Role of plasma exchange in the treatment of primary vasculitides

Plasma exchange (PLEX) has been part of the therapeutic armamentarium for vasculitis for over 40 years and this article reviews the indications, strength of evidence and safety of PLEX in the vasculitides. The relative rarity of these autoimmune diseases and incomplete understanding of their pathogenesis coupled with a lack of the development of a robust scientific rationale for PLEX therapy has hampered the conduct of large controlled trials. The use of PLEX has changed in recent years to reflect the improved evidence from controlled trials and PLEX is currently recommended for primary vasculitides such as ANCA-associated vasculitis with severe renal failure and cryoglobulinemia, whilst there is less evidence to guide its use in Henoch–Schönlein purpura and polyarteritis nodosa (PAN). PLEX remains a nonselective, costly therapy with common adverse events and uncertainty remains over the optimal method of application, frequency, dose, replacement solution, monitoring and integration of PLEX with other therapies. Further studies are required to more precisely define the indications and benefits of PLEX in vasculitis and assess more selective technologies such as immunoabsorption.

KEYWORDS: ANCA ■ cryoglobulinemia ■ exchange ■ hemorrhage ■ Henoch–Schonlein ■ indications ■ plasma ■ polyarteritis ■ renal ■ vasculitis

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Plasma exchange

Apheresis is derived from the Greek word 'apairesos' which means 'to remove'. The technology of apheresis was introduced over 40 years ago to collect red blood cells for blood transfusions and was subsequently used to remove circulating pathogenic factors, especially antibodies, in cryoglobulinemia in 1967, alloantibodies in transplantation in 1970 and antiglomerular basement membrane antibodies in 1976.

Plasmapheresis involves separating plasma from other cellular components, while plasma exchange (PLEX) involves the replacement of the removed plasma with a substitute, such as, albumin, plasma, crystalloid or a combination and return of the plasma substitute with the cellular components to the patient.

■ Therapeutic mechanism of PLEX

Ideally, the pathogenic substance being removed by PLEX should be known as well as measurable. However, PLEX is a nonselective process that can also remove useful substances (e.g., coagulations factors and immunoglobulins) and for most diseases it is not fully clear whether more than one pathogenic compound is being eliminated by PLEX although several mechanisms have been proposed, which are detailed below (Table 1).

The exchange of 1–1.5 plasma volumes (40–60 ml/kg) removes 60–70% of the desired substance from the plasma compartment. Exchanges beyond 1.5 plasma volumes have diminishing yield and only expose the patient to more plasma products without any real benefit (Figure 1).

In order to eliminate 1–2 g of pathologic substance, a typical PLEX removes as much as 110 g of albumin and 40 g of immunoglobulin.

A single PLEX only removes intravascular substances and extravascular to intravascular re-equilibration of a large molecular-weight substance is relatively slow at 1–3% per hour. Therefore, several consecutive PLEX sessions every 24–48 h are required to substantially reduce total body burden.

Even with a modest rate of antibody resynthesis, at least 5 PLEX treatments over 7–10 days are required to remove 90% of the patient's initial total body burden (Figure 2).

■ Types of technologies for PLEX

Centrifugation

This is used by the majority of centers and it involves separation of the blood components based on their specific gravity, with the most dense component at greatest distance from the axis of rotation and each layer can be harvested separately (Figure 3).

The separation is determined by the size and radius of the centrifuge, as well as the dwell time, the lifespan of the blood cells and the time

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Table 1. Potential mechanisms of action of plasma exchange.

Mechanism	Disease
Removal of 'evil humors': abnormal circulating factors	
Auto-antibodies, such as: ANCA Anti-GBM Antiganglioside	 ANCA vasculitis Goodpasture's disease Guillain-Barre
Immune complexes	Henoch–Schonlein purpura Crescentic IgA nephropathy
Super-antigens	Kawasaki disease
Cryoglobulins	Cryoglobulinemia
Permeability factor	Focal segmental glomerulosclerosis
Von Willebrandt multimers	Thromobotic thrombocytopenic purpura
Paraproteins	Myeloma
Removal of 'evil humors': excess physiological factors	
Complement	Vasculitis, lupus nephritis
Cytokines	General effect
Fibrinogen	General effect
Immunoglobulin components	General effect
Low density lipoproteins	Hypercholesterolemia
Replacement of deficient 'good humors'	
Protease enzymes (e.g., ADAMTS-13)	Thromobotic thrombocytopenic purpura
Antiproteases (e.g., α-1 protease inhibitor)	
Coagulation factor	Selective congenital coagulation factor deficiency
Immunomodulation: effect on lymphocyte function change in the idiotypic to anti-idiotypic antibody ratio	Transplantation
Improvement of the reticuloendothelial system function	Systemic lupus erythematosus, cryoglobulinemia

needed to pass through the centrifuge. There are two types of centrifugation: intermittent and continuous.

Intermittent

Blood is removed in several batches and separated into its constituents. The advantages are simpler technology, portable devices and the ability to use a single peripheral vein. However, intermittent centrifugation requires over 4 h to exchange the plasma and a large extracorporeal blood volume of over 225 ml.

Continuous

Blood is passed through a rapidly rotating bowl where erythrocytes, leucocytes, platelets and plasma are separated into layers which can be removed as necessary and the remaining ones returned to the patient together with replacement fluid.

These devices are rapid and feature computerized anticoagulation, blood collection and fluid replacement. The disadvantages are the complex instrumentation, high cost and the need for two peripheral veins or central venous access.

In comparison to filtration, centrifugation has the advantage of being less affected by a high hematocrit, however, it requires a stable interface for adequate separation.

Filtration

This alternative technique uses a parallel plate or hollow fiber filter whereby separation is based solely on the size of the substances and the pore size (0.2–0.6 μm) within the biocompatible filter membrane so that plasma is filtered through with its various constituents however, the cellular components are retained on one side of the filter (Figure 4).

The advantages of filtration are the shorter duration of up to 2 h, simple instrumentation, no need for a constant hematocrit and the extra option to carry it out using a dialysis machine in isolated ultrafiltration mode, although it is safer and more convenient to use a dedicated PLEX machine. On the other hand, the exposure of blood to the artificial membrane can cause complement activation, hemolysis and separation can be slowed by high viscosity that can clog the pores of the filter and causes inconsistent flow rates.

In the UK, PLEX centrifugation devices are used by dedicated apheresis units, whilst PLEX by filter separation is carried by nephrologists out in the larger renal units.

Anticoagulation

Anticoagulation plays a major role in preventing the blood from clotting within the PLEX devices. Citrate, heparin or a mixture of both are used.

Citrate is used for the majority of centrifugation devices. It does not induce systemic anticoagulation, chelates ionized calcium and lowers it to a level within the PLEX device of 0.2 to 0.3 mmol/l, however, calcium levels recover once the blood is returned to the patient as citrate is metabolized. Some patients require calcium supplementation post-PLEX. Other electrolyte abnormalities associated with citrate include hypomagnesemia, hypokalemia and high bicarbonate resulting from citrate metabolism by the Krebs cycle.

