



## ORIGINAL ARTICLE

# Plasma exchange for paediatric kidney disease—indications and outcomes: a single-centre experience\*

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## Abstract

**Background:** Outcome data in paediatrics regarding the use of plasmapheresis for immunological kidney disease are scarce.

**Objectives:** We aimed to evaluate the role of plasmapheresis in children presenting with severe renal impairment secondary to immunological kidney diseases.

**Methods:** A retrospective chart review of children admitted between January 2009 and August 2013 to the Paediatric Nephrology Unit, Christian Medical College, Vellore, India, and requiring plasma exchange was undertaken. Demographic and clinical data were studied and descriptive statistics applied for analysis.

**Results:** Sixteen children underwent plasmapheresis with a male:female ratio of 10:6 and a mean age of 10.2 years (range 5–15 years). Twelve children had atypical haemolytic uraemic syndrome, two had anti-glomerular basement disease and one each had lupus nephritis with neurological manifestation and anti-nuclear cytoplasmic antibody-associated vasculitis. The mean serum creatinine at presentation was 6.52 [interquartile range (IQR) 4.96–7.85] mg/dL with a mean eGFR of 43 (IQR 27.54–56.7) mL/min/1.73 m<sup>2</sup>. Other presenting features included nephrotic range proteinuria (69%), gross haematuria (27%), hypertension (94%) and seizures (37.5%). All children received 1.5 times plasma volume plasmapheresis (mean 11 sessions, range 5–26), dialysis and immunosuppressive therapy. The mean duration of follow-up was 4 months (range 2–24 months) with a majority of the children (15/16, 93.75%) surviving acute illness. One child died of overwhelming sepsis and another was lost to follow-up. Of the survivors, eight had eGFR >60 mL/min/1.73 m<sup>2</sup>, while eGFR was 15–60 mL/min/1.73 m<sup>2</sup> in the remaining six children. Eight children were still requiring antihypertensive medications and two were continuing peritoneal dialysis at the last follow-up. Thus early introduction of plasmapheresis along with other supportive therapy in immunological kidney disease may improve outcome.

**Key words:** acute kidney injury, children, end-stage kidney disease, plasmapheresis, therapeutic plasma exchange

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## Introduction

Therapeutic plasma exchange (TPE) removes circulating auto-antibodies, immune complexes and toxins from the blood. The patient's venous blood is drawn into the extracorporeal circuit and plasma is separated from the cellular component, which is retained. The patient's plasma is discarded and replaced with fresh frozen plasma [1]. When the replacement fluid used is other than plasma, the procedure is called apheresis. The process exchanges ~1.5–2 times the patient's plasma volume. Since its first use in patients with Waldenström's macroglobulinaemia in 1962 [2], there has been profound advancement in the technique with advances in transfusion medicine. The outcomes of plasmapheresis as a therapeutic modality reported in the paediatric nephrology literature are mainly based on case reports in individual diseases [3–6]. Therapeutic plasma exchange has been successfully used in various paediatric immunologically mediated diseases in the last few decades. Plasma exchange in the paediatric age group, however, is more challenging and requires greater expertise than in the adult population. The complications are procedure as well as access related. The large extracorporeal blood volume and blood loss in the circuit carry the risk of hypotension and anaemia, respectively. Further, blood product transfusion during plasma exchange exposes these children to the additional risks of viral infection and transfusion-related acute lung injury. Catheter-related complications are also reported and include access thrombosis and infection [7]. Given the paucity of data on TPE in children, the present study was conducted to study its role in the treatment of children presenting with acute kidney injury (AKI) secondary to immunological kidney diseases.

## Subjects and methods

This retrospective study was conducted in the Paediatric Nephrology Unit, Department of Paediatrics, Christian Medical College, Vellore, India. Institutional review board and ethics committee approval was obtained. Hospital records of children ages 5–18 years admitted to the Paediatric Nephrology Unit, who underwent TPE from May 2009 to August 2013, were reviewed. Demographic data, clinical features, treatment modalities, details of the plasma exchange procedure, complications and outcomes of these children were noted. Descriptive statistics were used to describe the results.

### Technical details

#### Plasma exchange machine

A Nikkiso haemodialysis machine (model DBB/27) with a Gambro PF 2000N plasma exchange filter was used. The procedure was performed by a trained senior haemodialysis technician who followed standard guidelines and a strictly aseptic procedure.

