Therapeutic plasma exchange for the treatment of pediatric renal diseases in 2013

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Abstract Therapeutic plasma exchange is an extracorporeal treatment modality that removes systemic circulating pathologic factors or replaces absent plasma components and plays a role in many nephrologic conditions. It presents a number of technical challenges in the pediatric population but has become an increasingly common practice in pediatric nephrology over the past several decades. While prospective evidence is often lacking, our increased understanding of the molecular pathogenesis underlying many pediatric renal diseases provides sound reasoning for the use of plasma exchange in treating these conditions. This review will present the currently accepted indications for plasma exchange in children, the technical aspects of the procedure and its potential complications.

Keywords Plasma exchange · Renal transplant · Renal indications · FSGS · atypical HUS · TTP · AMR

Brief history of plasma exchange

The first plasmapheresis procedure was reported in 1914 at Johns Hopkins University. Whole blood was manually removed from donor horses and centrifuged; the isolated erythrocytes were suspended in buffer and returned to the horse and plasma was conserved to be used as antitoxic sera [1]. Over the following decades, significant advancements in technology and transfusion science directed at the collection of human blood products for transfusion were achieved and later applied to plasma exchange. In 1960, the first

human treatment with plasma exchange was reported in a patient with Waldenstrom's macroglobulinemia [2]. Later that decade, a continuous-flow centrifugal apparatus was developed which has been modified over time to become the Cobe Spectra. Further refinements in the technology and advancements in our understanding of disease processes over the last three decades have made plasma exchange an important and safe treatment modality for children with renal and other immune-mediated diseases.

Indications and evidence for therapeutic plasma exchange in children

During therapeutic plasma exchange (TPE) whole blood is removed from the patient and passed through an extracorporeal medical device, which separates the plasma from the cellular components of the blood. The plasma is removed and replaced with a colloid solution (e.g. albumin and/or donated plasma) or a combination of crystalloid and colloid solutions [3]. The cellular components are returned to the patient. By removal of plasma, TPE non-selectively removes large molecular weight substances from the intravascular space. In clinical practice, there are two rationales for using TPE: to remove an inciting circulating pathogenic molecule (antibody, immune complex, toxin, etc.) or to replace a deficient factor, as in systemic thrombotic microangiopathy. TPE has been reported or investigated for use in a broad range of disease processes, and the list of indications is evolving as the underlying pathology of disease processes are discovered and more therapeutic trials are conducted. In addition, as new immunologic therapies are discovered and tested, TPE may cease to be the first-line treatment for some of these conditions. In some conditions TPE has not been proven to be beneficial, particularly in children, and the detailed pathophysiology of these is beyond the scope of this article. This

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review will focus on the conditions most pertinent to the pediatric nephrologist for which TPE is an accepted or recommended therapeutic modality. These include removal of preformed cytotoxic antibodies in the renal transplant candidate [anti-donor human leukocyte antigen (HLA) or ABO antibodies, or high panel reactive antibody], antibody-mediated renal allograft rejection, recurrent focal segmental glomerulosclerosis (FSGS) after renal transplantation, anti-neutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane antibody-associated rapidly progressing glomerulonephritis, and atypical hemolytic uremic syndrome (aHUS). We will briefly discuss lupus nephritis, for which TPE is currently not a recommended treatment, as well as immunoglobulin A (IgA) nephropathy, Henoch–Schönlein purpura (HSP) and sepsis with multi-organ failure, which are less well studied.

The American Society for Apheresis (ASFA) Special Issue, 5th Edition, published in 2010, includes a comprehensive review of the available literature for each disease process. ASFA classifies disorders into four categories, based on the quality of the available literature and the strength of the society's recommendation for TPE in each disorder. Category I includes disorders for which apheresis is accepted as first-line therapy; category II includes disorders for which apheresis is accepted as second-line therapy; category III includes disorders for which the optimum role of apheresis is not established and decision-making should be individualized; category IV includes disorders for which evidence demonstrates or suggests that apheresis is ineffective or harmful and should not be initiated without Institutional Review Board approval [3]. A list of conditions for which TPE is recommended (Category I or II) by ASFA is provided in Table 1 [3, 4]. A summary of the disease processes and current treatment recommendations is provided in Table 2.

