

## REVIEW

# Plasmapheresis for systemic vasculitis

Kazuhito Fukuoka | Mitsumasa Kishimoto | Takahisa Kawakami |  
Yosinori Komagata | Shinya Kaname

Department of Nephrology and  
Rheumatology, Kyorin University School  
of Medicine, Mitaka-shi, Tokyo, Japan

**Correspondence**

Kazuhito Fukuoka, Department of  
Nephrology and Rheumatology, Kyorin  
University School of Medicine, PO#  
181-8611, 6-20-2 Shinkawa, Mitaka-shi,  
Tokyo, Japan.

Email: kfukuoka@ks.kyorin-u.ac.jp

**Abstract**

Systemic vasculitides include a variety of, and numerous diseases. In 2012, the International CHAPEL HILL Consensus Conference (*CHCC2012*) led to a major reorganization of the classification of vasculitis, and this is still in wide use today. Although the results of plasmapheresis for individual diseases have been sometimes shown, there are few systematic reviews that discuss the effects along with vasculitis classification. Therefore, we will discuss the efficacy and the latest evidence for each vasculitis according to the *CHCC 2012* classification in this review. This review provides a comprehensive overview of the estimation of plasmapheresis in each of the vasculitides, with a particular focus on small vasculitides, which have recently discussed frequently. For some time now, plasma exchange therapy (PEX) has been frequently used and is expected to be effective in some diseases, most of which are included in small vessel vasculitides. In particular, data showing efficacy have been accumulated for immune complex vasculitis, and the recommendation seems to be high. For instance, anti-GBM nephritis, concomitant use of PEX is essential and strongly recommended. On the other hand, for ANCA-related vasculitis among small vessel vasculitis, RCTs have recently shown negative results. In particular, the PEXIVAS trial statistically showed that PEX has no potential to reduce the mortality and renal death in AAV, but the ASFA, ACR, and KDIGO guidelines following this trial all regard PEX as salvage therapy or selective treatment for severe cases. As plasmapheresis is often performed in combination with other therapies, it is difficult to evaluate to clarify its efficacy on its own, and this predisposition may be pronounced in vasculitis, a rare disease. Although statistically significant differences are not apparent, the diseases that

**Abbreviations:** SV, systemic vasculitis; LVV, large vessel vasculitis; MVV, medium vessel vasculitis; SVV, small vessel vasculitis; ANCA, antineutrophil cytoplasmic antibody-associated vasculitis; AAV, ANCA-associated vasculitis; VVV, Variable vessel vasculitis; SOV, Single-organ vasculitis; GCA, Giant cell arteritis; PAN, polyarteritis nodosa; KD, Kawasaki disease; MPA, microscopic polyangiitis; GPA, granulomatous with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; GBM, glomerular basement membrane; CV, cryoglobulinemic vasculitis; BD, Bechet's disease; HCV, hepatitis C virus; HBV, hepatitis B virus; PEX, plasma exchange; DFPP, double filtration plasmapheresis; CY, cyclophosphamide; RTX, rituximab; ASFA, The American Society for Apheresis; ACR, America College of Rheumatology; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; aHUS, atypical hemolytic uremic syndrome; APS, antiphospholipid syndrome; KDIGO, kidney disease: improving global outcomes; RA, rheumatoid arthritis; ESKD, end-stage kidney disease.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Therapeutic Apheresis and Dialysis* published by John Wiley & Sons Australia, Ltd on behalf of International Society for Apheresis and Japanese Society for Apheresis.

show a trend toward efficacy may possibly include treatment-sensitive subgroups. Further analysis is expected in the future.

#### KEYWORDS

ANCA-associated vasculitis, plasma exchange, plasmapheresis, systemic vasculitis

## 1 | INTRODUCTION

Systemic vascular syndromes (SV) include a variety of, and numerous diseases. In 2012, the International CHAPEL HILL Consensus Conference (*CHCC2012*) led to a major reorganization of the classification of vasculitis, and this is still in wide use today. According to this classification, vasculitis is classified as “large vessel vasculitis (LVV)”, “medium vessel vasculitis (MVV)”, “small vessel vasculitis (SVV)”, “variable vessels vasculitis (VVV)”, “single-organ vasculitis (SOV)”, “vasculitis-associated with systemic disease”, and “vasculitis associated with probable etiology” (Table 1) [1]. Each disease group includes multiple diseases, with varying etiologies and pathologies, and correspondingly, varying treatments. In most cases, glucocorticoids (GC) are administered, with additional immunosuppressive agents as support. On the other hand, plasmapheresis has been shown to be effective in some vasculitis but has also been shown to be ineffective in others (Table 2). [The details of the grades are appended in Table 3.] In general, the usefulness of plasmapheresis is the etiological molecule is abundantly distributed in the blood flow, and mainly demonstrated when the target molecule is a high molecular weight (molecular weight of 10 000 or more, mass of 60 kDa or more), having slow rate of production and degradation [2]. The most common molecules that fit for this characteristic, are  $\gamma$ -globulin (*m.w.* 10 000–100 000; for example, IgG has a daily production rate of 7%, a half-life of 22 days, and an intravascular distribution of 44–70%), complement (*m.w.* 100 000–400 000), and coagulation factors (several hundred kDa), which have been expected to be particularly effective in vasculitis, in which these factors are the etiological agents.

This review will discuss the latest findings on plasmapheresis for systemic vasculitis along with *CHCC2012*.

### 1.1 | Large vessel vasculitis

The major disorders of LVV include Takayasu's arteritis and giant cell arteritis. In these vasculitides, the lesions are localized in the aorta or its major branches, resulting in a systemic inflammatory reaction and, in advanced cases, stenosis in the affected vessels, leading to ischemic symptoms in the corresponding areas. Although the

mechanisms involved in the pathogenesis are not completely clear, it is thought that the pathological changes of these large vasculitis begin in the adventitia, and in the early stages, a large number of activated T cells are found mainly in the adventitia of the arteries, eventually damaging the smooth muscle tissue [4]. Even though, it has been suggested that some putative antigen leads the inflammation targeting the adventitia, there are few data showing the efficacy of plasmapheresis against these LVV. The reason for this is thought to be that these antigens are present locally in the tissues but are not abundant in the serum. As mentioned in the principle of efficacy, plasmapheresis requires a high concentration of the disease-causing macromolecules in the blood vessels to be effective [2]. CD4<sup>+</sup> T cells secrete interferon-gamma (IFN- $\gamma$ ), and inflammatory T cells stimulate macrophages, which in turn stimulate macrophages in the vessel wall to produce a series of inflammatory mediators, including matrix metalloproteinases (MMPs) and platelet-derived growth factor (PDGFs), and to secrete interleukin-6 (IL-6). Therefore, GC and tocilizumab are used to treat this disease [4].

### 1.2 | Small vessel vasculitis

This category is divided into two main groups: “immune complex SVV” and “Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).” In particular, plasmapheresis is often conducted and has been shown to be effective in immune complex SVV.