#### Access

A double-lumen haemodialysis (central venous) catheter (size 8/10 French) was used according to the age of the child. Femoral or internal jugular access was used, taking into account bleeding parameters, the child's haemodynamic stability and mobility and the expertise of the physician.

#### Technique

For the membrane filtration technique, the patient's blood passed at a continuous blood flow rate of 2 mL/kg/min (100–150 mL/min) through the hollow-fibre plasma filter (Gambro

with a pore size of 1000 nm for children <15 years and 2000 nm for those ≥15 years old. In most situations the 2000 nm pore size filter was utilized, as most of the children were adolescents. Moreover, the 1000-nm pore size filters are in short supply and are not freely available. This procedure separates the patient's plasma after retaining the blood cells. Adult-size haemodialysis tubing was used in all patients. The volume of the extracorporeal adult circuit was 191 mL (blood tubings, 150 mL; filter volume, 41 mL), as per the information provided by the manufacturer.

We did not do blood priming of the tubing since all the patients were >2 years of age and weighed >10 kg. The whole procedure took ~60–120 min.

#### Anticoagulation protocol

Heparin was used at an initial dose of 50 IU/kg stat followed by 1000 IU/h, while saline was used in children with a coagulation abnormality.

Premedications given were promethazine injection and paracetamol tablet.

#### Prescription

The TPE protocol followed was to start the procedure as early as possible within 24 h of admission, when indicated. Initially, once daily TPE was performed for 5 days, followed by five sessions per week for 2 weeks and then three sessions per week for 2 weeks.

Effective plasma volume was calculated as effective plasma volume (litre) =  $(0.065 \times \text{weight}) \times (1 - \text{haematocrit})$  [8]. The volume of the patient's plasma exchanged was  $1.5 \times$  the calculated effective plasma volume. Replacement fluid consisted of 60% colloid [fresh frozen plasma (FFP) and 5% albumin] and 40% crystalloid (0.9% saline).

For example, a 40 kg child with a haematocrit of 30% has an effective plasma volume of 1.8 L. As we have to calculate  $1.5 \times$  plasma volume, the total volume is ~2.7 L. Replacement fluid consists of 1000 mL normal saline as crystalloid, 100 mL 20% albumin mixed in 400 mL normal saline (equivalent to 500 mL 5% albumin) and 5 units FFP (~1150 mL). Replacement fluid was preferably FFP for patients of atypical haemolytic uraemic syndrome (HUS) and those who recently underwent a surgical procedure including kidney biopsy or central venous catheter insertion. FFP was preferentially used because the majority of our patients had atypical HUS and the proposed benefits of FFP in atypical HUS include replacement of missing or dysfunctional protein with a functional protein [9].

An injection of calcium gluconate was given during the procedure as an infusion (10 mL mixed in 1:1 dilution with distilled water) at the initiation of plasmapheresis and at half-hour intervals thereafter with strict cardiac monitoring. This was given to prevent hypocalcaemia associated with the use of colloid replacement fluids containing albumin [10]. Vitamin K and water soluble vitamins were replaced post-TPE. Children requiring both HD and TPE had HD prior to TPE. All medications except those that were urgent were given after TPE. Institutional review board and ethics committee approval was obtained.

## Results

A total of 16 children who underwent TPE during the study period were analysed. The male:female ratio was 10:6 with a mean age of  $10.17 \pm 2.8$  (range 8.25–13) years. Baseline characteristics of the study participants are presented in Table 1.

Table 1. Baseline characteristics of patients

Patient	Age (years)/ gender	Diagnosis	Lowest Hb (g/dL)	Lowest platelet (mm <sup>3</sup> )	Highest LDH (IU/L)	Highest creatinine (mg/dL)	C3 (mg/dL)	Biopsy
1	6/M	aHUS	5.0	29 000	8476	5.9	39.9	TMA
2	13/F	aHUS	7.8	53 000	2031	3.78	108	Not done
3	13/F	aHUS	4.4	70 000	3922	7.97	62.4	Not done
4	13/F	aHUS	6.5	17 000	3658	4.75	111	Not done
5	12/M	aHUS	6.7	26 000	1295	7.5	69	Not done
6	8/M	aHUS	6.8	119 000	1828	6.28	83	TMA
7	10/F	aHUS	4.2	76 000	2493	8	65	Not done
8	14/M	aHUS	3.6	45 000	6856	11.9	28.5	Not done
9	9/M	aHUS	4.2	23 000	7243	7.42	61.3	Not done
10	8/M	aHUS	6.5	33 000	2028	5.9	92.6	Not done
11	4/M	aHUS	6.5	90 000	2693	3.65	95	Not done
12	9/F	aHUS	5.5	26 000	1295	7.46	69.4	Not done
13	11/M	Anti-GBM	8.4	47 000	611	5.59	81	Linear IgG
14	14/F	Anti-GBM + anti-factor H antibody positive	7.9	59 000	785	11.07	80.8	Linear IgG + TMA
15	11/M	Lupus nephritis	6.7	28 000	1357	1	81.6	DPGN
16	11/M	MPA	6.8	79 000	668	6.2	101	Pauci immune