Renal transplant patients

Indications prior to renal transplantation

Desensitization for patients with high panel reactive antibody or positive cross-match

Concomitant with the improved survival rate after pediatric renal transplantation, more patients are requiring repeat transplantation. Exposure to foreign HLA antigens by previous organ transplant, blood transfusion or pregnancy induces the production of antibodies to HLA antigens of potential donors. The presence of these antibodies is a risk factor for acute antibody-mediated rejection (AMR), and patients with higher panel reactive antibody (PRA) spend more time waiting for kidney transplant than those with lower PRA [5]. Pre-transplant plasma exchange has been used in

patients who are highly HLA sensitized to reduce donor-specific antibody levels and allow for successful renal transplantation, either from the deceased donor pool (by lowering PRA) or from a potential living donor (by eliminating a positive cross-match). In several studies of adult patients with high PRA, protocols including TPE (with low-dose intravenous immunoglobulin (IVIG) $\pm$ anti-CD20 therapy) have been shown to be superior to treatment with IVIG alone for desensitization with the goals of lowering donor specific antibodies (DSA) levels, reducing PRA, achieving a negative cross-match, avoiding post-operative AMR and prolonging graft survival [6–8]. A recent series of adult patients with end-stage renal disease (ESRD) demonstrated that patients who underwent desensitization with TPE and IVIG followed by living donor kidney transplantation had significantly improved survival than those who remained on dialysis and waited for an HLA-compatible deceased donor [9]. Desensitization is not well studied among children, but TPE allowed a successful second renal transplant in an 11 year-old girl whose PRA was not sufficiently reduced with high-dose IVIG [10]. Medical therapy with high-dose IVIG and rituximab has been proposed as an alternative to serial TPE treatments for patients awaiting deceased donor renal transplantation [11, 12]. Among adult patients, desensitization is becoming an accepted method to expand the donor pool and thus decrease waiting time for kidney transplantation [13]. Whether the benefits of desensitization would also be observed in the pediatric population with ESRD is as yet unknown; children are less likely to have had potentially sensitizing exposures and generally spend less time waiting for an organ from a deceased donor, making the need for desensitization relevant for only a narrow population. However, for individual children who have donor-specific HLA antibodies to a potential living donor, TPE is an increasingly accepted treatment to overcome that barrier to transplantation.

ABO-incompatible living donor renal donation

ABO-incompatible living-donor kidney transplantation is another strategy to overcome barriers to renal transplantation and has become more frequent despite an increased risk of hyperacute or acute humoral graft rejection due to preformed antibodies to endovascular oligosaccharides [14]. Reduction of Immunoglobulin G (IgG) and Immunoglobulin M (IgM) titers to below 1:4 is recommended to prevent these adverse outcomes, because higher levels have been associated with acute rejection and worse graft survival [3, 15–17]. Antibody reduction with TPE is followed by rituximab therapy or splenectomy to minimize antibody synthesis in the peri-transplant period. Treatment with TPE results in lower isoagglutinin titers, low rates of hyperacute rejection and AMR, although randomized clinical trials have not been

Table 1 Indications for therapeutic plasma exchange in children

Renal diseases	Other conditions
Renal transplant conditions	Hematologic
ABO-incompatible kidney transplant ^a	ABO-incompatible stem cell transplant
Pretransplant desensitization ^a	Aplastic anemia (pure red cell aplasia)
Antibody-mediated rejection ^a	Autoimmune hemolytic anemia (Cold agglutinin)
Recurrent focal segmental glomerulosclerosis ^a	Catastrophic antiphospholipid antibody syndrome
Immune-mediated glomerular disease	Hyperviscosity in monoclonal gammopathies
Anti-glomerular basement membrane disease ^a	Post-transfusion purpura
ANCA-associated rapidly progressive glomerulonephritis ^a	Red cell alloimmunization in pregnancy
IgA nephropathy ^{a,b}	Neurologic
Henoch–Schönlein purpura nephritis ^a	Acute disseminated encephalomyelitis
Other immune-mediated glomerulonephritis ^{a,b}	Chronic focal encephalitis
Cryoglobulinemia	Guillain–Barre syndrome
Other	Chronic inflammatory demyelinating polyneuropathy
Atypical hemolytic uremic syndrome ^a	Multiple sclerosis
Sepsis with multiorgan failure ^{a,b}	Lambert–Eaton myasthenic syndrome
Thrombotic thrombocytopenic purpura ^a	Lupus cerebritis
Myeloma cast nephropathy	Neuromyelitis optica
	Myasthenia gravis
	PANDAS, Sydenham's chorea
	Paraproteinemic polyneuropathies (IgG/IgA, IgM)
	Metabolic
	Familial hypercholesterolemia (homozygotes, small blood volume)
	Mushroom poisoning
	Refsum's disease
	Wilson's disease, fulminant
	Solid organ transplant
	ABO-incompatible heart transplant
	Antibody-mediated heart transplant rejection
	Other
	Lupus with diffuse alveolar hemorrhage