Heparin, the anticoagulant of choice for filtration PLEX, does not cause electrolyte abnormalities but does induce systemic anticoagulation and double doses are required compared with hemodialysis due to heparin removal within the plasma.

Replacement fluid for PLEX

The standard replacement fluid is albumin, which has the advantages of minimal risk of infection transmission and fewer hypersensitivity reactions compared with fresh frozen plasma (FFP). However, unlike FFP, albumin does not replace any of the other plasma constituents and thus, causes coagulopathy. After a single PLEX with albumin, prothrombin time increases by 30% and partial thromboplastin time doubles. These increases often reverse the day after PLEX but can be prolonged after multiple consecutive treatments. FFP contains 14% citrate that causes hypocalcemia and metabolic alkalosis. FFP is recommended in patients at high risk of hemorrhage, requiring intensive daily PLEX for weeks or to replace deficient enzymes (a disintegrin and metalloproteinase with thrombospondin motifs ADAMTS13 in thrombotic thrombocytopenic purpura TTP) and clotting factors in selective congenital conditions.

Safety of PLEX

Mild adverse events due to PLEX are common, in up to one third of patients. The World Apheresis Registry reports a 5.7% incidence of adverse events and no related deaths in 838 patients undergoing therapeutic PLEX (centrifugation/filtration ratio 7:1) [1].

The Canadian Apheresis Group reported a 0.4% incidence of serious adverse events that required termination of PLEX [2]. All adverse events occur more frequently with plasma products as compared with albumin. Between 1991 and 2001 there were 14 deaths attributed to PLEX out of 91,000 PLEX sessions, corresponding to a mortality of 1.5 per 10,000. Ten patients died due to their underlying TTP, one transfusion-related lung injury (TRALI) and two due to complications of vascular access. Other data from the same source reveal that metabolic derangements associated with PLEX are common. The citrate contained in FFP, or used as anticoagulant, can cause hypocalcemia (by binding to free calcium) and alkalosis that exacerbates hypocalcemia as the dissociation of H^+ ions from albumin frees up the latter to bind with more calcium. PLEX is associated with up to a 9% risk of reduction in ionized calcium (by 0.8 mmol/l) which could result in subsequent seizures and hypotension responsive to calcium supplementation.

The most serious complications of PLEX are anaphylaxis, hemorrhage and TRALI secondary to FFP. Plasma protein products are associated with transfusion-related adverse reactions in 7.8% of patients versus 3.3% with albumin [3].

Whilst most reactions to FFP are mild, the life-threatening TRALI reaction is one of the top three causes of transfusion-related fatality reported to US FDA. Its pathogenesis involves HLA antibodies in donor plasma and it prompted the use of male-only plasma in the UK since 2003 (TABLE 2) [4].

Vasculitis

Primary vasculitis is a heterogeneous group of uncommon multisystem autoimmune diseases, characterized by inflammation of blood vessels of various sizes.

This article will review the scientific rationale, evidence and safety for PLEX, focusing on the primary vasculitides for which PLEX has already been used as a therapeutic strategy: antineutrophil cytoplasm antibody (ANCA)-associated vasculitis, Henoch–Schönlein purpura (HSP)/crescentic IgA nephropathy, polyarteritis nodosa and essential mixed cryoglobulinemia (TABLE 3). Antiglomerular basement membrane disease, which is closely related to vasculitis, will not be discussed.

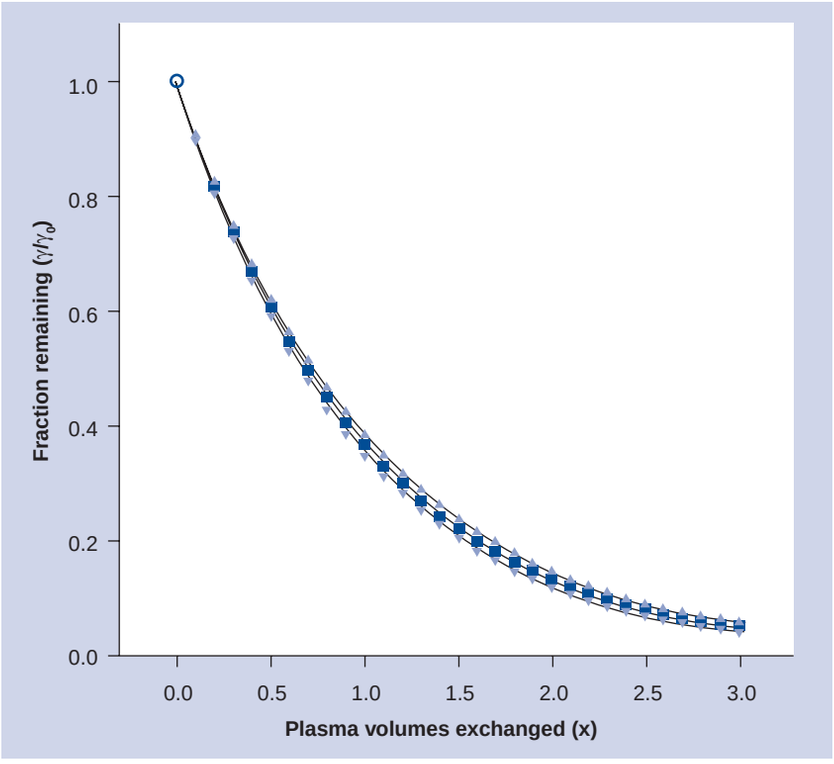

Figure 1. Therapeutic mechanism of plasma exchange. Removal of 60–70% of the desired substance from plasma by the exchange of 1–1.5 plasma volumes (40–60 ml/kg); diminishing yield of plasma exchanges beyond 1.5 plasma volumes. Reproduced with permission from AABB Press.

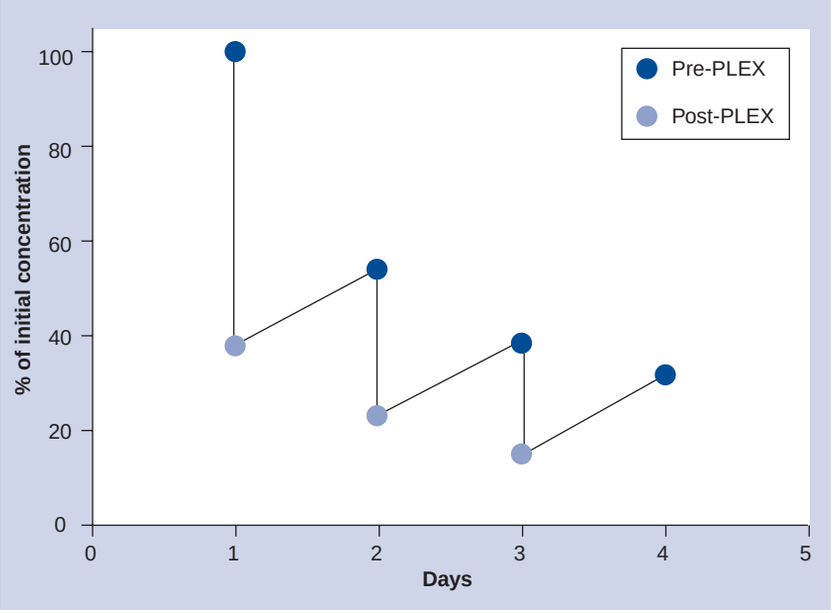

Figure 2. Progressive decrease in IgG levels after three consecutive therapeutic plasma exchange treatments equaling 1 plasma volume each.
Intertreatment increases between treatments represent a combination of extravascular to intravascular re-equilibration and a variable amount of new IgG synthesis.
PLEX: Plasma exchange.
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Pathophysiology

