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 metallopeptidase 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 [ANCAs]-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.

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

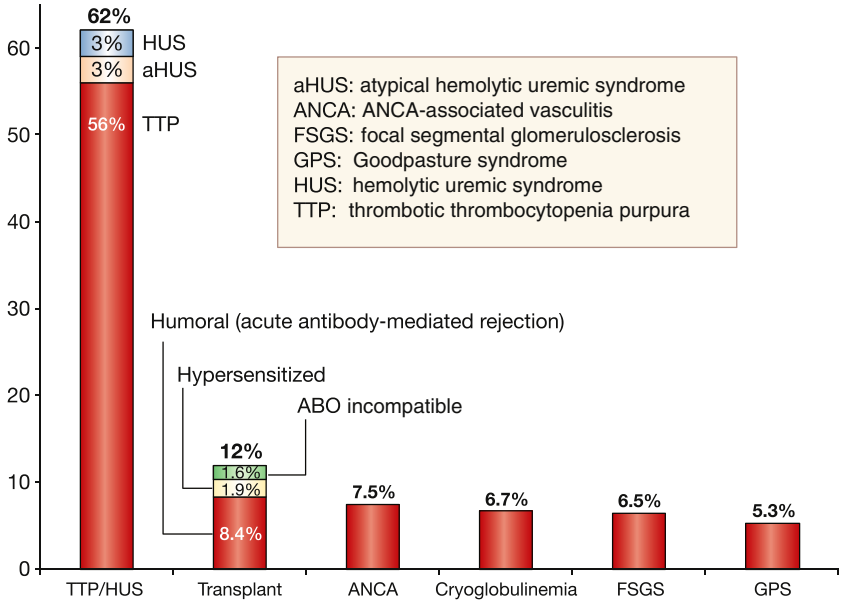

Figure 1 | The 6 most common renal indications for plasma exchange therapy in 2014. Created with data from Patriquin C, Clark WF. Canadian Apheresis Group 2014 plasma exchange data review: hematological, renal/collagen vascular, dermatological and transplant. Data review. Paper presented at: 35th Annual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