ANCA, Anti-neutrophil cytoplasmic antibodies; IgA, immunoglobulin A;

^a Discussed in the text

^b Disorders are categorized in American Society for Apheresis (ASFA) category III, but are included in this table because they are discussed in the text

performed [18, 19]. The largest case series of pediatric patients who received ABO-incompatible renal transplants included 52 Japanese children who were treated with three to four plasma exchange treatments (goal anti-A/B titers of <1:8) prior to transplant. Compared with ABO-compatible recipients during the same time period there were higher rates of AMR among the former, but 10-year outcomes were not significantly different [20]. The same center previously reported 16 pediatric ABO-incompatible living kidney transplants treated with plasma exchange or immunoabsorption prior to transplantation and splenectomy at the time of transplantation. The majority (56 %) had an increase in anti-ABO titers with an associated increase in serum creatinine (presumed AMR), and one child suffered graft loss due to

delayed hyperacute rejection, although the 10-year graft survival was similar to that of ABO-compatible transplantation [21]. These data are consistent with data from adult series [20, 22]. The use of antigen-specific column absorption, as opposed to TPE, to reduce ABO antibody titers before transplantation has also been recently reported to be successful in adults and children [23, 24].

Indications after renal transplantation

Acute antibody-mediated rejection

Acute AMR occurs in approximately 10 % of all renal transplant recipients and in up to 30 % of patients who have

Table 2 Summary of renal indications and recommended treatment for plasmapheresis in children

Diagnosis	ASFA category	Pathogenic molecule	Prescription		Frequency	Duration/endpoint	Notes	Selected reports on pediatric patient population
			Treatment volume and replacement fluid					
ABO-incompatible renal transplantation	II	Anti-A or Anti-B endothelial oligosaccharide antibodies	1–1.5 plasma volume	5 % Albumin, plasma (compatible with recipient and donor)	Daily or every other day for 2–5 days prior to transplant	Reduce IgM or IgG antibody titers ≤ 4 Usually 2–5 treatments	After transplant: consider daily TPE followed by IVIG for 2–3 days Follow daily ABO antibody levels after transplant $\times 2$ weeks	[20, 21]
		Donor-specific HLA antibodies	1–1.5 plasma volume	5 % Albumin Plasma if coagulopathy, preoperative	Preop: Daily or every other day until negative cross-match	Follow donor-specific antibodies to determine further treatments Minimum 3 treatments after surgery		[10]
Desensitization before renal transplantation								
Living donor positive cross-match	II							
Cadaveric donor high panel reactive antibody	III							
Antibody-mediated rejection (renal transplant)	I	Donor-specific HLA antibodies	1–1.5 plasma volume	5 % albumin	Daily or every other day	Protocols vary, 5–6 treatments Follow donor-specific antibody titers		[34]
Recurrent focal segmental glomerulonephritis (renal transplant)	I	Glomerular permeability factor, soluble urokinase plasminogen activating receptor (suPAR)	1–1.5 plasma volume	5 % albumin	Daily or every other day	Daily $\times 3$ days, then 6 treatments over 2 weeks Taper to be determined by clinical course	Proteinuria may take months to resolve Some patients require chronic therapy to maintain remission	[40, 44, 47, 48, 52]
Anti-glomerular basement membrane disease		Antibodies to type IV collagen	1–1.5 plasma volume		Daily or every other day	Minimum 14 days of therapy	Use TPE with immunosuppression	[73, 74]
Dialysis dependent	I		5 % albumin			If some response, continue until resolution of ongoing injury		
Diffuse alveolar hemorrhage	I	Plasma in diffuse alveolar hemorrhage						
ANCA-associated rapidly progressive glomerulonephritis		Anti-neutrophil cytoplasmic antibody, other associated antibodies	1–1.5 plasma volume	5 % albumin Plasma in diffuse alveolar hemorrhage	Daily or every other day	7–9 treatments, then taper	Use TPE with immunosuppression	[64]
Dialysis dependent	I							
Diffuse alveolar hemorrhage	I							
Dialysis independent	III							
IgA nephropathy, Henoch–Schönlein purpura, nephritis	III	Circulating immune complexes	1–1.5 plasma volume	5 % Albumin	Every other day	Treatment for 1–2 weeks, then taper Discontinue at 4 weeks if no improvement		[77–79]