ANCA-associated vasculitis

This small vessel vasculitis subgroup comprises Wegener's granulomatosis (predominantly proteinase 3, PR3-ANCA/cytoplasmic, C-ANCA), microscopic polyangiitis (mostly myeloperoxidase, myeloperoxidase (MPO)-ANCA/perinuclear, P-ANCA) and Churg-Strauss syndrome (associated with MPO–ANCA). ANCA-associated vasculitis (AAV) can affect any organ but commonly involves the kidneys, lungs, ear, nose and throat, joints, skin and nerves.

The prevalence of AAV is approximately 14–30 patients per 100,000 in England [5]. Untreated AAV has a dismal prognosis with almost 100% 5-year mortality. The introduction of immunosuppressive treatment with cyclophosphamide and glucocorticoids in the 1970s has transformed AAV from a rapidly fatal disease to a chronic relapsing–remitting condition with considerable comorbidity and reduced survival often preceded by end-stage renal disease. Therefore, outcomes of AAV are still unsatisfactory owing to inadequate disease control in up to 20% of patients, with 50% of patients relapse over 5 years and treatment-related toxicity in 25–50% of patients [5].

Wegener's granulomatosis is associated with a higher relapse rate [6] and more ear, nose and throat symptoms [7], but similar mortality to microscopic polyangiitis, once adjustments are made for renal function [8].

The pathogenesis of AAV is likely to be a complex multistage process involving genetic predisposing factors and environmental triggers. The pathogenic role of ANCA is supported by both clinical case reports of transient vasculitis caused by trans–placental transfer of MPO-ANCA [9] and *in vitro* experimental data from animal models. Small vessel vasculitis affecting multiple organs and necrotizing, pauci-immune crescentic glomerulonephritis can be induced by the transfer of anti-MPO antibodies into MPO knockout mice but not into control mice [10]. Activation of neutrophils is required to trigger these pathogenic changes that do not occur after neutrophil depletion by NIMP-R14 rat monoclonal antibodies [11] .

Neutrophil stimulation by ANCA-IgG releases factors that activate the alternative complement pathway. The pathogenic role of the latter is supported by the finding that decomplementation with cobra venom factor prevents glomerulonephritis induced by anti-MPO antibodies [12] and neutrophil C5a receptor blockade abolished neutrophil priming for ANCA-induced respiratory burst [13].

Another key step in AAV development is the interaction of ANCA IgG with primed, dysregulated neutrophils to induce adhesion of the latter to activated endothelial cells that subsequently release damaging microparticles such as vonWillebrand factor, CD42a, CD105 and E-selectin [14].

Other novel markers correlated with AAV activity include LAMP-2 (lysosome-associated membrane protein) antibodies [15], antiplasminogen antibodies [16], antiendothelial cell antibodies (AECA) [17]. AECA increase the expression of chemokines such as IL-1β, IL-6, IL-8, monocyte chemotactic protein MCP-1, granulocyte chemotactic protein GCP-2, adhesion molecules including intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM), E-selectin and vascular adhesion protein (VAP-1) and upregulate the Major histocompatibility complex class I chain related A (MICA) ligand for receptors on natural killer (NK) cells and $CD8^+$ T cells. These recently characterized molecules offer new targets for tailored therapies.

Plasma exchange has the potential to rapidly remove pathogenic auto-antibodies and some of the other mediators of coagulation and inflammation as previously described [18].

Cryoglobulinemia

Cryoglobulins are circulating immunoglobulins that reversibly precipitate below 37°C to form large immune complexes that can cause tissue injury by either direct deposition on small and, occasionally, medium blood vessels, or by complement activation and leucocyte recruitment. There are three major classes of cryoglobulins:

- Type I (least common): single monoclonal IgM, IgG, IgA or Bence–Jones protein associated with myelo-/lympho-proliferative disorders;
- Type II (most common): mixed monoclonal IgM with rheumatoid factor activity complexed with polyclonal IgG;
- Type III: mixed polyclonal IgG and IgM with rheumatoid factor activity.

Type I cryoglobulins directly obstruct blood vessels without inflammation, whilst type II and III cryoglobulins also cause vasculitis and complement activation.

Over 80% of mixed cryoglobulinemias are associated with hepatitis C infection. Whilst approximately half of hepatitis C positive patients are susceptible to develop type II or III cryoglobulinemia, overt vasculitis occurs in less than 50% of mixed cryoglobulinemias [19].

Cryoglobulinemia in hepatitis C occurs due to impaired hepatic clearance and B-cell proliferation that drives cryoglobulin production. Interestingly, as many as one third of patients with non-Hodgkin lymphoma have hepatitis C infection [20], suggesting a lymphotropic role for the hepatitis C virus.

Mixed cryoglobulinemia can also be associated with autoimmune, chronic inflammatory and lymphoproliferative diseases. Mixed cryoglobulinemia is called 'essential' when no underlying cause is detected.

Cryoglobulinemia is initially asymptomatic in the majority of patients, however it tends to persist and, over time, can give rise to vasculitic symptoms such as purpura and cutaneous ulcers, arthropathy, digital ischemia, peripheral neuropathy and, after several years, renal vasculitis with rapidly progressive glomerulonephritis (RPGN) or membranoproliferative immune complex glomerulonephritis (MPGN; both most common in mixed cryoglobulinemia).

Antineutrophil cytoplasm antibodies are typically absent. Low complement (especially C4) levels and a positive rheumatoid factor can be highly suggestive of type II cryoglobulinemia, especially as the detection of cryoprecipitate is sometimes difficult and the correlation between cryocrit and disease activity is usually poor. Cryoglobulinemia is a chronic relapsing condition despite treatment, and, in the case of underlying hepatitis C, immunosuppressive therapy is associated with an increased risk of death, independently from disease severity [21]. Adverse events, including infection and progression to end-stage renal failure, are common with all treatments. Specific therapy targeting any underlying cause of cryoglobulinemia should be considered before immunosuppression.

