

Plasmapheresis for the treatment of kidney diseases



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The purpose of this review is to examine the evidence supporting the application of plasma exchange in renal disease. Our review focuses on the following 6 most common renal indications for plasma exchange based on 2014 registry data from the Canadian Apheresis Group: (i) thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome; (ii) renal transplantation, (iii) anti-neutrophil cytoplasm antibodies-associated vasculitis, (iv) cryoglobulinemia, (v) focal segmental glomerulosclerosis, and (vi) Goodpasture syndrome. The rarity of these diseases and their rapid, often fatal course mean that randomized controlled studies of plasma exchange are rarely conducted. Although evidence from an adequately powered randomized controlled trial supports the use of plasma exchange to treat thrombotic thrombocytopenic purpura, the use of plasma exchange to treat other renal diseases is only supported by observational and mechanistic studies. Larger well-designed trials are needed to clarify the potential role of plasma exchange in renal disease. Growing international collaboration will improve the quality of future studies in this area.

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Manual plasmapheresis was first described in 1914 in animal experiments and was first used therapeutically in 1952 to control hyperviscosity in multiple myeloma.^{1,2} The advent of the automated cell separator in the 1960s led to its later application in therapeutic plasmapheresis (plasma exchange).^{3–5} In 1975, Lockwood *et al.*⁴ used plasmapheresis and immunosuppression to successfully treat pulmonary hemorrhage and renal failure in Goodpasture syndrome. In 1976, Jones *et al.*³ performed plasmapheresis of 8 patients with systemic lupus erythematosus, and the first with severe renal impairment responded. In 1977, Bukowski *et al.*⁵ used plasma exchange to successfully treat 2 patients with thrombotic thrombocytopenic purpura (TTP), renal impairment, hematuria, and proteinuria. Since then, plasma exchange has been employed in a variety of kidney disorders primarily directed at the following 2 mechanisms: (i) removal of an unwanted substance, such as Goodpasture syndrome, where the anti-glomerular basement antibody that cross reacts with the basement membrane of lung and kidney is removed, or (ii) in acquired TTP, with removal of an unwanted substance (inhibitor to ADAM metalloproteinase with thrombospondin type 1 motif 13 [ADAMTS13] that promotes platelet thrombosis) and replacement of a deficient substance (ADAMTS13 in the plasma that prevents platelet thrombosis).⁶ In acquired TTP, the exchange fluid is a plasma product (fresh frozen plasma, stored plasma, cryosupernatant plasma, or solvent detergent-treated plasma; all products appear equally effective). In other cases where plasma exchange is used to remove a putative pathogenic agent, 5% human serum albumin is employed to limit exposure to plasma antigen and lipid soluble viruses such as HIV, hepatitis B, hepatitis C, and hepatitis E. However, the use of frequent plasma exchange with 5% serum albumin poses an increased risk of bleeding, and the potential transient reduction in IgG may predispose to infection.^{7,8} Although there are no randomized controlled trials on prophylaxis, for patients with pulmonary hemorrhage (anti-neutrophil cytoplasm antibodies [ANCA]-associated vasculitis [AAV], Goodpasture syndrome), we would recommend 2 to 4 units of solvent detergent-treated plasma to replace missing coagulation factors at the end of exchanges; this replaces clotting factors with a reduced risk of an allergic reaction in patients with severe pulmonary compromise.

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This review examines the evidence supporting the application of plasma exchange in treating kidney diseases. We review the 6 most frequent renal indications for plasma exchange in Canada, as documented in the Canadian Apheresis Group registry, which has collected data on all apheresis procedures performed in Canada since 1980. The Canadian Apheresis Group registry was selected due to its unique property in the world of apheresis in accurately reflecting all plasma exchange activity within a national health care system. Based on 2014 registry data, the 6 most common renal indications for plasma exchange were (i) TTP/hemolytic uremic syndrome, (ii) renal transplantation, (iii) AAV, (iv) cryoglobulinemia, (v) focal segmental glomerulosclerosis, and (vi) Goodpasture syndrome (Figure 1).⁹

THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC UREMIC SYNDROME

Background and rationale for treatment with plasma exchange: A brief history of an evolving diagnosis

The first case of TTP, described by Moschcowitz in 1925,¹⁰ was a young woman who at autopsy had significant renal and systemic microthrombosis. By the 1960s, this rare fatal disorder was diagnosed by a pentad of features (thrombocytopenia, hemolytic anemia, neurologic signs, renal failure, and fever) often elicited at or near the time of death.¹¹ In 1955, Gasser *et al.*¹² described 5 children with hemolytic anemia, thrombocytopenia, and renal failure following a diarrheal illness that he called hemolytic uremic syndrome (HUS). Although there was a significant overlap in features between TTP and HUS, it was thought that they were clinically separable with a predominant neurologic picture in TTP and a diarrheal, renal picture in HUS. However, over time, a