Normal values: haemoglobin, 11–14 g/dL; platelets, 150 000–4 00 000/mm<sup>3</sup>; serum creatinine, 1–1.4 mg/dL; LDH, 225–460 IU/L; C3, 90–180 mg/dL.

M, male; F, female; Hb, haemoglobin; LDH, lactate dehydrogenase; C3, complement 3; aHUS, atypical haemolytic uraemic syndrome; anti-GBM, anti-glomerular basement membrane disease; DPGN, diffuse proliferative glomerulonephritis.

### Major presenting features

The median duration of illness at presentation was 14 days (3–85 days). At presentation, renal symptoms included nephrotic range proteinuria in 11/16 (69%), microscopic haematuria in 7/16 (63.5%) and gross haematuria in 3/16 (27%). The most common extrarenal symptoms included hypertension in 15/16 (94%; stage II in 89% and stage I in 25%) and seizures in 6/16 (37.5%). All our study subjects were in renal failure at presentation, with a mean serum creatinine of 6.52 (IQR 4.96–7.85) mg/dL.

When classifying the patients according to the underlying kidney disease, atypical HUS was most common and present in 12/16 (75%) patients, followed by anti-glomerular basement membrane (anti-GBM) disease in 2/16 (13%) and 1 patient each had p-anti-neutrophilic cytoplasmic antibody (ANCA)-positive vasculitis [microscopic polyangiitis (MPA)] and lupus nephritis with neurological features.

Among children with atypical HUS, 50% (6/12) were positive for anti-complement factor H (anti-CFH) antibody. One child each was positive for perinuclear ANCA (pANCA) and anti-GBM antibody. Another child was positive for both anti-factor H antibody and anti-GBM antibodies. Kidney biopsy was performed in six children. Of these, three children had thrombotic microangiopathy (TMA), two had anti-GBM disease and one had pauci-immune vasculitis.

### Details of the treatment received

Therapeutic plasma exchange was performed in 16 children with a mean of 11 sessions (range 5–26). The mean time to initiation of TPE after onset of kidney failure was 4 weeks (range 1–12). The median duration of hospital stay was 42 days (range 14–95). All children required some form of renal replacement therapy; 10 children had haemodialysis, 4 had haemodialysis followed by peritoneal dialysis and 2 had peritoneal dialysis. All children received steroids; six children with atypical HUS with positive anti-CFH antibody titres also received cyclophosphamide, whereas

one received azathioprine along with TPE. The child with ANCA vasculitis (MPA) and the one with anti-GBM disease also received oral cyclophosphamide. Patients received blood transfusions during haemodialysis if the pre-dialysis haemoglobin was <8 g/dL or if there were signs of congestive cardiac failure, as per our unit's policy. We did not find an increased requirement of blood transfusion due to TPE *per se*.

### Clinical outcome

The mean duration of follow-up was 4 months (range 2–24). Details of patient outcomes are described in Table 2. Fifteen (93.75%) children survived; however, one child was lost to follow-up. Another child died of overwhelming sepsis. At discharge, 6/12 (50%) children with atypical HUS had complete haematological recovery (normal haemoglobin, platelets, reticulocyte count, LDH, blood smear and C<sub>3</sub> levels).

One child with MPA and another with atypical HUS progressed to end-stage kidney disease (eGFR <15 mL/min/1.73 m<sup>2</sup>) and were discharged on chronic ambulatory peritoneal dialysis. Fifty per cent (8/16) of the children achieved significant renal recovery (i.e. eGFR >60 mL/min/1.73 m<sup>2</sup>) and resolution of proteinuria, while another six (37.5%) had an eGFR in the range of 15–60 mL/min/1.73 m<sup>2</sup> on long-term follow-up. Three patients had relapses on follow-up; all of them had atypical HUS. Two had a relapse after 3 months and one at 12 months after diagnosis. Of these, only one child with a relapse required repeat TPE and haemodialysis, one recovered with plasma infusions and one had spontaneous recovery. Eight children were still on antihypertensive medications at the time of the last follow-up.