Henoch–Schönlein purpura & crescentic IgA nephropathy

Henoch–Schönlein purpura is the most common vasculitis in childhood and rare above 15 years of age. The disease may be preceded by upper respiratory tract infection and appears to have a common pathogenesis with IgA nephropathy as it also features aberrant IgA1 glycosylation, mesangial IgA deposition and IgA immune complexes. However, HSP is also characterized by a vasculitic skin rash and crescentic glomerulonephritis with rapidly deteriorating renal function in a minority of patients (24% of children and 31% of adults [22]), unlike IgA nephropathy, which is a chronic progressive condition that eventually progresses to renal failure in approximately 50%

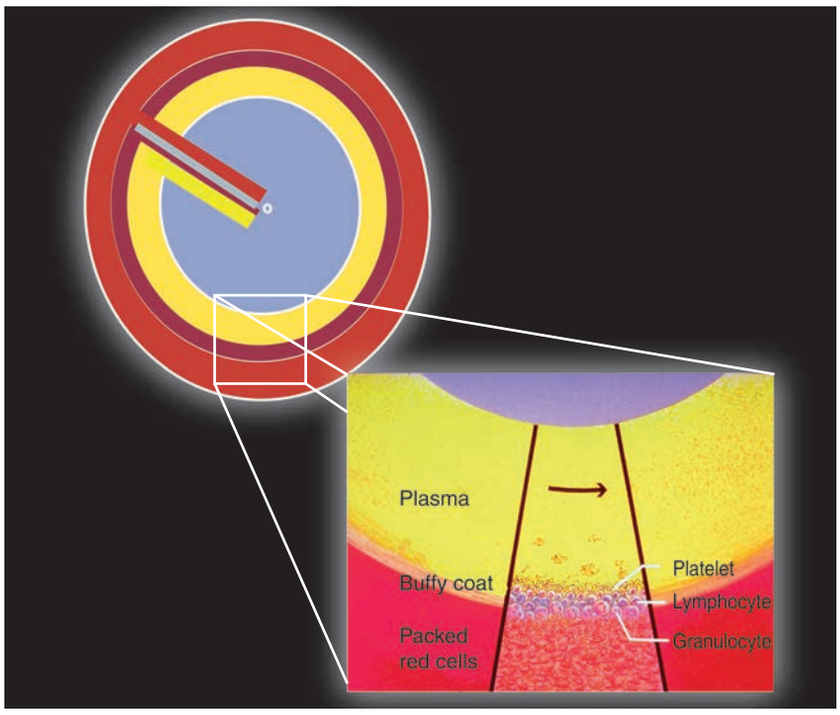

Figure 3. Plasma exchange by centrifugation. Separation of the blood components based on their specific gravity, so that the most dense component is at greatest distance from the axis of rotation.
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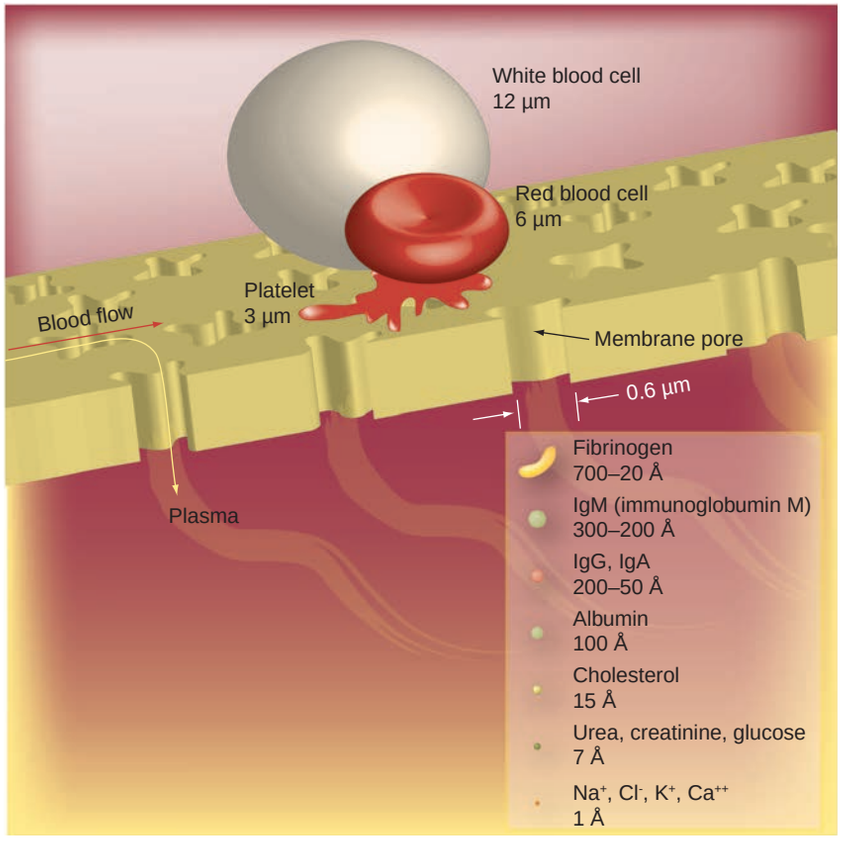

Figure 4. Plasma exchange by filter separation across a biocompatible membrane.
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of cases. The literature reports variable renal outcomes but the majority of children with HSP tend to recover.

Several studies also report that crescentic IgA nephropathy without a skin rash responds well to immunosuppression which is associated with an improved renal survival [23]. However, other studies have found that vasculitic renal lesions in such patients are associated with an increased mortality that may be partially related to the immunosuppression used [24]. There are no relevant randomized controlled trials so far.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) was the first vasculitis to be described in 1866 by Kussmaul and Meier. It is a rare small and medium-sized arteritis with immune complex deposition causing renal and mesenteric microaneurysms, neuropathy, cutaneous purpura and ulcers. Earlier studies of PAN have often combined microscopic polyangiitis with 'classical' polyarteritis nodosa. Another reason for the current rarity of PAN is that the Chapel Hill consensus definitions (1995) may have reclassified most PAN patients as microscopic polyangiitis.

During the 1970s, a causal association with hepatitis B was reported in as many as half of the patients with PAN. Screening of blood products coupled with vaccination in developed countries has drastically reduced the overall incidence of PAN (three to four per million in the UK) and few cases are currently HBe-antigen positive. Other viruses such as hepatitis C, HIV and parvovirus B19 are only rarely associated with PAN.

Without treatment, PAN is almost invariably fatal within 2–5 years. Cyclophosphamide and prednisolone are effective at inducing initial remission in primary PAN. However, in patients with coexisiting hepatitis B, immunosuppression impairs viral clearance thus predisposing the patient to infection and cirrhosis [25]. Therefore, antiviral medication and PLEX are a safer therapeutic strategy in this group.

Long-term treatment is usually not needed as PAN is mostly a 'one-hit' disease and, after the induction of remission, relapses occur in only 6% of patients [25].

PLEX in vasculitis

PLEX for ANCA+ renal vasculitis

The severity of renal dysfunction at presentation is an important predictor of mortality in vasculitis [8], which may explain why the majority of attempted PLEX controlled studies in vasculitis are based on patients with RPGN in whom PLEX has been used for over 30 years.