number of cases with TTP were reported to have presented with a preceding diarrheal illness and renal failure, and many cases of HUS were reported to have significant neurologic dysfunction.^{13–16} Both disorders also shared a similar pathogenic coagulation profile with predominant platelet consumption.¹⁷ To further complicate clinical diagnosis, there was a growing awareness that both primary and secondary forms of TTP and HUS existed. These diagnostic difficulties remained academic until the 1977 report by Bukowski *et al.*⁵ of successful treatment of TTP patients with plasma exchange. In 1991, the Canadian Apheresis Group's definitive randomized controlled trial demonstrated the superiority of plasma exchange over plasma infusion for treating patients presenting with unexplained thrombocytopenia and hemolytic anemia.¹⁸ Introduction of the diagnostic dyad (unexplained thrombocytopenia and microangiopathic hemolytic anemia) expanded the application of plasma exchange to prevent early mortality within the thrombotic microangiopathy spectrum.^{19–21} The superiority of plasma exchange over infusion was thought to be due to removal of a mystery substance and provision of a necessary/deficient substance. In 1998, 2 different laboratories identified the mystery substance as an antibody inhibitor to the ADAMTS13 enzyme, and the deficient substance as the ADAMTS13 enzyme, which cleaves von Willebrand factor multimers and prevents widespread microthrombosis.^{22,23} Furlan *et al.*²³ further demonstrated that most TTP patients had a deficiency of von Willebrand factor–cleaving protease, whereas most HUS patients had normal von Willebrand factor–cleaving protease activity, indicating that TTP and HUS were 2 distinct disorders. This led to the emergence of 2 schools of thought regarding the diagnosis of primary (acquired) versus secondary TTP. Many believed that if patients

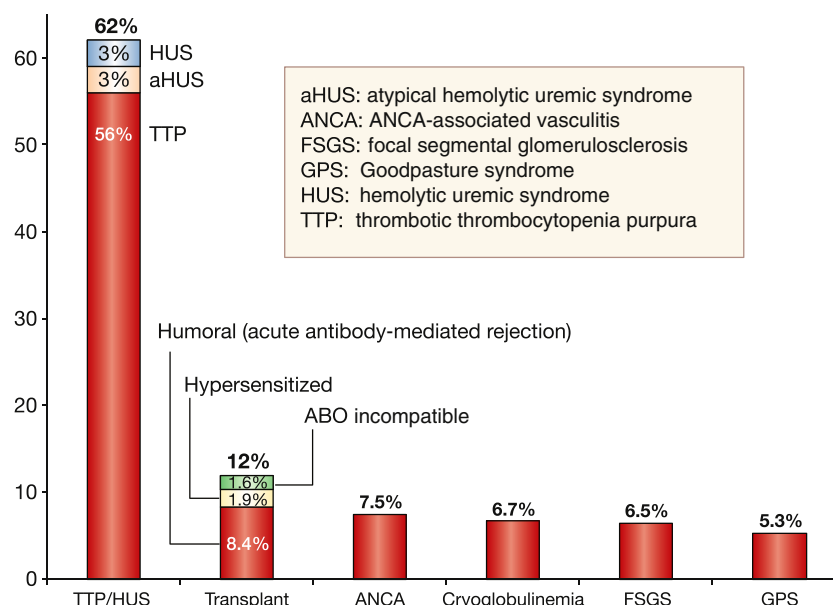


Figure 1 | The 6 most common renal indications for plasma exchange therapy in 2014. Created with data from Patriquin C, Clark WF. Canadian Apheresis Group 2014 plasma exchange data review: hematological, renal/collagen vascular, dermatological and transplant. Data review. Paper presented at: 35th Annual General Meeting of the Canadian Apheresis Group. September 18–20, 2015; Winnipeg, Manitoba.⁹ ANCA, anti-neutrophil cytoplasm antibodies. Source: Canadian Apheresis Group.

did not have a functional ADAMTS13 deficiency, they were not suffering from primary TTP;^{24–27} however, an opposing school of thought indicated this should not be the sole diagnostic criterion, since many patients with the classical TTP pentad present with normal ADAMTS13 enzyme activity and respond to plasma exchange.^{20,28} Current diagnostic classification for the spectrum of thrombotic microangiopathic syndromes are described in the following discussion and in Table 1.

Treatment considerations and empiric evidence

Acquired TTP. Acquired TTP is characterized by unexplained thrombocytopenia and Coombs negative microangiopathic hemolytic anemia with a normal international normalized ratio for prothrombin time and partial thromboplastin time. Presenting clinical features of acquired TTP are diverse: symptoms may (or may not) include abdominal pain, purpura, fever, or focal neurological abnormalities. Severe ADAMTS13 deficiency (<10%) is supportive of the clinical diagnosis; however, the published literature does not uniformly support severe deficiency as a necessary diagnostic criterion for acquired TTP.²⁹ Although these features are characteristically associated with acquired TTP, other

thrombotic microangiopathies can have similar presentations, but a different underlying pathophysiology and require different treatment strategies as described herein.³⁰ Nonetheless, because the differential diagnosis of TTP is often challenging and mortality is high in untreated TTP patients, current guidelines support the initiation of plasma exchange in the presence of unexplained thrombocytopenia and microangiopathic hemolytic anemia in patients without a predisposing condition (Table 1).²⁹ In such patients, treatment with plasma exchange was shown in a randomized controlled trial to reduce mortality from 90% to <20%.^{18,29}

