randomized trials led to a standardized therapy to which the anti-CD20 antibody rituximab has been added recently.[49]

Because of the prior successful use of TA for anti-GBM disease, TPE had been used for the treatment of pauci-immune glomerulonephritis before ANCA was discovered in 1982. Today, pathogenic relevance of ANCA gives a clear rationale for the systematic use of TPE in cases with severe renal and pulmonary involvement. Because of beneficial effects in the approximately 5% ANCA negative cases of small-vessel vasculitis, TPE also may interfere with the disease apart from antibody removal. In summary, so far nine controlled (eight of them randomized) trials have proven the effectiveness of TPE in patients with severe renal involvement, defined as a serum creatinine of more than 500 μmol/L or 5.8 mg/dL. The largest trial included 132 patients with severe renal involvement and found a 24% reduction of end-stage renal disease in patients receiving additional TPE treatment (MEPEX).[50] Less severely affected patients with severe renal involvement and rapidly worsening, but still better, renal function have been included in only one randomized trial, also suggesting effectiveness.

Patients with acute alveolar hemorrhage have not been investigated specifically in randomized trials, although cohort studies suggest effectiveness of TA. This has to be weighed against the risk of worsening pulmonary hemorrhage. Current guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO) initiative clearly recommend the use of TPE in cases of severe renal and pulmonary involvement, including patients with overlapping positivity of ANCA and anti-GBM antibodies.[51]

Antiglomerular Basement Membrane Disease

Anti-GBM disease is characterized by the presence of circulating antibodies binding the alpha-3 chain of type IV collagen. This leads to the subsequent development of a necrotizing glomerulonephritis with linear deposition of IgG along the GBM. Comparably to GPA and MPA, anti-GBM disease leads to the rapid loss of renal function and life-threatening pulmonary hemorrhage. Although anti-GBM disease is rare, it still has a comparatively poor prognosis but represents one of the first diseases that has ever been treated using TPE.[52] TPE will remove the pathogenic autoantibodies and immune complexes, thereby modulating the immune response.

Diagnosis of anti-GBM disease should lead to the rapid initiation of TPE in combination with immunosuppressive therapy.[51] Obviously, TA using IA or double-filtration plasmapheresis (DFPP) could lead to comparable results.[53,54]

Cryoglobulinemia and Cryoglobulinemic Vasculitis

Cryoglobulins are monoclonal and/or polyclonal immunoglobulins and complement components precipitating under decreased temperature. The main causes leading to the generation of cryoglobulins are lymphoproliferative disorders and chronic hepatitis C infections.[55] Cryoglobulins can lead to a number of direct organ manifestations, including cryoglobulinemic renal vasculitis. Under well-controlled preanalytic conditions, they can be measured directly in the patient's serum. In all cases, therapy of the underlying condition is the primary therapeutic goal, and newly established therapeutic approaches probably will lead to significantly improving results in patients with hepatitis C.[56–58]

Severe complications and progressive clinical courses represent an indication for TA. In detail, rapidly progressing glomerulonephritis, severe affections of the central nervous system, and organ ischemia represent such "category A" indications.[55] A high concentration of cryoglobulins also may promote the development of a hyperviscosity syndrome, representing a further indication for TA. The concentration of cryoglobulins, the so-called "cryocrit," frequently correlates with the presence of clinical complications and severity of symptoms. TPE clearly is indicated in these cases. In addition, cryofiltration, either by using DFPP or specific filter systems, is another effective approach to remove cryoglobulins from patient's serum,[59,60] leading to a rapid decline of the cryocrit. However, TA represents a symptomatic approach that has to be combined with a specific therapy for the underlying disease.

Thrombotic Microangiopathies

For many years, TPE represented the only available intervention in cases of thrombotic microangiopathy. In recent years, the growing pathophysiologic knowledge led to a further differentiation of distinct systemic dysregulations, affecting either the von Willebrand factor (vWF)–driven inhibition of platelet aggregation via the vWF cleavage protease (vWF-CP) ADAMTS-13 or the complement and coagulation pathways.[61–63] Today, atypical hemolytic syndrome (aHUS) as primary disease of a dysregulated complement cascade can be treated successfully by terminal complement pathway inhibition using the C5 inhibitor eculizumab.[64] TTP, a disturbance of vWF-CP function, is still dependent on the use of TPE, especially in cases with pathogenic autoantibodies, whereas genetic forms in childhood may be treated by plasma infusion alone. Because of the limited availability and high costs of vWF-CP tests, many centers will establish the