## 2 | IMMUNE COMPLEX SVV

Among immune complex SVV, the disease that is most likely to benefit from plasmapheresis is anti-glomerular basement membrane (GBM) antibody nephritis and/or Goodpasture syndrome, which PEX is almost inevitable when treating these diseases. In this disease, when type IV collagen in the dense layer of the lung basement membrane is damaged by infection or inhalation toxicants, the basement membrane is disrupted, and anti-GBM antibodies against the NC domain (NC-1) of type IV collagen are subsequently produced, which are deposited in

TABLE 1 Classification of vasculitis CHCC2012

CHCC2012 vasculitis category and name [1]
Large vessel vasculitis, LVV
Takayasu arteritis, TAK
Giant cell arteritis, GCA
Medium vessel vasculitis, MVV
Polyarteritis nodosa, PAN
Kawasaki disease, KD
Small vessel vasculitis, SVV
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, AAV
Microscopic polyangiitis, MPA
Granulomatosis with polyangiitis (Wegener's), GPA
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss),
Immune complex SVV
Anti-glomerular basement membrane (anti-GBM) disease
Cryoglobulinemic vasculitis, CV
IgA vasculitis (Henoch-Schönlein), IgAV
Hypocomplementemic urticarial vasculitis, HUV (anti-C1q vasculitis)
Variable vessel vasculitis, (VVV)
Beçhet's disease, BD
Cogan's syndrome, CS
Single-organ vasculitis, SOV
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Vasculitis associated with probable etiology
Hepatitis C virus-associated cryoglobulinemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis

Note: CHCCC2012, 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.

the glomerular basement membrane with same antigenicity via the blood flow resulting in marked crescentic nephritis. When alveolar hemorrhage also occurs, it is

called Goodpasture's syndrome, and when rapid progressive glomerulonephritis (RPGN) occurs but is confined to the kidney, it is called anti-GBM antibody nephritis, and these diseases are collectively known as anti-GBM antibody diseases. The typical renal pathology and pulmonary imaging that we have experienced are shown in Figure 1. The renal prognosis of this disease is extremely poor compared with other RPGN diseases, with most patients requiring hemodialysis at the time of diagnosis or hospitalization, and the renal survival rate after 1 year of emergency dialysis is reported to be only 8%. Furthermore, while the prognosis of renal and life expectancy of patients with AAV, which is the most common disorder of vasculitis, has been improving in recent data, the prognosis of patients with anti-GBM antibody disease has not improved, obviously [5, 6]. Anti-GBM antibody can be extremely harmful, and therefore, PEX is important to remove it from patient's serum as first line treatment [7]. High-dose glucocorticoid therapy with pulse therapy and cytotoxic immune-suppressor (cyclophosphamide) used in its early phase to inhibit the production of anti-GBM antibody has been shown to improve renal prognosis and life expectancy when combined with PEX (renal function prognosis, HR 0.60,  $p = 0.032$ , life expectancy HR 0.31,  $p = 0.001$ ) [8]. The procedure of PEX varies from countries and from guidelines, but considering the harmful effects of anti-GBM antibody, it should be continued daily while monitoring the serum concentration of anti-GBM antibodies, ideally until the anti-GBM antibody disappear from the serum. In our experience, it takes about 1 month for anti-GBM antibodies to disappear from the serum, and during this period, even if PEX is performed, the anti-GBM antibody increase the next day (Figure 2). Anti-GBM disease is usually "a one-hit phenomenon", and once the anti-GBM antibody has disappeared from the serum, it does not rise again. In successfully treated patients, renal function and urinary abnormalities improve as the antibody titer decreases (Figure 2). The Japanese guidelines also indicate that these treatments are often ineffective in patients with serum Cr above 6.0 mg/dl [9]. Given this situation, the 2021 KDIGO guidelines recommend that "glucocorticoids and plasmapheresis should be initiated as soon as possible (within 24 h)" and that "high-dose glucocorticoids and plasmapheresis should be initiated before the return of anti-GBM antibody data" when the disease is suspected [10]. Based on this principle, it can be assumed that the initiation of PEX should be considered as early as possible in anti-GBM disease [7].

Immune complex SVV also includes cryoglobulin vasculitis. Cryoglobulins are immunoglobulin-related proteins that cause intravascular coagulation at low temperatures. Cryoglobulins are classified into three types

TABLE 2 ASFA category and grade in classification of CHCC2012

Category description and recommendation grade of systemic vasculitides in ASFA guideline [2, 3]						
Disease	Indication	Modality	Category	Grade		
Medium vessel vasculitis, MVV						
Polyarteritis nodosa, PAN		TPE	IV	1B		
Small vessel vasculitis, SVV						
ANCA-associated vasculitis, AAV <sup>a</sup>						
Microscopic polyangiitis, MPA	AAV	MPA/GPA/RLV: RPGN, Cr $\geq$ 5.7 mg/dl <sup>b</sup>	TPE	II	1B	
Granulomatosis with polyangiitis (Wegener's), GPA		MPA/GPA/RLV: RPGN, Cr < 5.7 mg/dl <sup>b</sup>		III	2C	
		MPA/GPA/RLV: DAH		I	1C	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	EGPA			III	2C	
Immune complex SVV						
Anti-glomerular basement membrane (anti-GBM) disease	DAH		TPE	I	1C	
		Dialysis-independence		TPE	I	1B
		Dialysis-dependence, no DAH		TPE	III	2B
Cryoglobulinemic vasculitis, CV		Severe/Symptomatic		TPE	II	2A
		Severe/Symptomatic		IA	II	2B
IgA vasculitis (Henoch-Schönlein), IgAV		Crescentic RPGN		TPE	III	2C
		Several extrarenal manifestations		TPE	III	2C
Variable vessel vasculitis, (VVV)						
Behcet's disease, BD			Adsorptive cytapheresis	II	IC	
Cogan's syndrome, CS			TPE	III	2C	
Single-organ vasculitis, SOV						
Vasculitis associated with systemic disease						
Lupus vasculitis		Severe complication		TPE	II	2C
		Catastrophic APS		TPE	I	2C
	TMA	Factor H autoantibody		TPE	I	2C
		Complement factor gene mutation			III	2C
		TTP			I	1A
Vasculitis associated with probable etiology						
Hepatitis C virus-associated cryoglobulinemic vasculitis						
Hepatitis B virus-associated vasculitis			TPE	II	2C	

Note: Category definitions for therapeutic apheresis: Category I, Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Category II, Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. Category III, Optimum role of apheresis therapy is not established. Decision making should be individualized. Category IV, Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB (institutional review board) approval is desirable if apheresis treatment is undertaken in these circumstances.

Abbreviations: APS, anti-phospholipid syndrome; Cr, serum creatinine; DAH, diffuse alveolar hemorrhage; RLV, renal limited vasculitis; RPGN, rapidly progressive glomerulonephritis; TTP, thrombotic thrombocytopenic purpura; TPE, therapeutic plasma exchange.

<sup>a</sup>Cr thresholds for renal function at presentation adopted from Yates, 2016.

<sup>b</sup>Reflects the 2020 update to ASFA 2019 Guideline.