Treatment recommendations are to initiate plasma exchange within 24 hours of presentation, with exchanges of 1.0 to 1.5 plasma volumes per session, performed daily until platelet count, lactate dehydrogenase, and hemoglobin levels are normalized.^{31,32} Premedications and/or cointerventions may include diphenhydramine and corticosteroids.^{26,31} Approximately 30% to 40% of patients with acquired TTP are refractory to initial therapy (i.e., they relapse within 30 days) or will relapse 30 days or more after their initial successful response (defined as relapsing TTP).^{14,20,33–35} Rituximab has been shown to be effective in both relapsing and refractory TTP; however, this evidence is based solely on data

Table 1 | Plasma exchange for TMA—excluding disseminated intravascular coagulation^{14,20,47–50,54,134,135}

TMA classification	Subclassification	Proportion of TMA cases ^a	Pathophysiologic features	Response to plasma exchange ^a
Primary TMA	Acquired TTP	29%–41%	Unexplained microangiopathic hemolytic anemia and thrombocytopenia (no predisposing condition). Severe ADAMTS13 deficiency <10% (present in 40% to 100% of patients).	80%–90%
	Hereditary/congenital TTP (Upshaw-Shulman)	1%–2%	Severe ADAMTS13 deficiency (<10%). No ADAMTS13 autoantibody inhibitor.	>90%
Secondary TMA	Autoimmune disease ^b	45%–50%	Endothelial injury (mediated by various insults). Variable ADAMTS13 activity.	50%–70%
	Drug-mediated ^c			80%–90% ^d
	Infection ^e			50%–70% ^f
	Pregnancy/postpartum			50%–70%
	Pancreatitis			50%–70%
Shiga toxin-mediated TMA (STEC HUS)	Malignancy	9%–10%	Shiga-toxin-mediated endothelial injury renal failure. Preserved ADAMTS13 activity. Patients have mutations in <i>CFH</i> , <i>CFHR1/3</i> , <i>CFI</i> , <i>C3</i> , <i>MCP</i> [<i>CD46</i>], <i>THBD</i> , or <i>CFB</i> , or carry anti- <i>CFH</i> antibodies. Preserved ADAMTS13 activity.	No response
	Malignant hypertension			No response
	Stem cell transplantation			No response
Complement-mediated TMA (atypical HUS)	STEC HUS	9%–10%	Shiga-toxin-mediated endothelial injury renal failure. Preserved ADAMTS13 activity. Patients have mutations in <i>CFH</i> , <i>CFHR1/3</i> , <i>CFI</i> , <i>C3</i> , <i>MCP</i> [<i>CD46</i>], <i>THBD</i> , or <i>CFB</i> , or carry anti- <i>CFH</i> antibodies. Preserved ADAMTS13 activity.	Inconclusive
Complement-mediated TMA (atypical HUS)	Familial	<2%	Patients have mutations in <i>CFH</i> , <i>CFHR1/3</i> , <i>CFI</i> , <i>C3</i> , <i>MCP</i> [<i>CD46</i>], <i>THBD</i> , or <i>CFB</i> , or carry anti- <i>CFH</i> antibodies. Preserved ADAMTS13 activity.	30%–70% ^g
	Sporadic			

ADAMTS13, ADAM metalloproteinase with thrombospondin type 1 motif 13; C3, complement C3; CFB, complement factor B; CFH, complement factor H; CFHR1/3, complement factor H receptor 1/3; CFI, complement factor I; HUS, hemolytic uremic syndrome; MCP, membrane cofactor protein; STEC, Shiga toxin-producing *E. coli*; THBD, thrombomodulin; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

^a14,20,47–50,54,134,135.

^bIncluding, but not limited to, systemic lupus erythematosus.

^cIncluding ticlopidine, clopidogrel, quinine, Valacyclovir, oral contraceptives, chemotherapy, cyclosporine, tacrolimus, sirolimus.

^dExcept mitomycin C—no response.

^eIncluding but not limited to, HIV, *Streptococcus pneumoniae*.

^fExcept *E. coli* 0157:H7—no response.