Table 2 (continued)

Diagnosis	ASFA category	Pathogenic molecule	Prescription		Notes	Selected reports on pediatric patient population
			Treatment volume and replacement fluid	Frequency	Duration/endpoint	
Atypical hemolytic uremic syndrome Factor H antibody	I	Factor H antibody	1–1.5 plasma volume 5 % Albumin Plasma	Daily	Daily ×5 days, then 5 days/ week ×2 weeks, then 3 ×/ week ×2 weeks, taper as tolerated	[84, 90, 94]
	II	Replace deficient factors, remove defective factors				
Complement mutations		Replace deficient				
		ADAMTS 13, ADAMTS 13 Antibody				
Thrombotic thrombocytopenic purpura	I		1–1.5 plasma volume	Daily	Daily until platelet count >150,000/L ×2 days, then taper	
			Plasma or cryo poor plasma			

TPE, Therapeutic plasma exchange; IVIG, Intravenous immunoglobulin; HLA, human leukocyte antigen; ASFA, American society for apheresis; IgM, Immunoglobulin M; IgG, Immunoglobulin G; ANCA, Anti-neutrophil cytoplasmic antibodies

undergone desensitization for known donor-specific HLA antibodies [11, 25]. AMR is most commonly caused by anti-donor HLA antibodies, although other endothelial targets have also been identified [26, 27]. The diagnosis of AMR is based on decreased graft function, positive donor-specific antibodies, and histological changes, including C4d positive staining of peritubular capillaries, graded according to Banff 07 criteria on renal biopsy [28]. The role of plasma exchange in treating AMR varies by center. TPE achieves rapid reductions in circulating antibody levels, but concurrent medical therapy aimed at reducing antibody production is also required, including corticosteroids, IVIG and rituximab. At Cedars-Sinai TPE is used in severe AMR, including those cases of patients showing a rapid decline in renal function and more severe abnormalities on kidney biopsy, while patients with less severe cases are treated with medical therapy (pulse steroids, IVIG and rituximab) [29]. Other centers include TPE as part of the regimen for all cases of AMR [30]. AMR generally responds well, and recovery of renal function has been reported in >80 % of patients for whom TPE was included in their therapy [31–33]. Kranz et al. reported four episodes of AMR in three pediatric renal transplant recipients with acute renal failure shortly after renal transplantation [34]. All were treated with pulse steroids, IVIG, rituximab and plasma exchange, and three had preserved graft function. In another study, TPE used in conjunction with IVIG and anti-CD20 antibody was better than IVIG alone in lowering donor-specific antibodies and prolonging graft survival in subjects with acute AMR [35]. Emerging therapies in the treatment of AMR include immunoabsorption for antibody removal [36], and eculizumab and bortezomib to target antibody synthesis and effect [25, 29].

Post-transplant recurrence of FSGS

Idiopathic (primary) FSGS is caused by a circulating factor that increases glomerular permeability to albumin, with recent data strongly implicating overexpression of soluble urokinase plasminogen activating receptor (suPAR) in the pathogenesis of FSGS in adults and children [37, 38]. FSGS accounts for 9 % of pediatric patients with ESRD receiving a transplant in North America, and children with ESRD secondary to FSGS have a high rate (30–86 %) of recurrence of proteinuria after renal transplant [39–42]. Graft failure is more common among patients with recurrence, and the duration of graft survival is lower among patients with FSGS than among those with other causes of glomerular disease [43, 44]. Treatment with plasma exchange reduces proteinuria and prolongs graft survival in pediatric case series and is most successful in preserving renal function in patients who are treated early after recurrence is diagnosed [42, 45–48]. Greenstein et al. [47] reported recurrence in 40 % (8/20) of pediatric patients who underwent renal transplantation for ESRD secondary to FSGS. TPE was

performed in six of those patients, with five of the six achieving remission and more rapid remission achieved in patients who were treated in the first 48 h after diagnosis of relapse [47]. Cochat et al. [49] reported similarly promising results in another case series of three pediatric patients with recurrent FSGS within 2 weeks of renal transplant; all patients were treated with TPE, and all achieved remission and had preserved renal function. Recurrence of FSGS is associated with worse graft outcomes, and achieving remission may improve graft survival [50].