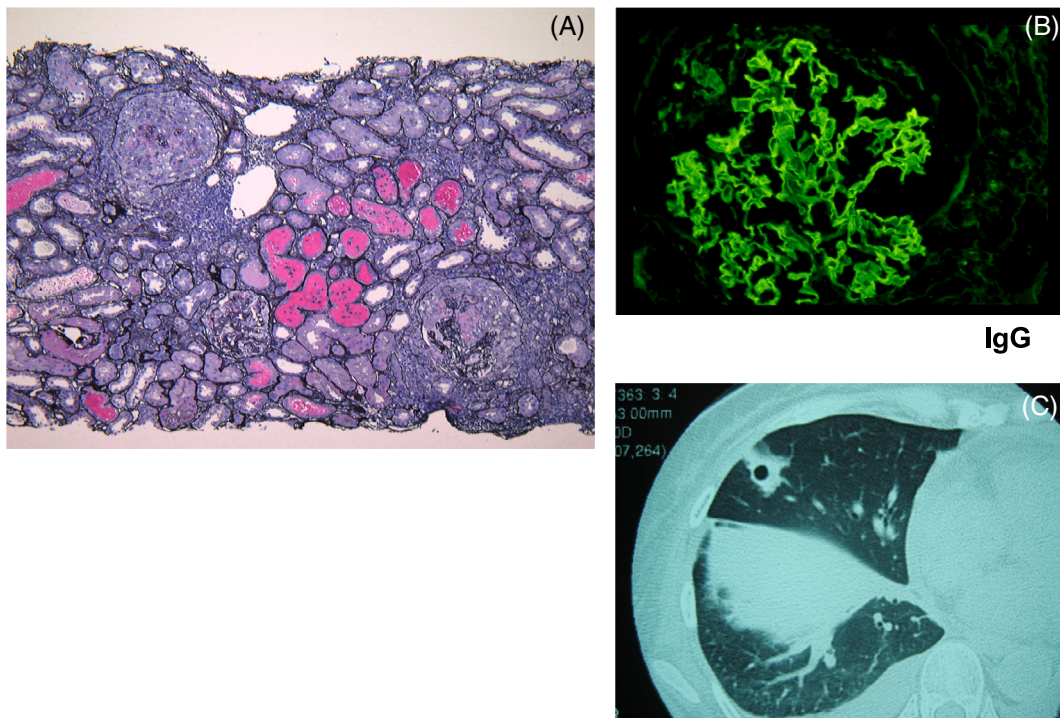
TABLE 3 Category description and recommendation grade of vasculitides in ASFA guideline

Recommendation	Description	Methodological quality of supporting evidence	Implication
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCT with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Weak recommendation, low quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or social values
Grade 2B	Weak recommendation, moderate quality evidence	RCYs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, but action may differ depending on circumstances or patients' or social values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

according to the components of the increased gamma globulin (Table 4). Type I (10%) is caused by B-cell lymphoproliferative disease, Type II (65%) by monoclonal immunoglobulins (IgM $\kappa$ ) and polyclonal immunoglobulins (IgG), and Type III (65%) by polyclonal immunoglobulins (IgM) and polyclonal immunoglobulins (IgG) [11]. Patients with cryoglobulin vasculitis present clinically with purpura, hyperpigmentation, and occasionally ulceration of the skin, and histopathology shows leukocytoclastic vasculitis. In the kidneys, RPGN is often shown, with a membranous proliferative glomerulonephritis (MPGN) pattern on histopathology and deposition of amorphous hyaline-like material in the glomerular capillaries (sub-endothelium) on PAS staining. There are no large-scale prospective studies of cryoglobulinemia, and the level of evidence is not entirely high, but the plasmapheresis is considered to be effective in the pathogenesis of this disease [12]. In the Italian Group for the Study of Cryoglobulinemia (GISC), PEX was used in 84% of patients and in the majority (87%) in combination with cytotoxic immunosuppressive drugs, especially for the treatment of life-threatening serious complications (renal failure, neuropathy, and hyper-viscosity

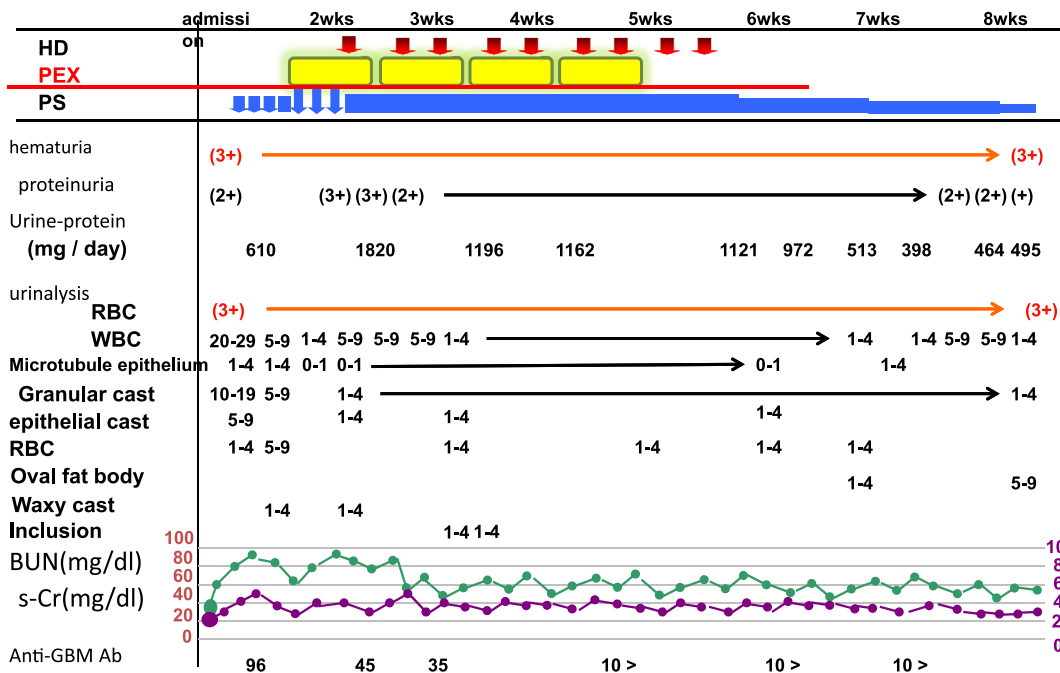
syndrome) [13]. Single PEX and double filtration plasmapheresis (DFPP) could be the best approaches. Immune-absorption therapy has also been shown to be useful [12].

IgA vasculitis is a type of vasculitis with three main features: abdominal pain, arthralgia, and purpura, sometimes accompanied by renal involvement. In particular, patients with IgA nephropathy have a carbohydrate chain that lacks galactose between the constant-region domains 1 and 2 of IgA1, and when its concentration in the serum increases due to infection and so on, it is recognized by anti-glycan antibodies (IgA or IgG) in the serum, and circulating immune complexes could be formed [14]. It has been shown that some of these immune complexes are deposited in the kidneys and blood vessels, causing vasculitis. Hattori et al. reported a retrospective study of early PEX (three with glucocorticoids) in nine patients, and Shenoy et al. reported a retrospective study of early PEX (three with glucocorticoids) in nine patients with RPGN of International Study of Kidney Disease in Children (ISKDC) grade 3 or higher, and reported the effect of PEX, all with favorable results [15, 16]. Thus, the efficacy of plasmapheresis for immune



**FIGURE 1** Imaging and renal pathology of Goodpasture syndrome. (A) Renal tissue (PAS staining). Glomeruli show a circumferential crescentic body with marked cellular infiltration in the periglomerular interstitium. (B) Glomerular staining by immunofluorescent antibody. Linear deposits of IgG are seen along the walls of glomerular capillary vessels. (C) CT findings of the lung. Pleural effusion was seen in interlobular and subpleural areas, and infiltrative shadows with cavities were shown in this right median lobe in lung