^gExcept abnormal membrane cofactor protein—no response.

from observational studies.^{18,36,37} Patients with refractory TTP and no detectable ADAMTS13 at presentation may benefit from increased volume and frequency of plasma exchange, other agents including bortezomib or cyclophosphamide, or splenectomy, or a combination of these.^{36,38–45}

Hereditary TTP. Hereditary TTP (Upshaw-Schulman Syndrome) is extremely rare, affecting <2% of patients with TTP. Hereditary TTP is characterized by a severe ADAMTS13 deficiency (<10%), and no ADAMTS13 autoantibody inhibitor.²³ Diagnosis of hereditary TTP requires genetic documentation of ADAMTS13 mutations.³⁰ Patients with hereditary TTP can be treated with plasma infusion on an elective basis to prevent further relapses, but may receive plasma exchange therapy at the time of their initial presentation.^{30,46}

Secondary thrombotic microangiopathies. More than 50% of patients who are referred to plasma exchange centers for TTP suffer from secondary forms of thrombotic microangiopathies.^{14,47,48} Plasma exchange appears to be of no benefit for treating secondary TTP resulting from malignancy, mitomycin C therapy, stem cell transplant, or malignant hypertension;^{49,50} however, for other secondary forms of TTP, the benefit of plasma exchange is less clear. Thrombotic microangiopathies associated with infections, pregnancy, drugs, or autoimmune diseases are acutely treated with plasma exchange, but if they do not respond, plasma exchange is abandoned and all efforts are directed at treating the secondary cause.

Hemolytic uremic syndrome. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and severe renal impairment. The most common form of HUS is secondary to Shiga toxin-producing bacteria, typically *E. coli* O157:H7 (STEC). Among children, most cases of HUS are caused by STEC. Although current evidence does not support the use of plasma exchange for treating STEC HUS,^{51,52} it is still offered as rescue therapy in the minority of individuals who develop severe neurologic symptoms. As well, positive results were seen in a recent uncontrolled trial of 12 patients who were treated with immunoadsorption during a 2011 German outbreak of Shiga toxin-producing enterohemorrhagic *E. coli* O104:H4.⁵³

Atypical HUS. Historically, the term atypical HUS (aHUS) has been used to classify HUS cases with no bloody diarrheal prodrome.⁵⁴ However, extensive research has now established that 60% to 70% of patients with aHUS have a latent genetic predisposition in the complement system (patients have mutations in complement factor H [CFH], complement factor H receptor 1/3 [CFHR1/3], CFI [complement factor I], complement C3 [C3], membrane cofactor protein [MCP (CD46)], thrombomodulin [THBD], or complement factor B [CFB], or carry anti-complement factor H antibodies).^{55–57} In these individuals, aHUS often manifests after a triggering stimulus such as non-STEC infection, pregnancy, an autoimmune disorder, endothelial-affecting drug use, malignancy, or transplantation.⁵⁵ Over the last decade, a series of case reports and uncontrolled trials have shown that eculizumab

may be an effective therapy for treating aHUS in both adults and children.^{55,58,59} These studies also show that eculizumab may induce remission in patients resistant to plasma exchange and may prevent dependency on chronic plasma exchange. Current guidelines recommend eculizumab as a first-line treatment for children with a clinical diagnosis of aHUS.⁵⁷ These guidelines recommend that eculizumab be initiated within 24 to 48 hours of disease onset; however, if eculizumab is not available, treatment with plasma exchange is recommended except for the small minority patients who have been identified as having defects in cofactor membrane proteins.⁵⁷

The absence of rapid accurate diagnostic testing can make it difficult to differentiate aHUS from other thrombotic microangiopathies.^{60–62} For this reason, plasma exchange is often used as an initial therapy for individuals who present with unexplained thrombocytopenia and hemolytic anemia with normal ADAMTS13 (>10%), and no obvious secondary cause, or with a secondary cause that has received appropriate therapy.^{54,56} This approach is predicated on the amount of time needed for genetic testing, the expense of eculizumab therapy, and the ready availability of plasma exchange therapy. In observational studies, plasma exchange for undiagnosed aHUS has been associated with a 50% to 60% reduction in mortality; however, long-term outcomes are poor, with a high risk of relapse, increased mortality, and progression to end-stage kidney disease.^{54,56} The advent of eculizumab for treating aHUS has created a new urgency to safely and quickly differentiate patients with this low-frequency disorder (<1 per million) from the majority suffering from primary TTP or secondary thrombotic microangiopathy.^{60,61} Many are now working to develop diagnostic algorithms to identify patients who would most benefit from this extremely expensive, but effective therapy.^{54,57,62}

HLA-SENSITIZED TRANSPLANTATION, ABO-INCOMPATIBLE TRANSPLANTATION, AND ANTIBODY-MEDIATED REJECTION Background and rationale for plasma exchange

Approximately 35% of patients wait-listed for kidney transplants have high anti-human leukocyte antigen (HLA) antibodies.⁶³ Historically, transplantation was contraindicated in these “HLA-sensitized” patients; however, the use of immunologically incompatible kidneys is growing due to advances in methods of characterizing anti-HLA antibodies and the availability of effective regimens to suppress antibody-mediated responses.⁶³ These advances, coupled with the shortage of transplantable kidneys, has resulted in the increasing use of plasmapheresis to broaden access to transplantation in patients who have high anti-HLA antibodies or ABO blood-group incompatibility (Figure 1).⁶⁴