The use of prophylactic TPE in patients at risk for FSGS recurrence has also been evaluated in children. In a study of Japanese children, the rate of recurrence of FSGS in renal transplant recipients was 33 % in the group who received TPE prior to transplantation, compared with 66 % among those who did not receive prophylactic or early TPE [51]. Couloures et al. reported a single case of a patient at high risk for recurrence treated with pre-transplant TPE who did not have recurrence of proteinuria after transplantation [52]. The described clinical risk factors for recurrence of FSGS after kidney transplantation include younger age of onset of disease, race, rapidity of progression and lack of genetic mutations to explain nephrotic syndrome. Patients with podocin mutations may be at lower risk of recurrence [53]. However, recurrence is still unpredictable, making identification of those who would benefit from prophylactic TPE difficult [48, 54, 55]. Prophylactic TPE would likely be most beneficial in patients with a history of recurrent FSGS in a previous transplant [56] or in those with an identified glomerular permeability factor [54, 57].

Immune-mediated glomerulonephritis

ANCA-associated rapidly progressive glomerulonephritis

Anti-neutrophil cytoplasmic antibodies-associated renal disease is characterized by a rapid loss of renal function, crescents on light microscopy with minimal glomerular immune deposits on immunofluorescence ('pauci-immune') on renal biopsy and presence of serum ANCA [cytoplasmic (c)-ANCA or perinuclear (p)-ANCA]. The disease spectrum includes granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis and Churg–Strauss syndrome. The primary treatment for ANCA-associated vasculitis with non-dialysis-dependent renal disease is immunosuppression, but TPE may be beneficial for patients who are dialysis dependent or have diffuse alveolar hemorrhage, a potentially life-threatening complication of ANCA-associated diseases.

To date there have been no trials of TPE for the treatment of ANCA-mediated renal disease in children, and data from studies of adult patients are conflicting. However, two recent adult reports have shown that patients with severe renal

dysfunction (requiring dialysis [58] and a serum creatinine concentration of >5.8 mg/dL [59]) from ANCA-mediated disease who were treated with TPE have a higher likelihood of renal recovery. Other older studies did not show a benefit of treatment with TPE [60, 61].

In a case series of 25 children with GPA, two children who were dialysis dependent at the time of diagnosis were treated with plasma exchange and subsequently showed sufficient improvement in their renal function to allow termination of hemodialysis for the long term [62]. In this report, the three other children who presented requiring dialysis and were not treated with TPE did not recover renal function. Other smaller series have reported children with ANCA-associated glomerulonephritis responding to therapeutic regimens that included TPE [63, 64]. Given the poor prognosis of ANCA-associated glomerulonephritis, a trial of TPE is reasonable even without strong supporting evidence. A large clinical trial for patients 15 years and older is currently in the recruiting process to better determine the benefits of TPE in ANCA-associated vasculitis (Clinicaltrials.gov NCT00987389).

Anti-glomerular basement membrane antibody glomerulonephritis

Anti-glomerular basement (anti-GBM) antibody syndrome is characterized by linear IgG deposits to type IV collagen on renal biopsy. It presents as rapidly progressive glomerular nephritis, usually associated with diffuse alveolar hemorrhage, although 30–40 % of cases do not have pulmonary involvement [65]. This syndrome was discovered to be an antibody-mediated disease in the 1960s, and at that time patients had a dismal prognosis. Since the 1970s, TPE, in conjunction with immunosuppression (usually corticosteroids and cyclophosphamide), has become a mainstay of therapy. TPE is effective in lowering circulating antibody levels and decreasing pulmonary hemorrhage in children and adults [66, 67]. The only clinical trial comparing treatment with TPE + immunosuppression to treatment with immunosuppression alone demonstrated a more rapid reduction in circulating anti-GBM antibodies and better renal function in the group treated with a regimen that included plasma exchange [68].

The standard treatment for anti-GBM disease is intensive daily plasma exchange for at least 2 weeks. Prior to the standard implementation of this treatment regimen, the prognosis of anti-GBM disease was poor; however, current survival rates have been reported to be 75–95 % in several case series. The renal prognosis is dependent on renal function at the time of presentation, with few patients with a creatinine level of >6.6 mg/dL recovering sufficient renal function to avoid renal replacement therapy despite aggressive treatment with plasma exchange and immunosuppression [65, 69]. Anti-GBM disease is rare in children and described in only small case series and case reports

[70–72]. In these series, patients treated with plasma exchange show a reduction in levels of anti-GBM antibodies, but reported cases of improved renal function are rare [73, 74].