### Clinical Course of Anti-GBM disease (our case)



**FIGURE 2** Clinical course of anti-GBM disease we experienced. Serum anti-GBM antibodies were re-elevated daily, requiring daily plasma exchange therapy in addition to glucocorticoids. The anti-GBM antibody level disappeared from the serum after about 1 month, and the patient was able to discontinue maintenance hemodialysis after 5 weeks. The disappearance of serum anti-GBM antibody preceded the abnormal blood and urine findings. BUN, blood urea nitrate; HD, Hemodialysis; GC, glucocorticoid; PEX, plasma exchange; s-Cr, serum creatinine; wks, weeks

TABLE 4 Classification of cryoglobulinemia

Classification of Cryoglobulinemia [11]			
Types	Prevalence	Composition	Main associated or underlying disease
Type I	10%	Monoclonal Ig (IgM > IgG > IgA)	B cell lymphoproliferative disease, plasma cell dyscrasia, multiple myeloma, Waldenstrom macroglobulinemia, MGUS, chronic lymphocytic leukemia, B cell non-Hodgkin lymphoma and hairy cell leukemia
Type II	65%	Monoclonal Ig (IgM $\kappa$ ) + Polyclonal Ig	Chronic infections [HCV(80–90%) and other infection such as HBV], B cell lymphoproliferative diseases, autoimmune diseases, essential, mixed cryoglobulinemia
Type III	25%	Polyclonal IgM + polyclonal IgG	
Type II–III		Oligoclonal IgM + polyclonal IgG	HCV and other infections, autoimmune disease and lymphoproliferative disease

complex SVV has been highly evaluated, and it has been placed as the first line treatment for anti-GBM disease in the ASFA guidelines [3]. However, cryoglobulin is considered as a second line and IgA vasculitis as a treatment option, and this is due to the fact that it has not been proven by RCTs, which may be an issue for the future.

### 3 | ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)-ASSOCIATED VASCULITIS (AAV)

This category includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

For the treatment of MPA and GPA, after diagnosis and evaluation of organ damage, treatment with GC and cyclophosphamide (CY) is initiated as a standard therapy for remission induction [17]. Rituximab (RTX) may be used instead of CY if RTX treatment is deemed appropriate. Treatment with methotrexate or mycophenolate mofetil (MMF) may be used in the absence of severe organ involvement and minimal renal dysfunction. Plasmapheresis should be considered in patients with severe renal involvement or high risk of adverse effects. The effectiveness of plasmapheresis in the treatment of AAV was supported by the Randomized Trial of Plasma Exchange or High-Dose Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis (MEPEX) study reported in 2007 [18]. This study prospectively compared 137 patients with severe RPGN with serum Cr levels higher than 5.8 mg/dl (500  $\mu$ mol/L) who were randomized to receive steroid pulse therapy with ( $n = 67$ ) or without ( $n = 70$ ) PEX (43% vs. 19%, 95% confidence interval 18 to 35%,  $p = 0.02$ ). The results showed that,

although there was no statistical significance in mortality, there was significantly less initiation of dialysis at 3 months in the PEX group (95% CI 6.1 to 41%). There was also no difference in the incidence of severe adverse events at 1 year between 32 of 67 patients (48%) and 35 of 70 patients (50%). However, it was subsequently reported that the effect of PEX shown in MEPEX was not different in the long term (median 4 years) regarding both dialysis initiation and mortality [19]. After the MEPEX study, Walter et al. reported a meta-analysis of five randomized trials in 2019 that showed PEX reduced the incidence of end-stage kidney disease (ESKD) requiring hemodialysis at 3, 6, and 12 months [20]. In addition, Walsh et al. also performed a meta-analysis of nine RCTs and reported that PEX reduced ESKD and mortality [21]. The results of MEPEX were largely responsible for these data. However, in 2020, the results of the PEXIVAS trial, which included more than 300 patients with severe AAV (eGFR < 50 ml/min/1.73  $\text{m}^2$  or) and pulmonary bleeding, were reported [22]. The patients were randomized to PEX or non-PEX after standard treatment with RTX or CY. This was a 2  $\times$  2 study to evaluate the therapeutic efficacy of PEX as well as to compare outcomes between the low- and high-dose GC groups. For the mortality and renal death (ESKD requiring replacement therapy or pulmonary hemorrhage) outcomes estimated in this trial, death or ESKD from any cause occurred in 100 of 352 patients (28.4%) in the PEX group and 109 of 352 patients (31.0%) in the control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.65–1.13;  $P = 0.27$ ). The results also showed that the low-dose GC group was as effective as the regular-dose GC group, with fewer serious adverse events. The authors concluded that “the current trial did not show that the addition of PEX to standard therapy conferred benefits in patients with

severe AAV”, and the results of PEXIVAS study did not show a preferred effect, reversing the previous finding that plasmapheresis could prevent kidney death in the short term. In response to these results, the ASFA guidelines, which are usually updated every 3 years, reported an update in 2020, even though the 8th edition was published in 2019. In this update, PEX for RPGN ( $\text{Cr} \geq 5.7 \text{ mg/dl}$ ) in AAV was changed from Category I in first line to Category II in second line [23]. However, it was added that the change to Category II was not interpreted as adding PEX to first-line treatment failure, but as a concomitant therapy from the time of initial introduction. This is because all previous studies demonstrating a benefit from PEX used as part of the initial induction therapy. In addition, the level of evidence was changed from grade 1A to 1B. This change in the level of evidence reflected the “limitations” of the PEXIVAS study [22]. In PEXIVAS trial, kidney biopsy was not performed to define the severity of the disease. In addition, because of the long follow-up period, the study was not limited to first-time visiting patients, and thus did not detect an improvement in patients without irreversible renal damage. The authors also pointed out that the confidence intervals for the outcomes were wide and may have been statistically underpowered to detect differences between subgroups. In fact, although there was no statistical significance in patients older than 60 years, with serum creatinine  $5.6 \text{ mg/dl}$  or higher, or those with alveolar hemorrhage, but all cases showed a trend toward a smaller hazard ratio (HR [95% CI];  $0.75 [0.54, 1.04]$ ,  $0.77 [0.53, 1.11]$ , and  $0.64 [0.33, 1.24]$ , respectively). Furthermore, “the 2021 American College of Rheumatology (ACR)/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis” noted that integrating data from four studies, including MEPEX and PEXIVAS, may reduce ESKD risk (HR  $0.72 [0.53, 0.98]$ ) [24]. On the other hand, it was also confirmed that the risk of severe infection was higher treating with PEX (risk ratio  $1.19 [95\% \text{ CI } 0.99\text{--}1.42]$ , moderate certainly), and if the risk of progression to ESKD outweighed the disadvantages of infection, the combination of PEX should be chosen. Meanwhile, the study that evaluated PEX for patients with diffuse alveolar hemorrhage (DAH) noted that its efficacy in patients with alveolar hemorrhage has not been established because there was no difference in mortality or remission rates. Although the PEXIVAS trial published a negative conclusion, PEX in AAV has been finally kept in the position as a “salvage” or “rescue” treatment for some patients with active glomerulonephritis or severe disease who do not respond to the recommended remission induction therapy. Furthermore, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for 2021 have been published,