Treatment considerations and empiric evidence

HLA-sensitized transplant recipients. Compared with non-sensitized patients, HLA-sensitized patients typically wait 3-to-4 times longer for a compatible donor kidney, and if

transplanted, they are at increased risk for early graft loss.^{65–67} Plasma exchange is increasingly used in pretransplantation desensitization protocols for patients with living donors with an incompatible crossmatch because of donor-specific antibodies. Desensitization protocols typically include plasmapheresis or i.v. Ig (IVIG) (high dose: 2 g/kg or low dose: 100 mg/kg) or both and rituximab to down-regulate antibody-mediated immune responses.^{64,68} Additional immunosuppression with corticosteroids, anti-CD20 antibodies, or bortezomib may also be used.^{64,69} The number of plasmapheresis or IVIG treatments or both is influenced by both the antibody levels and the degree of mismatch. Guidelines recommend performing plasmapheresis daily or every other day until crossmatch becomes negative.^{64,70,71} Because anti-HLA antibody titers will rebound within a few weeks after treatment stops, transplantation within 1 week of the last desensitization treatment is recommended.⁷⁰ Posttransplantation monitoring and rapid treatment of antibody-mediated rejection are essential to preserve the graft.

Until recently, it was not clear whether HLA-incompatible kidney transplantation, after desensitization, conferred a survival advantage relative to waiting for a compatible transplant.^{68,72} However, strong evidence for a survival benefit is now provided in 2 recent cohort studies.^{70,73} In the most recent of these,⁷³ a significant survival benefit was seen in 1025 HLA-sensitized patients who underwent desensitization before receiving a kidney transplant from a living donor. Transplantations took place at 22 centers between 1997 and 2011, and each center followed their own desensitization protocol. The 8-year survival rates of HLA-sensitized recipients were 13.6 and 32.6 percentage points higher, respectively, than rates in the following 2 groups of matched control subjects: (i) patients who were on a waiting list or who received a transplant from a deceased donor, and (ii) those who were on a waiting list and did not receive a transplant ($P < 0.001$ for both comparisons). The risk of death was reduced, respectively, by a factor of 1.83 (95% confidence interval [CI]: 1.58–2.12) and 3.37 (95% CI: 2.92–3.90). A significant survival benefit was also observed at 1, 3, and 5 years post-transplantation and across all levels of donor-specific antibodies. Despite the risks of undergoing sensitization (which can increase the risk for anaphylaxis, hypotension, and infection),^{70,74} these pragmatic studies demonstrate that transplantation from an incompatible live donor (after desensitization treatment) is superior to the next best real-world treatment option: continuing to wait for a compatible kidney transplant.

ABO-incompatible transplantation. The potential benefit of using plasmapheresis in ABO-incompatible transplantation was first shown in the 1970s and 1980s.^{75–77} ABO-incompatible transplantation is also affected by both the alloantibody titer and the degree of mismatch.⁷⁸ It was initially felt that splenectomy was a necessary part of the desensitization protocol.⁷⁹ However, successful ABO-incompatible renal transplantation can be achieved by combining plasmapheresis with an IVIG protocol without

splenectomy.⁸⁰ The goal of treatment is to reduce the antibody titer to less than a specific critical threshold prior to transplantation; however, this threshold titer varies with center-specific titration methods and techniques.⁶⁴ Patients at high risk for rejection may require additional management, including splenectomy and anti-CD20 therapy.⁸¹ Although there are no controlled trials on using plasma exchange to facilitate ABO-incompatible transplantation, an abundance of supportive evidence exists. In particular, a study from Japan has reported excellent outcomes in >2000 cases of ABO-incompatible living kidney transplantations performed since the 1990s, with 5- and 10-year graft survival rates of 95% and 90%.^{82,83}

Antibody-mediated rejection. Antibody-mediated rejection is defined based on the presence of serum donor-specific antibodies, allograft histology, and allograft immunochemistry. Antibody-mediated rejection in the kidney allograft occurs in up to 60% of high-risk recipients (HLA-sensitized or ABO-incompatible) but also in up to 23% of unselected low-risk recipients.^{84,85} Therapeutic strategies typically include combinations of plasma exchange (5 or 6 daily or alternate-day exchanges using 5% human serum albumin), IVIG (2 g/kg or 100 mg/kg), and anti-CD20 antibody to clear donor-specific antibodies and suppress antibody production.⁷¹ However, evidence on safety and efficacy is weak, and the optimal treatment protocol has yet to be determined.⁷²

ANTI-NEUTROPHIL CYTOPLASM ANTIBODIES

Background and rationale for plasma exchange

Granulomatosis with polyangiitis and microscopic polyangiitis are associated with circulating ANCA and rapidly progressive glomerulonephritis.^{86,87} Although ANCAs play a prominent role in diagnosing AAV, the degree to which ANCAs are pathogenic is debated. Because ANCAs are typically IgG antibodies, the potential for plasma exchange to improve outcomes by rapidly reducing ANCAs is apparent. Additionally, plasma exchange may benefit patients by removing clotting factors and inflammatory mediators.^{88–93}