Early data from randomized controlled trials in rapidly progressive glomerulonephritis [26] revealed mixed results but they were characterized by small numbers of patients, short duration of follow-up, insufficient volume exchanges [27], collective analysis of heterogenous diseases, immunosuppressives and PLEX regimens. The renal recovery rate of 75% in patients with presenting creatinine above 500 µmol/l receiving PLEX appears superior to that of 40–50% reported in the other nonrandomized controlled studies where PLEX was not used [28,29].

Both controlled and uncontrolled studies have suggested that the routine addition of PLEX is unnecessary but PLEX may be an effective adjunct to immunosuppression during the acute phase of severe ANCA vasculitis (Table 4). Patients with more severe renal impairment (serum creatinine >250 µmol/l) [30] and dialysis-dependent RPGN [31] were identified by randomized controlled trials as groups benefiting from PLEX, which increased their chance of renal recovery.

These findings are supported by the largest trial in renal vasculitis so far (MEPEX), which analyzed 137 patients with severe ANCA

vasculitis and presenting creatinine above 500 µmol/l and demonstrated an absolute reduction in the development of end-stage renal disease (ESRD) by 24% (95% CI: 6.5–41%) after 12 months for patients treated with seven sessions of adjunctive PLEX versus three daily infusions of 1000 mg methylprednisolone in addition to standard oral cyclophosphamide and prednisolone [28]. Renal recovery occurred in 69% of the PLEX group and 49% of the control group at one year. Mortality at 12 months was 25% in both the PLEX and methylprednisolone group, partially due to the side-effects of immunosuppression. A multivariate analysis of predictive factors for renal recovery in MEPEX reveals that a significantly better outcome remains associated with PLEX despite severe histological findings [32].

Table 2. Adverse events associated with plasma exchange.

Type of adverse event	Incidence	Mechanism of adverse event	Other comments
Related to vascular access	29%	Hemorrhage, thrombosis, catheter-related infection, hematoma, pneumothorax	Lower risk with peripheral access Peripheral access not always possible Peripheral venous access: central venous access performed in a 1:1 ratio in Europe Peripheral venous access: central venous access performed in a 1:4 ratio in America
Paresthesia	20%	Citrate-induced hypocalcemia	
Hypotension	4–7%	Hypovolemia, anaphylaxis, cardiovascular, hypocalcemia, hypo-oncotic fluid replacement	More common in neurology patients due to autonomic instability
Serious reactions: anaphylaxis, hemorrhage, thrombocytopenia	0.5–3.1%	Allergic reaction to proteins in the replacement fluid	Higher risk of hemorrhage with uremia, coagulopathy, invasive procedure
Coagulopathy	More common with albumin	Depletion of clotting factors Depletion of anticoagulant factors	Clotting factors reduced by 60%, high PT, activated partial thromboplastin time, international normalized ratio post-PLEX with albumin (normalize after 1 day) Fibrinogen returns to 50–75% of baseline 48 h post-PLEX Avoid invasive procedures 4–6 h post-PLEX Higher risk of hemorrhage if uremic
Electrolyte abnormalities: Hypocalcemia	1.5–9%	Due to citrate (anticoagulant or in FFP)	Up to 9% risk of reduction in ionized calcium (by 0.8 mmol/l) and subsequent hypotension which responds to calcium supplementation
Hypokalemia			Commoner with albumin:K^+ less than 2 mEq/l in albumin replacement fluid
High bicarbonate/alkalosis		Due to citrate as converted to bicarbonate in Krebs cycle	
Aluminium toxicity			4–24 mmol/l aluminium in albumin products (higher risk with renal failure)
Infection		Transfusion of blood products	Low risk of viral transmission now Prions remain a potential risk
		Immunoglobulin depletion	Occurs with albumin replacement fluid 60% reduction with one single volume PLEX No increase in infection risk [6] No evidence of Ig replacement benefits
Removal of medications with high protein binding	Variable		Insignificant removal for steroids Minimal removal for azathioprine and cyclophosphamide Significant removal for rituximab (delay PLEX for more than 48 h post-rituximab) Administer daily drugs post-PLEX
Hemolysis		Hypo-oncotic (3%) albumin High transmembrane pressure Mechanical trauma (kinks in the tubing of PLEX disposables)	

FFP: Fresh frozen plasma; PLEX: Plasma exchange; PT: Prothrombin time.

Table 3. Indications for plasma exchange in vasculitis.

Disease	Strength of evidence
Antineutrophil cytoplasm antibody vasculitis	Randomized controlled trials
Cryoglobulinemia	Uncontrolled studies with more than ten patients
Henoch–Schonlein purpura/crescentic IgA nephropathy	Case reports and small uncontrolled studies

However, long-term data from MEPEX did not demonstrate a statistically significant difference between the treatment groups in terms of ESRD or death (p = 0.57) after 1.5 years. MEPEX would have benefited from larger patient numbers and longer follow-up.

A meta-analysis of nine randomized studies of PLEX in AAV included patient populations who were skewed towards severe renal impairment and often included diseases other than AAV (Table 5). PLEX was associated with a reduction in dialysis dependency (relative risk [RR]: 0.64; 95% CI: 0.47–0.88) but no reduction in mortality (RR: 1.01; 95% CI: 0.71–1.43). The relative risk was 0.81 (95% CI: 0.66–1.00) with regards to the composite endpoint of death or dialysis.

Plasma exchange is still not commonly performed as an induction treatment of AAV if serum creatinine is below 500 µmol/l although cumulative data from the European Vasculitis Group revealed poor outcomes (54% 5-year renal survival) in patients with eGFR below 50 ml/min, even if the creatinine is below 500 µmol/l [Walsh M, Catapano F, Szpirt WM, Throlund K, Jayne DRW: Plasma exchange for renal vasculitis: a meta-analysis. (2008) Submitted]. In 2004 the Pexivasc survey (Szpirt *et al.*) analyzed cumulative data from the European Vasculitis Study Group (EUVAS) that showed geographical variability with regards to the indications, duration, frequency, immunosuppression and number of sessions of PLEX between different centers. Persistence of ANCA, lack of renal recovery and active extra-renal vasculitis indicate that prolonged PLEX may be required. Some clinicians also use PLEX for the rare life-threatening neurological or gastrointestinal manifestations of AAV although there is no consistent evidence of benefit [33].

Table 4. Indications for plasma exchange in antineutrophil cytoplasm antibody vasculitis.

Indication	Strength of evidence
Presenting creatinine over 500 µmol/l	Nine randomized controlled trials (Table 3)
Alveolar hemorrhage	Uncontrolled studies
Presenting creatinine below 500 µmol/l	One randomized controlled trial [31], presenting creatinine above 250 µmol/l
Refractory or life-threatening vasculitis affecting the gastrointestinal tract, neurological and musculoskeletal system	Case reports

In view of the evidence available for PLEX in antiglomerular basement disease, PLEX is recommended for the minority (<10%) of ANCA vasculitis with coexisting anti-GBM antibodies, although this patient group has a poor prognosis despite PLEX treatment [34].