which state that PEX remain in the treatment algorithm and described as “Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of RTX if CY induction had been used previously or vice versa, plasmapheresis can be considered” [10]. The guideline also states that DAH with hypoxia should be considered for use in addition to other immunosuppressive therapies (steroids plus CY or RTX). As these guidelines indicate, PEX has been recognized as an option that has shown some efficacy in the treatment of AAV. An excerpt of evaluation of plasmapheresis for AAV treatment in the recently presented guidelines is shown in Table 5. At our hospital, we experienced a GPA case that responded to treatment with PEX for, who had failed to achieve remission after long-term treatment with multiple combinations of immunosuppressant (Figure 3). This case was refractory to treat, because a number of complications including SIADH, kidney insufficiency, methotrexate-associated lymphoproliferative disorders (MTX-LPD), and pulmonary tuberculosis after prolonged and massive immunosuppressive therapy. As a matter of course, there is a need to be concerned about catheter infection, but PEX is not a direct immunosuppressive therapy and can be administered relatively safely to vulnerable patients. In order to identify the subgroup of AAVs for which PEX is particularly effective, we studied 11 patients treated with PEX at our hospital over the past 10 years. These patients were characterized by high pre-treatment ANCA levels, and when ANCA levels were lowered after PEX, Birmingham vasculitis activity score (BVAS) also tended to decrease along with them. The correlation coefficient was  $0.716 (p = 0.046)$  at 1 month after the start of treatment,  $0.630 (p = 0.033)$  at 3 months, and  $0.484 (p = 0.092)$  at 12 months. For the definition of cut-off value, we attempted to analyze the relationship between ANCA levels and BVAS improvement rate by ROC curve, but the AUC was  $0.533$  with low accuracy.

To explain the therapeutic effect of PEX on AAV, some serum molecules which are removed by PEX (including ANCA) should be associated with disease activity, but so far it is vague. Xiao et al. used a model of renal crescent formation in mice administrated with mouse MPO-IgG, and found that C6 knockout mice, which produce complement attack complex (MAC), mice with knockout of C5aL, which is the other receptor of C5a, and mice with replacement of human C5aR did not suppress crescent formation, whereas C5a R receptor knockout mice suppressed crescent formation to 1%. Then, the clinical symptoms of nephritis were significantly suppressed in wild-type mice treated with anti-CD5a antibody [25]. This suggests that the complement system is involved in ANCA, and that neutrophil activation by C5a is involved in the progression of the disease. These findings led to the ADOVOCATE study, a randomized placebo-controlled



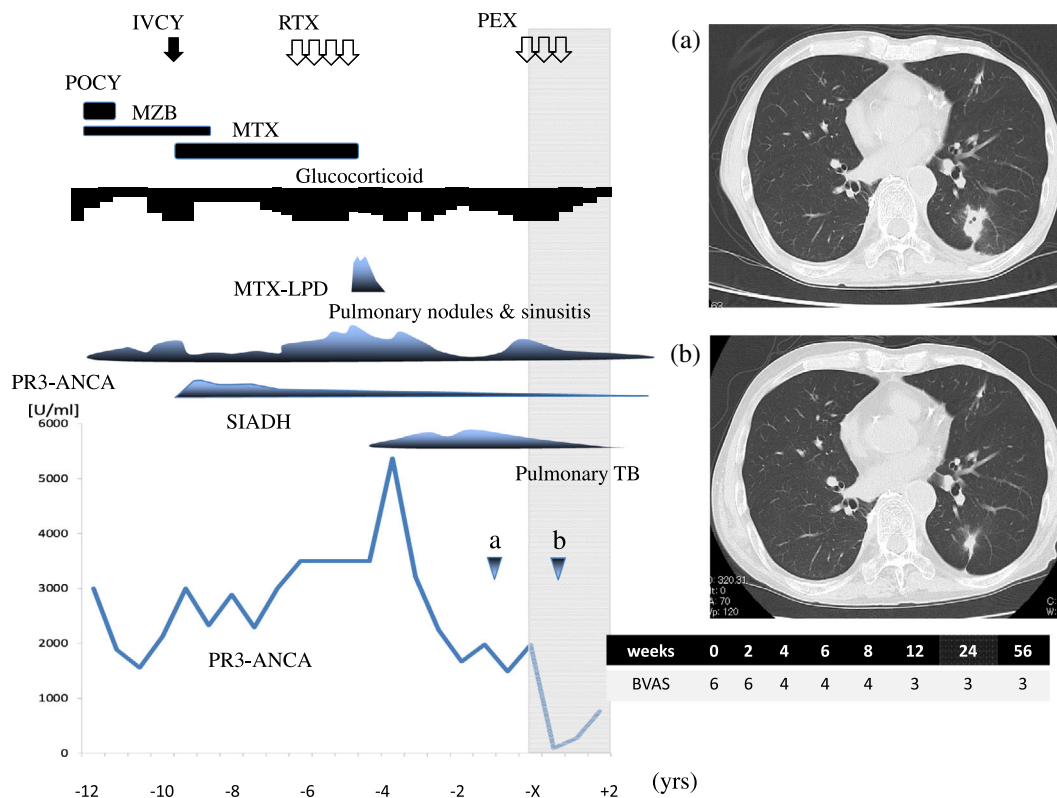
TABLE 5 Evaluation of plasmapheresis for AAV treatment in the recently published guidelines

Evaluation of plasmapheresis for AAV treatment in the recently published guidelines [2, 3, 10, 23, 24]			
Guidelines	Organization	Year	Excerpt from guideline
Guidelines on the Use of Therapeutic Apheresis in Clinical Practice -Evidence-Based Approach from the Writing Committee of the American Society for Apheresis	The American Society for Apheresis (ASFA)	2019	PEXIVAS failed to show a benefit of TPE, it does not exclude a clinically useful benefit in further sub-analyses. Editorial deadline of this fact sheet was before the full publication and meta-analysis of data with previous studies were available, which might necessitate future modification of recommendations.
Update to the ASFA guidelines on the use of therapeutic apheresis in ANCA-associated vasculitis		2021	In cases of biopsy proven RPGN with acute glomerular inflammation and/or fibrinoid necrosis, crescents, with minimal fibrosis (chronic damage) and a fulminant clinical course (Cr $\geq$ 5.7 mg/dL or DAH), immediate multimodal immunosuppression, including prompt initiation of TPE, to prevent irreversible changes are reasonable.
2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis	American College of Rheumatology (ACR)/Vasculitis Foundation	2021	Therefore, the Voting Panel does not recommend plasma exchange for all patients with active glomerulonephritis but favors consideration of the treatment for patients at a higher risk of progression to ESRD.
Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. "KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.	Kidney Disease: Improving Global Outcomes (KDIGO)	2021	Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered (9.4.1. refractory disease). In the absence of hypoxemia, diffuse alveolar hemorrhage has a benign prognosis and responds as extrapulmonary disease is controlled. Alveolar hemorrhage with hypoxemia has a high early mortality risk, and plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab (Practice Point 9.4.1.2).

trial of avacopan (CCX168), a selective C5a receptor inhibitor, in adult AAV [26]. The results showed that avacopan significantly reduced relapses at 12 weeks and was an effective alternative to high-dose GC [HR for relapse 0.46 (95% CI, 0.25–0.84)]. C5a is also increased in various acute inflammatory diseases [27], and the effect of PEX with AAV may be related to the removal and normalization of complement components including C5a.