Treatment considerations and empiric evidence

A systematic review and meta-analysis of 9 trials including 387 patients suggested a 20% relative risk reduction in the composite outcome of death or end-stage renal disease (95% CI: 1%–25%) after treatment with plasma exchange.⁹⁴ Despite statistical significance, Walsh *et al.*⁹⁵ warned that the results were sensitive to several assumptions and could be due to the play of chance. Confidence in results is further eroded by the low methodological quality of the trials and lack of consistency in the effect on death (95% CI: 29% risk reduction to 42% risk increase) compared with the effect on end-stage renal disease (where the relative risk was reduced by 36% [95% CI: 12%–53%]).⁹⁴

Uncertainty in the benefits of plasma exchange for AAV is further increased by the observation that the largest long-term follow-up study of plasma exchange in AAV, the MEPEX (Plasma Exchange for Renal Vasculitis) trial, did not

demonstrate a significant reduction in end-stage renal disease or death (hazard ratio of 0.81; 95% CI: 0.53–1.23).⁹⁶ Furthermore, there was a nonsignificant increase in infection-related deaths, bringing into question the possibility of unanticipated harm with plasma exchange in immunosuppressed patients.⁹⁶ This brings into question the role of IVIG in patients exchanged with 5% serum human albumin; we presume this risk is reduced by adding solvent detergent-treated plasma (reduced allergic risk vs. plasma in a patient with pulmonary compromise due to hemorrhage) at the end of each exchange.

Plasma exchange is particularly advocated in patients with AAV with either severe renal dysfunction or diffuse alveolar hemorrhage.⁹⁷ However, a substudy of the MEPEX trial found that patients most likely to benefit from plasma exchange were those who did not have severe scarring on their renal biopsy.⁹⁸ Although this finding is only hypothesis generating, it stands to reason that patients with established end-stage renal disease have little to no benefit from adjuvant therapies aimed at improving renal function and instead are more likely to suffer the associated harms of plasma exchange. This theory is supported by the large effect of plasma exchange in patients with preserved renal function in randomized trials.⁹⁴ These trials lacked statistical power due to low event rates, but they suggested a greater effect of plasma exchange on mortality than trials that recruited patients with worse renal function.

This role of plasma exchange in patients with diffuse alveolar hemorrhage is based on observational data from noncontemporaneous case series. It is important to consider that the severity of lung hemorrhage ranges from asymptomatic disease to ventilator-dependent disease and prognosis likely varies directly with severity.⁹⁹ Also, infection is the most common cause of death for AAV in patients with diffuse alveolar hemorrhage.^{96,100} The removal of Igs by plasma exchange may increase the risk of infections. The absence of reasonable evidence and the potential to cause harm has led some to question the broad recommendation to consider plasma exchange in all AAV-related diffuse alveolar hemorrhage.¹⁰¹

More or larger trials or both are needed to clarify the potential role of plasma exchange in AAV. The PEXIVAS (Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody [ANCA]-Associated Vasculitis) trial will help fill many of these knowledge gaps.¹⁰² PEXIVAS plans to randomize ≥ 700 participants to either 7 plasma exchanges of 60 ml/kg within 14 days, in addition to standard care, or to standard care alone. Importantly, PEXIVAS will include patients with a broad range of kidney function (estimated glomerular filtration rate anywhere between 50 ml/min and requiring dialysis) or lung hemorrhage (including ventilator-dependent patients) or both. PEXIVAS is currently recruiting with an expected completion date in 2017. In the interim, we recommend that plasma exchange be considered in any patient who is not responsive to conventional therapy (i.e., cyclophosphamide, rituximab, and

corticosteroids) and who is not a suitable candidate for entry into the PEXIVAS study. We would also recommend that any patient with uncontrolled pulmonary hemorrhage with pulmonary deterioration be offered adjunctive plasma exchange therapy with solvent detergent-treated plasma to reduce the risk of allergic reaction or coagulopathy.

CRYOGLOBULINEMIA

Background and rationale for plasma exchange

Cryoglobulins are a group of Igs and complement components that precipitate when exposed to cold temperatures and typically resolubilize at body temperature (37°C).¹⁰³ Three types of cryoglobulinemia have been described based on the clonality of the cryoglobulin and rheumatoid factor binding activity.¹⁰⁴ The most common cause of cryoglobulinemia is infection with hepatitis C virus; however, several other conditions have been associated, including other viral infections, lymphoproliferative disorders, and connective tissue diseases.¹⁰³ Depending on the location of precipitation of cryoglobulins, manifestations can range from purpura, arthralgias, or peripheral neuropathy to more severe neurologic involvement or rapidly progressive glomerulonephritis.¹⁰³ Management is directed at treating the underlying cause with combination immunosuppressive therapy and antiviral therapy for hepatitis C–associated cryoglobulinemic vasculitis.^{105–107}