The past lack of consensus has prompted the design of PEXIVAS, an international multicenter randomized controlled trial that will appraise the effect of PLEX on ESRD and mortality in 500 patients with severe ANCA associated vasculitis (eGFR <50 ml/min and/or pulmonary hemorrhage) recruited over 5 years and followed up for an extra 2 years afterwards.

PLEX for pulmonary hemorrhage due to ANCA vasculitis

Severe alveolar hemorrhage is a major cause of morbidity and a predictor of vasculitis-related mortality, sometimes reported as stronger than renal failure [35], with an unclear long-term outcome of survivors from lung hemorrhage. Most patients with alveolar hemorrhage and ANCA vasculitis have extrapulmonary vasculitis manifestations, however some exceptions are reported [36], although it is unclear if their outcomes differ.

A similar pathogenic process to the capillaritis affecting the kidneys causes alveolar hemorrhage, giving rise to the pulmonary-renal syndrome that can be fulminant and is due to AAV in 80% of cases. Alveolar hemorrhage occurs in approximately one quarter of patients with ANCA vasculitis and may clinically present with hemoptysis in up to 70%, dyspnea, hypoxia, iron-deficiency anemia or diffuse alveolar infiltrates on imaging without an alternative explanation such as infection, fluid, malignant cells or alveolar proteinosis. The definition of alveolar hemorrhage differs between the studies.

Bronchoscopy is the best tool for excluding infection and diagnosing pulmonary hemorrhage. Progressively blood stained bronchoalveolar lavage (BAL) fluid confirms an alveolar source of hemorrhage as opposed to an endobronchial source where the BAL is always blood-stained. Over 5% hemosiderin-laden alveolar macrophages, suggestive of subclinical alveolar hemorrhage are a common finding in the BAL fluid of patients with ANCA vasculitis (53%) but not with other connective tissue diseases [37].

The evidence for PLEX in alveolar hemorrhage is based on cohort data and experience with antiglomerular basement membrane disease but has never been rigorously tested in randomized trials. There are also no consistent data on the benefit of PLEX in other

Table 5. Meta-analysis of nine controlled studies: the effect of adjunctive plasma exchange on the end point of end-stage renal disease or death in patients with rapidly progressive glomerulonephritis.

Study	Patients (n)	Disease(s) studies	Renal failure at presentation	Plasma exchange regimen	Outcomes	Relative risk (95% CI) ESRD & death	Ref.
Rifle *et al.* (1980)	14 8: no PLEX (6 immune complexes: IC) 6: PLEX (5 IC)	New RPGN + greater than 50% crescents 11 pts: immune complexes	79% dialysis-dependent PLEX: mean creatine 894 µmol/l Non-PLEX: 1140 µmol/l	5 daily then 3 /week until 15 days after creatine plateaus 1.5 plasma volumes albumin (FFP if coagulopathy)	Off dialysis at 2 months: PLEX: 83% No PLEX: 12.5% $p < 0.05$ Off dialysis at 12 months: PLEX: 80% No PLEX: 16.7%	0.57 (0.25, 1.33)	[48]
Mauri *et al.* (1985)	14 PLEX, no PLEX	RPGN with greater than 60% crescents	79%: on dialysis PLEX: mean creat 1193 µmol/l Non-PLEX: 1158 µmol/l	Six PLEX on alternate days ≥3.5 l exchanges with 3.5% albumin + 2 u FFP	Discontinuation of dialysis at 4 months: 75% in the PLEX group 0% in the no PLEX group	0.83 (0.45, 1.56)	[49]
Glockner *et al.* (1988)	26 in total 14: PLEX, 12: no PLEX	RPGN with greater than 70% crescents	46%: on dialysis PLEX: mean creat 579 µmol/l no PLEX: 604 µmol/l	Nine PLEX over the first 4 weeks; 50 ml/kg PLEX 3–5% albumin	Improved creat at 8 weeks PLEX: 69% No PLEX: 73% Creatine at 6 months: PLEX: 150 µmol/no PLEX: 486 µmol/l	0.86 (0.29, 2.56) Mortality: PLEX: 7% No PLEX: 8%	[50]
Pusey *et al.* (1991)	48 in total 25: PLEX 23: no PLEX	Focal crescentic necrotizing GN	39% dialysis dependent PLEX: mean creatine 793 µmol/l Non-PLEX: 637 µmol/l	5 × 4 liter PLEX in the first week Mean nine PLEX (5–25) 5% albumin + two units FFP	Patients off dialysis at 12 months: PLEX: 91% No PLEX: 37% ($p < 0.05$) No benefit if not on dialysis Mortality: PLEX: 48% No PLEX: 35%	1.15 (0.69, 1.91) $p = 0.004$	[51]
Cole *et al.* (1992)	32 in total 16: PLEX 16: no PLEX	RPGN with greater than 50% crescents 71% ANCA+	34% on dialysis PLEX: mean creat 643 µmol/l No PLEX: 769 µmol/l	≥ 10 PLEX in the first 16 days; 1 volume replaced 5% albumin	On dialysis at 1 year: PLEX: 75% of patients No PLEX: 71%. Similar change in creat. at 1,3,6,12 months	1.00 (0.36, 2.79) Mortality: PLEX: 13% No PLEX: 0%	[26]
Guillevin *et al.* (1997)	28:MPA (18:PLEX 10:no PLEX) 4 Churg-Strauss (1:PLEX 3:no PLEX)	28 MPA 4 Churg-Strauss 5: MPO 3: PR3	PLEX: mean creat 439 µmol/l non-PLEX: 287 µmol/l	9–12 PLEX within 4 weeks 60 ml/kg exchanges 4% albumin + 500 ml fluid gelatin	Reduction in creatiine at 1 year: PLEX: 22.5% No PLEX: 40.8% 5 year survival rate: PLEX: 74% no PLEX: 54%	0.50 (0.19, 1.33)	[52]

ANCA: Antineutrophil cytoplasm antibody; FFP: Fresh frozen plasma; IC: Immune complex; PLEX: Plasma exchange; RPGN: Rapidly progressive glomerulonephritis.
Adapted from [Walsh M, Catapano F, Szpirt WM, Throlund K, Jayne DRW: Plasma exchange for renal vasculitis: a meta-analysis. (2008) Submitted].

Table 5. Meta-analysis of nine controlled studies: the effect of adjunctive plasma exchange on the end point of end-stage renal disease or death in patients with rapidly progressive glomerulonephritis.