differential diagnosis with a certain delay. This interval of 24 to 48 hours, before aHUS can be differentiated from TTP and also *Shiga*-toxin (STEC)–induced HUS, frequently has to be bridged by TPE, because especially TTP can demonstrate with a rapid drop of platelet counts and complications within the central nervous system. With availability of the vWF-CP activity test, TPE has to be continued in cases of the category A indication TTP and immunosuppressive therapy has to be added, whereas patients with vWF-CP activity of more than 10% should be switched to eculizumab therapy. Most centers continue TPE in TTP until platelets have reached a count of more than 150/nL (and LDH was normalizing) for 2 consecutive days, followed by a careful monitoring.[3] In all types of TMA, TPE will remove dysfunctional components (vWF, vWF-CP, complement, coagulation factors, autoantibodies) from plasma, and FFP should be used as a substitute to supply the corresponding functional plasma components. However, a number of studies recently have shown that, in aHUS[65,66] as well as in STEC-HUS,[67] this intervention is not without considerable risk for the treated patients, either short-term (STEC-HUS) or long-term (aHUS) and therefore should be avoided.

APHERESIS IN KIDNEY TRANSPLANTATION

ABO-Incompatible Kidney Transplantation

All existing protocols for ABO-incompatible (iABO) kidney transplantation (KTx) are based on the early introduction of IA in combination with B-cell depletion and elimination of isoagglutinins by TA. Modern protocols no longer rely on systematic use of splenectomy before iABO-KTx.[68] Initially, TPE has been introduced as a key procedure to remove isoagglutinins.[69] Later, for efficacy reasons isoagglutinin-selective IA columns (GlyocSorb) were developed and were followed by an expanding use of IA to prepare recipients for iABO-KTx.[70] Meanwhile, unselective IA, using Ig adsorbers is used more commonly with comparable effectiveness and also has been combined with double-filtration plasmapheresis to improve the removal of IgM.[15,71,72] The established therapeutic goals are isoagglutinin titers of less than 1:8 (1:16). Because of the clear-cut clinical result, randomized trials have not been performed, neither for TPE nor IA.

Humoral Kidney Transplantation Rejection

Despite the increasing awareness of acute and also chronic humoral rejection, no standardized protocol has been established. Existing trials have used various combinations of TPE, IA, or DFPP with immunosuppressive regimens to remove proven donor-specific antibodies (DSA) and halt acute or chronic rejection.[73] For acute rejection, it also has been shown that DSA may be below the detection level in plasma but later may be found on relevant concentrations on IA columns.[74]

Although the combination of intravenous immunoglobulins (IVIG) with TPE as well as the triple intervention with IVIG, TPE, and rituximab gave beneficial results in trials for patients with acute humoral rejection,[75] so far the results in patients with chronic humoral rejections have been disappointing. However, randomized trials are lacking. TA also can be used for desensitization of transplant recipients or cross-match conversion, but systematic clinical results are lacking.[76–78]

APHERESIS IN SEPSIS AND MULTI-ORGAN FAILURE

In parallel to trials testing various interventional dialysis/hemofiltration strategies in septic patients with acute kidney injury,[79] several studies investigated apheresis techniques to interfere with multi-organ dysfunction and improve outcomes in patients with septic shock.[6,7,80–86] Today, not a single interventional strategy has demonstrated reliable beneficial results.[3] Although there is a clear pathophysiologic reason to interfere with a number of identified pathways, the major issue arises from a lack of selectivity: for instance, TPE, which may remove and replace a number of mediators, proinflammatory and antiinflammatory. From a pathophysiologic point of view, it also may be necessary to understand the extent to which these mediators have to be modulated by TA. Of additional concern, TPE also interferes with other standard of care procedures such as antimicrobial therapy by the removal of active drugs. The activity of distinct signaling pathways also may depend on the extent of organ dysfunction, cause, and time course of sepsis. In summary, sepsis therapy necessitates the development of more selective strategies, and novel approaches will have to undergo further investigation.[13,14]

Key Points

1. Depending on the pathophysiologic knowledge, a decision regarding the system selectivity should be made.
2. Apheresis in critical ill patients may exert a wide range of pleiotropic and immunomodulatory effects.
3. Selective systems can eliminate the therapeutic target with a higher effectiveness and a lower risk than TPE.
4. A wide spectrum of mainly acute disorders out of different specialties can be treated by apheresis.
5. Every apheresis treatment should be based on individual, patient-specific considerations.

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