### 3.1 | Medium vessel vasculitis

This category includes classical polyarteritis nodosa (PAN) and Kawasaki disease (KD). Guillemin et al. conducted three RCTs in patients with both PAN and EGPA and reported that all data showed no advantage of PEX over conventional therapy without PEX [28–30]. According to ASFA guidelines 2019, apheresis for HBV unrelated PAN is



**FIGURE 3** Clinical course of a plasmapheresis-responsive case of GPA experienced at our hospital. We experienced a case of GPA that could not improve despite long-term treatment with a combination of immunosuppressant, but achieved improvement after treatment with PEX. The activity of vasculitis assessed by Birmingham vasculitis activity score (BVAS) after the beginning plasma exchange also showed improvement. This case was difficult to treat because of severe multiple complications such as SIADH, renal failure, MTX-LPD, and pulmonary tuberculosis after long-term high-dose immunosuppressive administration. (A) Chest-CT imaging before plasmapheresis. A nodular shadow with a cavity in the left lung field had seen. (B) Two months after the beginning of plasmapheresis. The nodular lesion improvement has seen. BVAS, Birmingham vasculitis activity score; IVCY, venus infusion cyclophosphamide; MTX, methotrexate; MZB, mizoribine; PEX, plasma exchange; POCY, cyclophosphamide per os; RTX, rituximab; SIADH, the syndrome of inappropriate antidiuretic hormone secretion; TB, tuberculosis;

**TABLE 6** Outcome of plasmapheresis treatment of KD

Plasmapheresis in KD [31–35]					
Author	Year	Design	Number of cases	Outcome	Remarks
Mori et al. [32]	2008	Retrospective	130	PE vs. without PE, OR 0.052, $p = 0.012$	Nippon Rinsho [Japanese]
Hokosaki et al. [31]	2011	Retrospective	125	Onset < 9 days-97.2%CR> 10 days-85% CR, 100% CR if coronary arteries were normal at the time PE was initiated	Pediatrics International
Imagawa et al. [33]	2004	Retrospective	27	PE vs. without PE, OR 0.041, $p = 0.0004$	Eur J Pediatr.
Takagi et al. [34]	1995	Case report	1	CR	The Lancet
Harada et al. [35]	2008	Case report	2	CR	Ther Apher Dial

Abbreviations: KD, Kawasaki disease, OR, odds ratio, PE, plasma exchange.

indicated as category IV; “Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Institutional Review Board (IRB) approval is desirable if apheresis treatment is undertaken in these circumstances” [3]. It should be noted that HBV-related PAN is positioned as a second-line treatment in Category II (Table 6). HBV-related PAN is discussed in detail in the section on “Vasculitis associated with probable etiology.”

On the other hand, PEX in the KD has known to inhibit coronary artery progression in patients with IVIG refractory disease, and early intervention in particular has been shown to improve coronary artery dilation and coronary aneurysms [31]. As for the reason of plasmapheresis efficacy in KD, the report by Noval et al. is informative. They described that serum IgA elevation in the acute phase of Kawasaki disease leads to decreased intestinal tightness due to decreased intestinal function, causing an overflow of serum IgA and cellular infiltration of IgA, C3, and IgA-positive cells into the vessel wall [36]. The removing of these molecules might be responsible for the inhibitory effect of PEX on coronary artery progression in refractory KD. The reported plasmapheresis results for non-HBV related-PAN and HBV-related PAN, and KD are shown in Table 6 [31–35].

### 3.2 | Variable vessel vasculitis

This includes Bechet's disease (BD) and Cogan's syndrome. In BD, inflammation of the venous system, most commonly thrombophlebitis (superficial veins), is common, but inflammation of the medium to large arteries, suggestive of Takayasu's disease or GCA, is not so frequent. Therapeutic PEX is recommended for BD's vasculitis in the ASFA guidelines as category II (second line) [37]. Its efficacy is based on the removal of pro-inflammatory cytokines and putative immune complexes, but these have not been verified. No RCTs have been conducted due to the small number of cases, and the results of case reports and case series have shown the efficacy of PEX, but they were mostly concentrated in the 1970s, and it is considered to be an option for the treatment of severe cases.

No data on the efficacy of plasmapheresis for Cogan's syndrome was found in our search.

### 3.3 | Vasculitis associated with systemic disease

This category includes lupus vasculitis, rheumatoid vasculitis, and sarcoid vasculitis.

In systemic erythematosus (SLE), a variety of vasculitis has been shown to be present, mainly in medium to

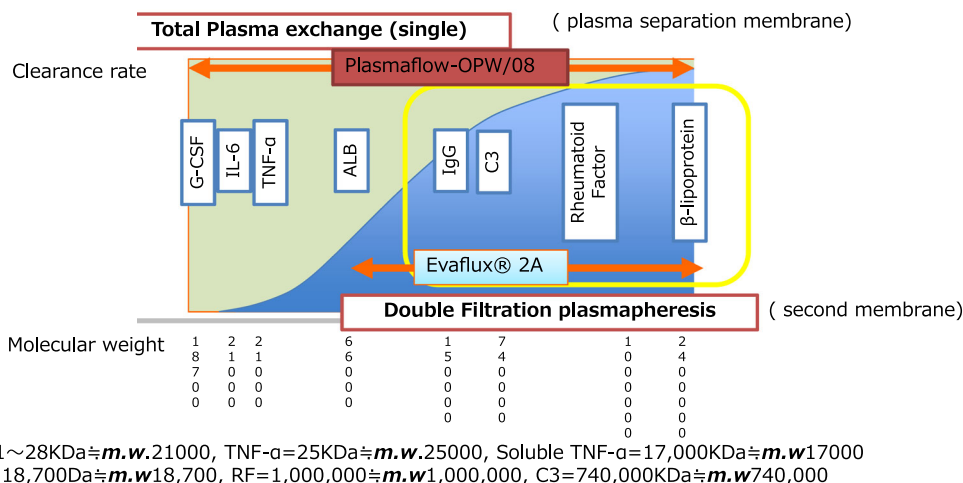
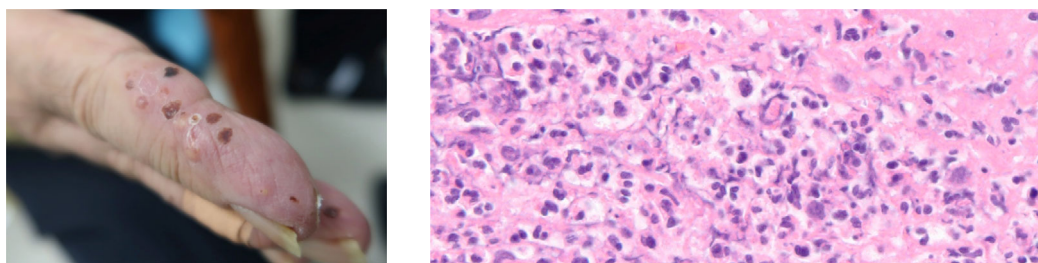
small sized vessels, with a diversity of symptoms [38]. In addition to SLE-specific vasculitis, cryoglobulin vasculitis and urticarial vasculitis are also shown. Medium-sized vasculitis of the abdominal arteries has also known to cause some parts of intestinal involvement. In SLE, plasmapheresis is sometimes attempted in the case of severe disease. Especially, the patients complicated with thrombotic microangiopathy (TMA), and catastrophic antiphospholipid antibody syndrome (APS) should be considered to perform combined therapy with PEX. In some cases of SLE, who develop thrombocytopenic purpura (TTP) due to autoantibodies, and rarely, atypical hemolytic uremic syndrome (aHUS) due to deficiency of complement regulatory factors. KDIGO guidelines also recommended plasmapheresis for low a disintegrin-like and metalloprotease with thrombospondin type 1 motifs (ADAMTS13) (i.e., TTP) and normal ADAMTS13 with positive antiphospholipid antibodies in the algorithm for lupus nephritis associated with TMA. Treatment with eculizumab, a recombinant humanized monoclonal antibody against the complement protein C5, is recommended for patients with aHUS, but treatment with PEX may also be tried before a definitive diagnosis is made, because of its transient effect [10].