### Complications

Complications noted during TPE were most commonly catheter-related infection in 3/16 (18.75%), which was treated with

Table 2. Outcome of patients

Patient	Age (years)/gender	Diagnosis	At discharge	At 3 months	At last follow-up
1	6/M	aHUS	HTN, anaemia	HTN, anaemia, relapse	HTN, anaemia,
2	13/F	aHUS	HTN	HTN, CKD, CR	CR
3	13/F	aHUS	HTN, PR	HTN, CKD	HTN, ESRD, PD
4	13/F	aHUS	HTN, PR	CKD	CKD, one mild relapse
5	12/M	aHUS	HTN, anaemia, ESRD, PD	ESRD	Lost to follow-up
6	8/M	aHUS	HTN, anaemia	Anaemia, CKD, HTN relapse	Anaemia, CKD, HTN, relapse
7	10/F	aHUS	Death		
8	14/M	aHUS	HTN	CKD, HTN	CKD, HTN
9	9/M	aHUS	CR	CR	CR
10	8/M	aHUS	CR	CR	CR
11	4/M	aHUS	HTN, CKD	CKD, HTN	CKD, HTN
12	9/F	aHUS	HTN, CKD	CKD, HTN	CKD, HTN
13	11/M	Anti-GBM	CKD, PR	CKD, CR	CKD, CR
14	14/F	Anti-GBM + anti-factor H	antibody positive	ESRD, HD	None
15	11/M	Lupus nephritis	PR	CR	CR
16	11/M	MPA	HTN, PD	ESRD, HTN, PD	ESRD, HTN, PD

M, male; F, female; aHUS, atypical haemolytic uraemic syndrome; anti-GBM disease, anti-glomerular basement membrane disease; HTN, hypertension; PD, peritoneal dialysis; CR, complete remission (haematological); PR, partial remission (haematological).

intravenous antibiotics. Allergic reactions (fever and chills) were seen in 2/16 (12.5%) and hypotension in 1/16 (6.25%). These responded to short cessation of TPE and an additional dose of hydrocortisone. One patient developed catheter-related thrombosis (6.25%) that resolved after a 3-month treatment with low molecular weight heparin. We did not see any complications due to hypocalcaemia, including numbness, tingling, muscle spasms or seizures. Calcium gluconate infusion given at regular intervals during the procedure may have ensured that such complications did not occur. In addition, heparin was used for anticoagulation instead of citrate, in which case ionized calcium needs to be frequently monitored since the risk of hypocalcaemia is far greater.

Discussion

TPE has earned its place as an aggressive therapeutic modality in the management of a variety of immunological renal diseases, especially when presenting with renal failure with a rapidly progressive course. Despite being technically challenging in the paediatric population, TPE has quickly become the standard of care in children with these diseases, but there is a paucity of paediatric data. The American Society for Apheresis has provided guidelines on definite indications of TPE in kidney diseases that present as rapidly progressive glomerulonephritis [10]. Kidney diseases in which TPE has been reported to be useful are summarized in Table 3 [11]. The 16 children in our study who underwent TPE had different causes of renal failure. Most other studies have focused on the outcome of TPE in individual diseases [6, 12]. Among the kidney transplant recipients, there are data available demonstrating its use in ABO-incompatible renal transplant, antibody-mediated rejection and post-transplant recurrence of focal segmental glomerulosclerosis [10]. However, our experience with TPE in this group of patients is limited.

Six of 12 (50%) patients with atypical HUS had a positive anti-CFH antibody titre. Previous studies in European children have reported a lower incidence of anti-factor H positivity of ~22% [13]; however, a recent study by Sinha et al. [9] from India reported

Table 3. Indications of plasmapheresis in kidney diseases in children

Rapidly progressive renal disease
Pauci immune GN
Anti-glomerular basement membrane GN
Ig A nephritis
Henoch Schlein purpura nephritis
Cryoglobulinaemia
Renal transplant recipient
Pre-transplant desensitization
ABO-incompatible transplant
Acute antibody-mediated rejection
Post-transplant recurrence of FSGS
Others
Atypical haemolytic uraemic syndrome
Thrombotic thrombocytopenia
Multi-organ dysfunction
Multiple myeloma with renal failure

GN, glomerulonephritis; IgA, immunoglobulin A; FSGS, focal segmental glomerulosclerosis.

results (56%) similar to our study. One child with a diagnosis of atypical HUS died. She had severe refractory hypertension with neurological involvement. In a recent study in Indian children, 5% of children with atypical HUS developed ESRD. Our study also revealed similar results of 8% (1/12) for atypical HUS patients.