Study	Patients (n)	Disease(s) studies	Renal failure at presentation	Plasma exchange regimen	Outcomes	Relative risk (95% CI) ESRD & death	Ref.
Zauner *et al.* (2002)	33 with pauci-immune RPGN 18: PLEX 15: no PLEX	Pauci-immune RPGN 31 ANCA+	Mean creatine: PLEX group: 450.8 µmol/l non-PLEX: 362.4 µmol/l	PLEX: 6 (mean) Range 3–12 PLEX 40 ml/kg; FFP	Probability of dialysis-free survival 0.42 in PLEX group 0.49 in non-PLEX	1.18 (0.61, 2.28)	[27]
Jayne *et al.* (2007)	137 in total 70: PLEX 67: no PLEX	ANCA-associated necrotising GN	Creatine greater than 500 µmol/l in all patients PLEX: mean creatine 754 µmol/l Non-PLEX: 718 µmol/l	7 PLEX in the first 2 weeks; 60 ml/kg	ESRD at 1 year: No PLEX: 69% PLEX: 49% (p = 0.02) mortality: PLEX: 27% no PLEX: 24%	0.73 (0.52, 1.03)	[28]
Szpirt *et al.* (2009)	32 in total 16: PLEX 16: no PLEX	Wegener's	Mean creatine PLEX: mean creat 320 µmol/l non-PLEX: 330 µmol/l	PLEX: 6–12 4 l exchanged	1 month creatine: PLEX: 170 µmol/ No PLEX: 270 µmol/l 1 year creatine: PLEX: 155 µmol/l Non-PLEX: 203 µmol/l 5 year creatine: PLEX: 200 µmol/l Non-PLEX: 413 µmol/l	0.50 (0.19, 1.33)	[30]

ANCA: Antineutrophil cytoplasm antibody; FFP: Fresh frozen plasma; IC: Immune complex; PLEX: Plasma exchange; RPGN: Rapidly progressive glomerulonephritis. Adapted from [Walsh M, Catapano F, Szpirt WM, Throlund K, Jayne DRW: Plasma exchange for renal vasculitis: a meta-analysis. (2008) Submitted].

life-threatening extra-renal manifestations of ANCA vasculitis. In fact, PLEX could theoretically exacerbate hemorrhage through the removal of clotting factors.

The results differ between the studies and one demonstrated a trend towards increased survival of patients with pulmonary-renal syndrome and CRP above 6 mg/dl (66.7% survival with PLEX versus 56.7% without PLEX) [38]. Another study reported that all 20 AAV patients receiving PLEX had resolution of their pulmonary hemorrhage and 19 survived the initial disease episode [36]. However, no comparison cohort was available and 30% of patients did not present with renal impairment, a prognostic factor known to be associated with mortality.

On the other hand, a mortality as high as 36% in the first month was reported in 14 patients with alveolar hemorrhage treated with PLEX and immunosuppression [39]; only seven patients were alive at 2 years, with sepsis as the predominant cause of death. The high mortality could also be partially attributed to renal failure, as 86% of these patients presented with dialysis-dependent renal failure.

Another study reported a 68% 5-year survival of patients with microscopic polyangiits and alveolar hemorrhage and 69% of these had complete recovery of lung function whilst the sequelae included pulmonary fibrosis or obstructive bronchiolitis.

A total of 41% of surviving patients had a relapse of alveolar hemorrhage and 18% of this group died as a result. PLEX was administered in only 24% of patients and did not correlate with survival [38].

PLEX in vasculitides not associated with ANCA

Role of PLEX in cryoglobulinemia

Plasma exchange has intuitively been used to treat cryoglobulinemia for over 30 years but has not been studied in a randomized controlled trial. As cryoglobulins are restricted to the plasma compartment, PLEX rapidly lowers the cryocrit, thus reducing the need for immunosuppressives which carry a high risk of infection in hepatitis C.

The indications for PLEX therapy in cryoglobulinemia are not fully established and patients with no or mild symptoms probably do not need treatment.

Several uncontrolled studies (Table 6) support the effectiveness of PLEX for all types of severe cryoglobulinemia manifesting as advanced neuropathy, rapidly deteriorating renal function or nephrotic syndrome, leg ulcers or purpura. Renal function improved in 55–87% of patients, mortality was lower at 25% compared with a previous mortality rate of 55% in patients with cryoglobulinemia and no PLEX. However, the use of historical controls may bring confounding factors such as the diagnostic or therapeutic advances over time, patient selection and variability in disease manifestations, rather than a true benefit of PLEX.

Plasma exchange can be combined with the slower acting antiviral agents to treat cryoglobulinemia associated with hepatitis C and to help spare the use of antivirals where poorly tolerated or contraindicated. Warming of the replacement fluid is necessary to avoid aggregation of cryoglobulins.

Cryocrit, rheumatoid factor and complement levels, proteinuria and serum creatinine can be used to titrate the frequency of PLEX. Albumin in combination with 0.9% saline should be used as replacement fluids, avoiding plasma products that would add to the immunoglobulin load.

Since the 1980s the selective technology of cryofiltration via large 3 µm pore membranes has emerged as a specific and more effective method for removing large amounts of aggregated cryoproteins from plasma that is cooled at 4°C in the extracorporeal circuit [40]. Cryofiltration also has the advantages of not causing complement activation and not requiring replacement fluids.

Overall, only half of the patients achieve complete remission with PLEX because underlying hepatitis C frequently responds sub-optimally to antiviral agents.

If the hepatitis C virus is cleared, prolonged PLEX is usually unnecessary, however, symptoms may sometimes persist and require ongoing PLEX therapy [41].

On the other hand, mixed essential cryoglobulinemia is more likely to require long-term intermittent PLEX to control inflammation, which is usually refractory to immunosuppression [42]. Return of cryoglobulins without inflammation post-PLEX does not necessarily warrant ongoing PLEX and may be controlled with immunosuppression.

In order to prevent a rebound increase in cryoglobulin synthesis, it is safer not to stop PLEX abruptly and, instead, to gradually reduce its

Table 6. Studies of plasma exchange in cryoglobulinemia.

Study (year)	Patients (n)	Type of cryoglobulinemia	Renal impairment	PLEX	Immunosuppression	Clinical outcome	Mortality	Ref.
Schena *et al.* (1983)	10	Mixed	7/ 10	12–17	Glucocorticoids + azathioprine	Clinical improvement in 75%	Not reported	[53]
Valbonesi *et al.* (1984)	15	Mixed	8/15	3–5	Glucocorticoids + azathioprine	Clinical improvement in 75%	13%	[54]
L'Abbate *et al.* (1985)	11	Mixed	11/11	4–28	Glucocorticoids + cyclophosphamide + arabinoside-C	Improved or stable GFR in 73%	9%	[55]
Sinico *et al.* (1985)	20	Mixed	16/20	3–34 (mean 18)	Glucocorticoids + cyclophosphamide	Improved creatine in 87% (from 256 µmol/l to 141 µmol/l)	5%	[56]
Singer *et al.* (1986)	16	Mixed	10/16	3–12	Glucocorticoids + cyclophosphamide	Improved or stable creatine in 80% (no further quantification reported)	25%	[57]
Ferri *et al.* (1986)	9	Mixed	9/9	15–113	Glucocorticoids	Improved creat in 55% from 406 µmol/l to 185 µmol/l	Not reported	[58]
Frankel *et al.* (1992)	13	Mixed (type II)	10/13	4–238	Glucocorticoids + cyclophosphamide	Improved or stable in 67%	62%	[59]

PLEX: Plasma exchange.

frequency to the minimum number of sessions required to maintain control.