Treatment considerations and empiric evidence

Although plasma exchange is frequently used as adjunctive therapy for the treatment of cryoglobulinemia, its role has not been systematically evaluated in controlled trials, and support for plasma exchange is primarily based on mechanistic grounds, given the potential to remove circulating cryoglobulins and interrupt immune-complex deposition.^{108,109} Results of case reports and case series weakly support the use of plasma exchange for treatment of life-threatening or organ-threatening complications (including severe neuritis, refractory cutaneous vasculitis, and rapidly progressive glomerulonephritis) or symptomatic hyperviscosity.^{64,103,110,111} However, plasma exchange does not prevent formation of new cryoglobulins or treat the underlying disease, and rebound production of cryoglobulins can occur after cessation of apheresis without therapy directed at the cryoglobulin-producing B-cell clones (such as rituximab or cyclophosphamide).¹¹² Furthermore, the concentration of cryoglobulin does not correlate with clinical severity nor with response to therapy; therefore, the decision to initiate plasma exchange should be based on the severity of the disease manifestations.¹¹³

The optimal frequency, dose, and replacement fluid has not been studied; however, it is reasonable to start exchanging ≥ 1 plasma volume 3 times per week for 2 to 3 weeks when indications exist, using the clinical response to guide subsequent therapy.¹¹² Plasma should be replaced with 5% albumin and the room, lines, and replacement fluid should be warmed to prevent precipitation of circulating

cryoglobulins.^{103,112} Successful plasma exchange should lead to rapid resolution of clinical manifestations including improvement in skin lesions and renal function; however, resolution of neurologic manifestations may be delayed.¹¹⁴

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Background and rationale for treatment with plasma exchange

Focal segmental glomerulosclerosis (FSGS) is not a single disease but rather a set of clinical-pathological findings that include nephrotic-range proteinuria, biopsy-proven segmental sclerotic glomeruli lesions, and injured epithelial podocytes. The primary cause is unknown in approximately 80% of cases¹¹⁵ and available treatments have limited effectiveness. Even with treatment, 30% to 60% of patients progress to kidney failure within 5 to 10 years. Treatment with plasma exchange became a logical step when several subtypes of FSGS were found to recur in allograft-transplanted kidneys, and with the discovery of potential pathological circulating factors.^{116–119} Among those who receive a kidney transplant, severe proteinuria recurs in 30% to 55% of patients, often within hours or days of grafting.^{120–122} This led to an early hypothesis that etiological factors in primary FSGS are plasma borne and can equally damage a healthy transplanted kidney by injuring the filtration barrier or by increasing glomerular permeability to albumin or both.¹²¹

Treatment considerations and empiric evidence

Whereas current guidelines support the use of plasma exchange for recurrent posttransplantation FSGS, evidence on treatment efficacy comes largely from case reports, uncontrolled case series, and narrative reviews.^{71,116,117,121–123} In a recent systematic review and meta-analysis of this literature,¹²⁴ 71% of patients ($n = 423$) achieved full or partial remission from proteinuria after treatment with plasma exchange (95% CI: 66%–75%). Importantly, patients treated with plasma exchange within 2 weeks of recurrence appeared to have a higher likelihood of remission from proteinuria (OR = 2.16; 95% CI: 0.93–5.01); however, this effect did not achieve statistical significance and the observational nature of the data prevent any causal inferences about the efficacy of plasma exchange. Nonetheless, these data are consistent with a beneficial effect of prompt treatment with plasma exchange.

Careful observation for transplant recipients with a previous diagnosis of FSGS or minimal change nephrotic syndrome is warranted; we recommend daily proteinuria testing for ≥ 14 days after transplantation, and if proteinuria is detected, immediate initiation of plasma exchange therapy is recommended.⁶⁴ Guidelines recommend 3 daily exchanges followed by ≥ 6 more in the subsequent 2 weeks, for a minimum of 9 procedures with concomitant immunosuppression treatment.⁶⁴ Long-term regimens of weekly to monthly exchanges depending on the degree of proteinuria may be required to achieve remission.¹²⁵ However, many questions remain unanswered, and future research should examine and refine the treatment protocol, including timing, dosage, and

prescription (e.g., 5% serum albumin solution vs. fresh frozen plasma), duration of plasma exchange treatment after remission,¹¹⁷ the role of IVIG in reducing the risk of infection in those treated with 5% serum human albumin in patients receiving transplant immunosuppression,^{7,8} and the efficacy of pretransplantation plasma exchange for preventing recurrence.

GOODPASTURE SYNDROME

Background and rationale for treatment with plasma exchange

Goodpasture syndrome is a rare autoimmune disorder caused by antibody binding the NC1 domain on the alpha-3 chain of type 4 collagen of the glomerular basement membrane in isolation (anti-GBM disease) or with alveolar basement membrane binding.¹²⁶ Early cases between the 1920s and 1960s experienced nearly universal fatality, due to pulmonary hemorrhage or renal failure. With improved understanding of disease pathophysiology, attempts at treatments emerged in the 1960s, including salvage bilateral nephrectomies, prednisone, immunosuppression, and eventually plasma exchange. Plasma exchange removes circulating anti-GBM antibodies, whereas the immunosuppressive agents suppress new antibody formation.