Sana et al. [14] demonstrated the long-term efficacy and safety of intravenous cyclophosphamide pulses along with TPE and corticosteroids in anti-CFH antibody-related atypical haemolytic uraemic syndrome in decreasing antibody titres and decreasing relapses. Higher response in our study may be due to the higher prevalence of anti-factor H antibody in our study group, who showed good response to TPE and immunosuppressive therapy.

Six of 12 (50%) children with atypical HUS in our study achieved remission. Around 5–20% of atypical HUS patients were reported to achieve remission by Sellier et al. [15], depending upon the type of genetic mutation. We currently do not have



facilities for genetic mutation testing for patients presenting with atypical HUS and hence an exact genetic diagnosis could not be elucidated in the remaining six patients. Among other diseases, one child with anti-GBM disease and an other child with lupus nephritis made a partial recovery. In addition to a Ahus child with ESRD, other patient who developed ESRD has MPA. Corral-Gudino et al. [16] reported that ~30% of children with MPA progress to ESRD.

TPE was found to be safe and effective in our experience. This was despite the fact that many patients were referred late due to a missed diagnosis, resulting in delayed initiation of plasmapheresis and other specific therapies.

TPE has an advantage in that it allows delivery of FFP containing missing factors without the risks of fluid overload, hypertension and cardiac failure, which may result from plasma infusions. It also has the benefit of removing dysfunctional factors and antibodies involved in endothelial dysfunction and activation of cytokine storm, resulting in activation of the complement cascade and enhanced platelet aggregability [17].

There is a paucity of data on the use of TPE in children, but reports from a few case series on children treated for immune-mediated glomerulonephritis have demonstrated a higher likelihood of renal recovery if given TPE with immunosuppression compared with those given immunosuppression alone [18]. Similarly, TPE has been shown to decrease circulating antibody levels and decrease pulmonary haemorrhage in children with anti-GBM disease—and has become the mainstay of treatment, along with corticosteroids and cyclophosphamide. Johnson et al. [19] demonstrated a much better clearance of antibody levels and the improvement in renal function was far better than in those receiving immunosuppression alone. The most common complication noted in our series was catheter-related infection, followed by allergic reaction, hypotension and thrombosis. This was similar to previous reports in children, although hypotension noted in our experience was lower [7].

The major limitations of our study are the small sample size, retrospective nature of the study and relatively short period of follow-up.

A recent addition to the treatment of atypical HUS is eculizumab, which is a humanized monoclonal antibody that is a first-in-class terminal complement inhibitor (C5b-9) initially approved for the treatment of paroxysmal nocturnal haemoglobinuria [20]. Eculizumab is also the first pharmacologic agent approved for the treatment of atypical HUS. It acts by inhibiting the progression of the complement cascade and blocking terminal complement activation [21]. Specifically it prevents the cleavage into C5a and C5b—the latter being an essential component of the membrane attack complex. A clinical phase II trial of eculizumab by Licht et al. [21] at the 2-year follow-up has shown significant improvement in baseline GFR and discontinuation of the need for dialysis and plasmapheresis. These advantages were observed especially when treatment with eculizumab is started early after ruling out thrombotic microangiopathy. It was found to be safe without any major side effects. However, the optimal duration of treatment is unknown and the cost of treatment remains prohibitively high.

Currently no data are available on its use in the Indian subcontinent.

## Conclusions

Early presentation, high index of suspicion among treating physicians and early introduction of TPE along with dialysis and

appropriate immunosuppression may be promising in effectively decreasing morbidity and improving outcome in children with immunological renal disease.

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## Conflict of interest statement

None declared.

(See related article by Sanchez-Niño and Ortiz. Thrombotic microangiopathy: expanding genetic, clinical and therapeutic spectra and the need for worldwide implementation of recent advances. *Clin Kidney J* (2015) 8: 686–689.)

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