Rheumatoid vasculitis (RV) is considered to be an immune complex type of vasculitis due to the high blood levels of rheumatoid factor and low complement. Patients with RV sometimes cause small-sized vasculitides such as skin ulcers and eruptions, and medium-sized arteritis such as coronary and mesenteric artery stenosis. Treatment with disease-modifying anti-rheumatic drugs (DMARDs) or GCs combined with plasma exchange may be effective, probably because it can remove the gamma globulin and normalize the complement component. DFPP may be sufficient to improve the vascular symptoms, since the target molecules are assumed to be in the gamma globulin fraction, but IL-6 and TNF- $\alpha$ , which drive arthritis of rheumatoid arthritis, can easily pass through secondary membranes such as Evaflux<sup>®</sup>, suggesting that DFPP may not be effective in improving joint symptoms than total PEX [39] (Figure 4).

The results of plasmapheresis for sarcoid vasculitis have not been shown.

### 3.4 | Vasculitis associated with probable etiology

This includes hepatitis C virus-associated cryoglobulinemic vasculitis, hepatitis B virus-associated vasculitis, Syphilis-associated aortitis, Drug-associated immune complex vasculitis, drug-associated ANCA-associated vasculitis, and cancer-associated vasculitis. In addition to antiviral



**FIGURE 4** Upper: Skin lesions on the fingers shown in the patient with rheumatoid vasculitis. Hematopoietic bullae were present on the fingertips (left), and biopsy of the same area showed remarked leukocytoclastic vasculitis (right). Bottom: Differences in filtration characteristics between TPE and DFPP plasmapheresis: DFPP removes mainly the gamma-globulin fraction, which is the etiologic agent of vasculitis, while the inflammatory cytokines that cause arthritis may pass through the secondary membrane and be returned to the body. DFPP, double filtration plasmapheresis

**TABLE 7** Outcome of plasmapheresis treatment of non-HBV-associated PAN and HBV-related PAN

Plasmapheresis in PAN and EGPA [28–30, 40–43]						
Hepatitis B virus infection						
infection	Author	Year	Design	n	Outcome	Remarks
Unrelated	Guillevin L. et al. [28]	1992	RCT multicentric	36	No significant difference compared with PSL alone	Arthritis Rheum
	Guillevin L. et al. [29]	1997	RCT	140	No significance	Ann Med Interne
	Guillevin L. et al. [30]	1995	RCT multicentric	62	Combined PSL+CY+PE is not superior to PSL+CY	Arthritis Rheum
Related	Guillevin L. et al. [40]	1993	Prospective multicentric	33	Vira A+PEX effectiveness 51%, 78.8% survival rate (7yrs)	J Rheum
	Guillevin L. et al. [41]	1994	Prospective multicentric	6	Vasculitis improved in all patients, seroconversion 66.6%.	Ann Med Interne
	Guillevin L. et al. [42]	2004	Case series	10	3TC+PE; 9 survivors had achieved clinical recovery and by 9 months, 6 of 9 (66%) had seroconverted.	Arthritis Rheum
	Filer A. et al. [43]	2001	Case report	1	3TC alone had an effect on vasculitis.	Rheumatology

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; HBV, hepatitis B virus infection, KD, Kawasaki disease; PAN, polyarteritis nodosum.

therapy, the efficacy of plasmapheresis in hepatitis C vasculitis is in accordance with that of cryoglobulins in immune complex vasculitis [13]. In primary PAN, plasmapheresis has not been shown to be effective or even harmful, whereas in HBV-related PAN, the combination of plasmapheresis and antivirals has been shown to be effective (Table 7) [3]. Guillelevin et al. reported that interferon-2 $\alpha$  and lamivudine (3TC) in combination with PEX was more effective after short-term treatment with steroids for only 2 weeks due to concerns about the severity of HBV infection [40–42]. They showed therapeutic effects on both vasculitis and infection were favorable, and HBV seroconversion occurred within 6 months. Although 3TC is superior because it is equivalent, can be administered orally, and has fewer side effects, it has a risk of causing mutant disease if used for more than 6 months. But this combined procedure also shortens the duration of active disease and reduces the risk of mutation. Since some results suggest that antivirals alone are useful, the combination of antivirals and 3TC is recommended in patients with severe gastrointestinal and renal dysfunction, cardiovascular disease, and central nervous system symptoms [43]. The latest evidence would be desirable, but the report on which it is based dates back to 2004, and no new data have been presented.

## 4 | CONCLUSION

We discussed the effectiveness of plasmapheresis on SV for each classification of *CHCC2012*. SV is a group of diseases that includes a variety of pathologies, and unlike common disease, it is not easy to organize prospective clinical trials due to their rarities. In addition, plasmapheresis is often performed in combination with other therapies, making it difficult to obtain a high level of evidence for its own. However, the plasmapheresis could be expected as an optional therapy in cases where the target molecules related to the pathogenesis present in the serum, or where immunosuppressive agents are difficult to add due to serious organ damage such as liver or kidney damage. It is hoped that further accumulation of data will lead to the development of new evidence.

Written informed consent was obtained from the patient for publication of this review and any accompanying images.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Kazuhito Fukuoka wrote a draft with the help of Mitsumasa Kishimoto, Takahisa Kawakami, Yosinori Komagata, and Shinya Kaname reviewed the final version of the manuscript.

All authors read and approved the final version of the manuscripts.

## DATA AVAILABILITY STATEMENT

All data presented or analyzed data were obtained from Kyorin University Hospital are included in this published article.