Treatment considerations and empiric evidence

Because Goodpasture syndrome is very rare (0.5–1.0 cases per million in the general population),¹²⁷ there are no high-quality randomized controlled trials on which to base treatment recommendations. Only 1 underpowered randomized controlled trial has studied the treatment effect of plasma exchange.¹²⁸ Seventeen patients were randomized to immunosuppression (oral prednisone and cyclophosphamide for 3 to 4 months) alone or with concurrent plasma exchange. Plasma exchange was performed every 3 days until titers were undetectable, but exchange stopped if patients remained dialysis dependent for 1 month. The majority of patients were young men (average age <25 years) with pulmonary hemorrhage. Addition of plasma exchange rapidly cleared anti-GBM titers within 2 months, and at end of therapy, mean serum creatinine in these patients was one-half that of the patients receiving immunosuppression alone. However, analysis of baseline characteristics revealed important prognostic differences that advantaged patients in the plasma exchange group (lower presenting serum creatinine concentrations and crescent scores). Pulmonary hemorrhage prevalent in both groups responded promptly to i.v. steroids.

A large retrospective review conducted at Hammersmith Hospital shed light on presenting clinical characteristics and response to treatment with combination immunosuppression and plasma exchange.¹²⁹ Mean age of patients was 48 years, with 2 bimodal peaks (20s and 60s) and more young men with pulmonary hemorrhage. In those who did not require dialysis at presentation, there was a strong correlation between anti-GBM titers and renal severity. In 108 patients

treated for 8 weeks, all dialysis-dependent patients remained on dialysis, whereas a proportion of non-dialysis-dependent patients escaped dialysis, particularly when presenting serum creatinine was $<600 \mu\text{mol/l}$ [$<6.8 \text{ mg/dl}$]. Pulmonary hemorrhage was prevalent (52% of patients) and overwhelmingly responsive to therapy. The overall mortality rate was 21%, with only 8% due to pulmonary hemorrhage. A subset analysis of 30 patients who received what was defined as full therapy, oral cyclophosphamide; prednisone; azathioprine in younger patients; and at least 14 daily plasma exchanges, cleared anti-GBM rapidly within 2 months.

A second follow-up study examined the long-term treatment effect of the above-mentioned therapy in 71 patients.¹³⁰ It highlighted the correlation of crescent score and initial renal severity with overall renal and patient survival. It also highlighted the improbability of renal recovery in dialysis-dependent patients and the high likelihood of renal survival in those with less severe renal involvement. Overall patient mortality at 1 and 5 years was 21% and 44%, with pulmonary hemorrhage comprising a minority (13%) of deaths. Disease exacerbations were common when circulating antibody was still present and further pulmonary capillary insults had ensued. Long-term follow-up of transplanted patients with undetectable anti-GBM antibody at time of transplantation showed no disease recurrence.

Based on the evidence presented here and from other corroborating studies,¹³¹ guidelines recommend treatment with combined prednisone, cyclophosphamide, and plasma exchange.⁶⁴ In our opinion, treatment should be offered to all patients with pulmonary hemorrhage and those with renal potential for recovery. However, based on the largest retrospective review of plasma exchange in Goodpasture syndrome at the Hammersmith Hospital, it would appear that patients with no pulmonary hemorrhage, on dialysis, with 100% crescents do not respond to plasma exchange and therefore it is not indicated in this small subset of patients. When renal potential is unclear, a trial of therapy may be justified, depending on the patient's ability to withstand immunosuppression and transplant eligibility. Treatment should consist of oral cyclophosphamide (although anecdotal support for i.v. dosing also exists), i.v. pulse and subsequent oral prednisone therapy, and at least 14 daily plasma exchange treatments. Treatment goals, clinical response, and antibody titers should guide further therapy including additional plasma exchange procedures or intensified immunosuppression or both. Disease exacerbation can occur during treatment, more commonly (but not exclusively) with ongoing antibody circulation and preceded by pulmonary insults. Disease relapse is rare and patients can safely be transplanted following persistent clinical and antibody quiescence. Efficacy of antibody removal by plasma exchange is limited by ongoing production and rebound kinetics, highlighting the importance of concurrent immunosuppression and an adequate exchange prescription. Although controlled evidence is not available for patients receiving 5% human serum albumin replacement, adjunctive solvent detergent-treated plasma at

the end of each exchange, or IVIG, may reduce the risk of sepsis.

Compared to historic cohorts with nearly universal renal and patient fatality, the era of combination therapy has dramatically improved both outcomes. The rarity of disease, potentially rapidly fatal course, and established pathophysiology make it unlikely that randomized controlled studies of plasma exchange will be conducted. However, future studies should address nuances in therapy including refractory disease, recurrent disease, double-positive disease (with coexistent ANCA detected), seronegative disease, and the adjunctive role of IVIG and solvent detergent-treated plasma in patients being exchanged with 5% human serum albumin. We await results of ongoing studies into novel strategies including rituximab¹³² and the T-cell fusion protein CTLA4Ig.¹³³

CONCLUSIONS

This review summarizes the available evidence from both randomized controlled trials and mechanistic observational studies that examined the role of plasma exchange in the 6 most common renal indications in a relatively complete national registry in 2014. The authors hope that growing international collaboration will improve the quality of future studies examining the efficacy of plasma exchange in treating renal disease.

DISCLOSURE

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