Plasma exchange is effective for induction of short-term disease control in addition to more specific maintenance treatments including those targeting the underlying cause of cryoglobulinemia. Biologics such as rituximab and infliximab are emerging as competing treatments with PLEX for hepatitis C negative cryoglobulinemia [42].

With the increasing recognition of hepatitis C, randomized controlled trials and future strategies are required to stratify patients most likely to benefit from PLEX as well as to optimize the dose and timing of PLEX.

Role of PLEX in polyarteritis nodosa

Unlike cryoglobulinemia, PAN associated with hepatitis infection is much more responsive to antiviral therapies and PLEX that can facilitate rapid removal of immune complexes, induction of remission and discontinuation of therapy within 2 months [25]. However, no benefit for PLEX was demonstrated for polyarteritis nodosa without hepatitis B infection in a randomized trial [43].

Plasma exchange should be withdrawn when Hbe seroconversion occurs, in order to not remove the newly produced antibodies. In this case, relapse is unlikely after induction of remission. On the other hand, the absence of Hbe or Hbs antibodies and persistence of hepatitis B viral DNA are associated with a higher risk of relapse even if remission from PAN is achieved and it is prudent to continue antiviral agents for 6–12 months.

Role of PLEX in Henoch–Schönlein purpura/crescentic IgA nephropathy

The use of PLEX in these conditions is based on the rationale that circulating IgA immune complexes contribute to the disease pathogenesis. The current evidence suggests a possible beneficial effect of PLEX in crescentic IgA nephropathy/HSP and only consists of case reports and small uncontrolled studies. Six adults with crescentic IgA disease, treated with PLEX in addition to steroids and cyclophosphamide, improved initially but renal function subsequently deteriorated in more than half of these patients [44].

Another study reported that 16 children with HSP and severe renal involvement treated solely with PLEX recovered, except one patient who was referred late and progressed to end-stage renal disease [33]. PLEX, in combination with immunosuppression was shown to reverse acute histological changes and reduce proteinuria in children with HSP [45].

The evidence thus far is supportive of PLEX but inconclusive due to the small patient numbers, lack of controls and variability of PLEX regimens. There is also no consensus with regards to the indications for glucocorticoids or other immunosuppressives in HSP or rapidly progressive crescentic IgA nephropathy. Larger, randomized controlled trials are needed.

Future perspective

Several alternative technologies may emerge in the future to replace PLEX by achieving selective removal of the pathogenic substance with minimal loss of albumin and coagulation factors, these include:

- Cryofiltration;
- Immunoabsorption: perfusion through columns with adsorbents. No advantage over PLEX has been shown so far [46];
- Lymphocytapheresis: Greater improvement of renal function and selective removal of CD8/CD14 T cells were reported with lymphocytapheresis compared with PLEX in RPGN [47].

These techniques are not routinely available for clinical use and are mainly used in research. The therapeutic specificity of apheresis techniques in vasculitis is likely to be further improved by the future genome-wide association studies and characterization of novel disease biomarkers to predict treatment response and relapse.

PEXIVAS, the largest controlled trial in vasculitis to date, will investigate the role of PLEX in vasculitis with renal involvement or alveolar hemorrhage [101,102].

Acknowledgements

The authors would like to acknowledge: (1) Michael Walsh, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada (his relative risk figures from a plasma exchange meta-analysis are quoted in the last column of **Table 5***); (2) Peter Merkel, Professor of Medicine and Director of the Vasculitis clinic, Boston University School of Medicine, USA, for his relevant talk at the PEXIVAS investigators' meeting, Cambridge, UK, April 2009; (3) Wladimir Szpirt, Consultant Nephrologist, Rigshospitalet, Copenhagen, Denmark, for allowing us to quote some results from his plasma exchange paper* [30]*; (4) Jeffrey Winters, Director of the Therapeutic Apheresis Unit, Mayo clinic, Rochester, USA, for allowing us to use his slides*

from his talk at the PEXIVAS investigators' meeting, Cambridge, UK, April 2009; (5) Ulrich Specks, Professor of Medicines, Mayo Clinic, Rochester, USA, (6) Karen Quillen, Medical Director, Blood Bank, Boston University Medical Center, USA, and (7) Patrick Nachman, University of North Carolina at Chapel Hill, USA, for their relevant talks at the PEXIVAS investigators' meeting, Cambridge, UK, April 2009; and (8) William Clark, Director of the Plasmapheresis Services, University of Western Ontario, Canada.

Financial & competing interests disclosure

David Jayne has received research grant support from Caridian BCT. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- A scientific rationale exists to support the use of plasma exchange (PLEX) in several vasculitis syndromes.
- The low prevalence of vasculitis has hampered the conduct of adequately powered, randomized controlled trials required to define the therapeutic role of PLEX. Multinational collaborative networks are needed to conduct trials with sufficient statistical power to confirm impacts on longer term outcomes and benefits in less common vasculitic presentations.
- A strong scientific rationale and experience from nonrandomized controlled studies supports the efficacy of PLEX in cryoglobulinemia. The American Society for Apheresis (ASFA) guidelines (2007) categorized PLEX as a level 1 indication in cryoglobulinemia, both as a primary therapy or a valuable first line adjunct therapy for severe disease.
- Evidence in support of plasma exchange in ANCA vasculitis with severe renal involvement has emerged from several small, and one larger randomized trial. The ASFA guidelines classified the indications for PLEX in AAV in category II, as a useful adjunct therapy for severe disease, rather than as primary first-line treatment.
- Further evidence is required to ascertain the benefits of PLEX in other forms of ANCA vasculitis, crescentic IgA nephropathy, Henoch–Schönlein purpura and refractory vasculitis affecting the gastrointestinal tract, neurological or musculoskeletal system.
- PLEX can be a fast-acting, nonimmunosuppressive therapeutic adjunct to immunosupression to limit irreversible damage during the acute phase of severe vasculitis, second-line treatment of refractory disease or as a measure to spare the use of cytotoxic immunosupression and glucocorticoids. PLEX has been combined to act synergistically with intravenous immunoglobulin, but the combination of PLEX with biologic agents, removed by PLEX (e.g., rituximab) has not been explored.
- PLEX remains an expensive and nonspecific therapy with a high incidence of adverse events but few are serious. Metabolic derangements such as hypocalcemia and alkalosis are common. Adverse reactions are more frequent if fresh frozen plasma is used instead of albumin and, rarely, can be life-threatening in the case of transfusion associated lung injury.
- Further evaluation is awaited of selective technologies such as cryofiltration, lymphocytapheresis or immunoabsorption that may prove more efficacious and less toxic.

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