## REFERENCES

- Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1–11.
- Moussi-Frances J, Sallee M, Jourde-Chiche N. Apheresis to treat systemic vasculitis. *Joint Bone Spine*. 2018;85(2):177–183.
- Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the writing Committee of the American Society for apheresis: the eighth special issue. *J Clin Apher*. 2019;34(3):171–354.
- Harky A, Fok M, Balmforth D, Bashir M. Pathogenesis of large vessel vasculitis: implications for disease classification and future therapies. *Vasc Med*. 2019;24(1):79–88.
- Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. *Clin Exp Nephrol*. 2009;13(6):633–50.
- Flores JC, Taube D, Savage CO, Cameron JS, Lockwood CM, Williams DG, et al. Clinical and immunological evolution of oligoanuric anti-GBM nephritis treated by haemodialysis. *Lancet*. 1986;1(8471):5–8.
- McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. *Clin J Am Soc Nephrol*. 2017;12(7):1162–72.
- Cui Z, Zhao J, Jia XY, Zhu SN, Jin QZ, Cheng XY, et al. Anti-glomerular basement membrane disease: outcomes of different therapeutic regimens in a large single-center Chinese cohort study. *Medicine (Baltimore)*. 2011;90(5):303–11.
- No Author. Japanese Society of Nephrology: [JSN and MHLW clinical practice guidelines for RPGN 2014]. *Nihon Jinzo Gakkai Shi*. 2015;57(1):139–232.
- No Author. Kidney Disease: Improving global outcomes glomerular diseases work G: KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1–S276.
- Roccatello D, Saadoun D, Ramos-Casals M, Tzioufas AG, Fervenza FC, Cacoub P, et al. Cryoglobulinaemia. *Nat Rev Dis Primers*. 2018;4(1):11.
- Stefanutti C, Vivencio A, Di Giacomo S, Labbadia G, Mazza F, D'Alessandri G, et al. Immunoabsorption apheresis and immunosuppressive drug therapy in the treatment of complicated HCV-related cryoglobulinemia. *J Clin Apher*. 2009;24(6):241–6.
- Pietrogrande M, De Vita S, Zignego AL, Pioltelli P, Sansonno D, Sollima S, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients. *Autoimmun Rev*. 2011;10(8):444–54.
- Suzuki H. Biomarkers for IgA nephropathy on the basis of multi-hit pathogenesis. *Clin Exp Nephrol*. 2019;23(1):26–31.
- Hattori M, Ito K, Konomoto T, Kawaguchi H, Yoshioka T, Khono M. Plasmapheresis as the sole therapy for rapidly



- progressive Henoch-Schonlein purpura nephritis in children. *Am J Kidney Dis.* 1999;33(3):427–33.
16. Shenoy M, Ognjanovic MV, Coulthard MG. Treating severe Henoch-Schonlein and IgA nephritis with plasmapheresis alone. *Pediatr Nephrol.* 2007;22(8):1167–71.
  17. Isobe M, Amano K, Arimura Y, Ishizu A, Ito S, Kaname S, et al. JCS 2017 guideline on management of vasculitis syndrome: digest version. *Circ J.* 2020;84(2):299–359.
  18. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol.* 2007;18(7):2180–8.
  19. Walsh M, Casian A, Flossmann O, Westman K, Högglund P, Pusey C, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int.* 2013;84(2):397–402.
  20. Walters GD, Willis NS, Craig JC. Interventions for renal vasculitis in adults. A systematic review. *BMC Nephrol.* 2010;11:12.
  21. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. *Am J Kidney Dis.* 2011;57(4):566–74.
  22. Walsh M, Merkel PA, Jayne DRW. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med.* 2020;382(22):2169.
  23. Balogun RA, Sanchez AP, Klingel R, Witt V, Aqui N, Meyer E, et al. Update to the ASFA guidelines on the use of therapeutic apheresis in ANCA-associated vasculitis. *J Clin Apher.* 2020;35(5):493–9.
  24. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol.* 2021;73(8):1366–83.
  25. Xiao H, Dairaghi DJ, Powers JP, Ertl LS, Baumgart T, Wang Y, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol.* 2014;25(2):225–31.
  26. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor Avacopan in ANCA-associated Vasculitis. *J Am Soc Nephrol.* 2017;28(9):2756–67.
  27. Ohta R, Torii Y, Imai M, Kimura H, Okada N, Ito Y. Serum concentrations of complement anaphylatoxins and proinflammatory mediators in patients with 2009 H1N1 influenza. *Microbiol Immunol.* 2011;55(3):191–8.
  28. Guillevin L, Fain O, Lhote F, Jarrousse B, Le Thi HD, Bussel A, et al. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients. *Arthritis Rheum.* 1992;35(2):208–15.
  29. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. *Arthritis Rheum.* 1995;38(11):1638–45.
  30. Guillevin L, Cevallos R, Durand-Gasselien B, Lhote F, Jarrousse B, Callard P. Treatment of glomerulonephritis in microscopic polyangiitis and Churg-Strauss syndrome. Indications of plasma exchanges, meta-analysis of 2 randomized studies on 140 patients, 32 with glomerulonephritis. *Ann Med Interne (Paris).* 1997;148(3):198–204.
  31. Hokosaki T, Mori M, Nishizawa T, Nakamura T, Imagawa T, Iwamoto M, et al. Long-term efficacy of plasma exchange treatment for refractory Kawasaki disease. *Pediatr Int.* 2012;54(1):99–103.
  32. Mori M. Plasma exchange therapy for Kawasaki disease refractory to intravenous immunoglobulin. *Nihon Rinsho.* 2008;66(2):349–54.
  33. Imagawa T, Mori M, Miyamae T, Ito S, Nakamura T, Yasui K, et al. Plasma exchange for refractory Kawasaki disease. *Eur J Pediatr.* 2004;163(4–5):263–4.
  34. Takagi N, Kihara M, Yamaguchi S, Tamura K, Yabana M, Tokita Y, et al. Plasma exchange in Kawasaki disease. *Lancet.* 1995;346(8985):1307.
  35. Harada T, Ito S, Shiga K, Inaba A, Machida H, Aihara Y, et al. A report of two cases of Kawasaki disease treated with plasma exchange. *Ther Apher Dial.* 2008;12(2):176–9.
  36. Noval Rivas M, Wakita D, Franklin MK, Carvalho TT, Abolhesn A, Gomez AC, et al. Intestinal permeability and IgA provoke immune vasculitis linked to cardiovascular inflammation. *Immunity.* 2019;51(3):508–521 e506.
  37. Connelly-Smith L, Dunbar NM. The 2019 guidelines from the American Society for Apheresis: what's new? *Curr Opin Hematol.* 2019;26(6):461–5.
  38. Ramos-Casals M, Nardi N, Lagrutta M, Brito-Zeron P, Bove A, Delgado G, et al. Vasculitis in systemic lupus erythematosus: prevalence and clinical characteristics in 670 patients. *Medicine (Baltimore).* 2006;85(2):95–104.
  39. Mineshima M, Yokoi R, Horibe K, Eguchi K, Kaneko I, Agishi T, et al. Effects of operating conditions on selectivity of a plasma fractionator in double filtration plasmapheresis. *Ther Apher.* 2001;5(6):444–8.
  40. Guillevin L, Lhote F, Leon A, Fauvelle F, Vivitski L, Trepo C. Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges. A prospective trial in 33 patients. *J Rheumatol.* 1993;20(2):289–98.
  41. Guillevin L, Lhote F, Sauvaget F, Deblois P, Rossi F, Levallois D, et al. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. *Ann Rheum Dis.* 1994;53(5):334–7.
  42. Guillevin L, Mahr A, Cohen P, Larroche C, Queyrel V, Loustaud-Ratti V, et al. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. *Arthritis Rheum.* 2004;51(3):482–7.
  43. Filer A, Hughes A, Kane K, Mutimer D, Jobanputra P. Successful treatment of hepatitis B-associated vasculitis using lamivudine as the sole therapeutic agent. *Rheumatology (Oxford).* 2001;40(9):1064–5.

**How to cite this article:** Fukuoka K, Kishimoto M, Kawakami T, Komagata Y, Kaname S. Plasmapheresis for systemic vasculitis. *Ther Apher Dial.* 2022;26:493–506. <https://doi.org/10.1111/1744-9987.13829>