Other glomerulonephritis

Therapeutic plasma exchange has been studied in the treatment of other forms of immune-mediated glomerulonephritis, including lupus nephritis and IgA nephropathy, but benefit has not been demonstrated in these diseases. While plasma exchange reduces the levels of circulating lupus-associated antibodies, controlled studies have failed to show improvement in clinical outcomes when patients with lupus nephritis are treated with TPE [75, 76]—therefore treatment with TPE is not recommended for use in lupus nephritis. TPE may be beneficial in patients with other life-threatening manifestations of lupus, including diffuse alveolar hemorrhage or central nervous system involvement [3].

The ASFA groups IgA nephropathy and HSP together with other forms of immune-mediated rapidly progressive glomerulonephritis, for which there are no strong data to support the use of TPE [3]. Retrospective studies of children with crescentic HSP nephritis have demonstrated improvement in those treated with TPE alone [77, 78] and in combination with medical immunosuppression [79], although no prospective data exist. Neither HSP nor IgA nephropathy is a recommended indication for TPE at this time [3].

aHUS and thrombotic thrombocytopenic purpura

Atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (TTP) are rare conditions, but they are the most common thrombotic microangiopathies in children. Both conditions are characterized by hemolytic anemia, thrombocytopenia and variable degrees of renal and cognitive dysfunction caused by systemic microvascular thrombi. aHUS (HUS not associated with Shiga toxin) accounts for approximately 10 % of cases of pediatric HUS and portends a poor renal prognosis, with approximately 50 % of patients progressing to ESRD [80, 81]. In more than 50 % of pediatric aHUS cases, endothelial damage results from an identifiable genetic defect in the complement pathway, including defects in factor H, factor I, factor B, membrane cofactor protein (MCP), thrombomodulin or C3 [80, 82, 83]. Acquired antibodies to complement factor H have also been described, mostly in pediatric patients [84, 85]. Other causes of aHUS include calcineurin inhibitor therapy, hematopoietic stem cell transplantation, methylmalonic aciduria (in neonates) and infection with *Streptococcus pneumoniae*. TTP, which is very rare in children, is caused by a deficient activity of the von-Willebrand factor cleaving protein,

ADAMTS (A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif, member) 13, either resulting from an autosomal recessive mutation in the gene that encodes ADAMTS13 (congenital TTP or Upshaw–Schulman syndrome) or from an inhibitory antibody to ADAMTS13 (acquired idiopathic TTP). In aHUS and in congenital and acquired TTP, replacement of the deficient factor with donor fresh frozen plasma by TPE or plasma infusion inhibits the process driving the microangiopathy.

Until the recent Federal Drug Administration (FDA) approval of medical therapy with eculizumab (discussed below), the first line treatment for aHUS in children was intensive TPE. No randomized trials are available, but guidelines recommend to initiate TPE if possible within 24 h of presentation with five daily treatments followed by treatment five times weekly for 2 weeks, then three times weekly for 2 weeks [86]. Hematologic response to therapy is monitored by platelet count, assessment for fragmented red blood cells and lactate dehydrogenase level. Renal response is assessed by measuring renal function, proteinuria and blood pressure [86, 87]. Depending on the patient's response and results of genetic testing, the frequency of therapy can be gradually reduced. Children with aHUS are at high risk of relapse and graft failure after kidney transplantation and, therefore, must be followed closely as the frequency of treatment is decreased [83, 88]. In adults with TTP, treatment with plasma exchange has been shown to be both beneficial [87] and superior to plasma infusion, so TPE is also recommended for children with congenital TTP [89].

Prognosis and response to TPE differ depending on the underlying causative defect [84, 90]. While patients with defects in factor H or factor I have a better response to TPE than those with other complement pathway defects, the rates of progression to ESRD remain high at nearly 70 %. Patients with factor H mutations are often dependent on TPE to achieve and maintain remission of their disease [84, 90–93]. Children with aHUS secondary to mutations in MCP have better renal prognosis, including higher likelihood of complete remission, lower likelihood of progression to ESRD (approx. 20 %) and lower rates of disease recurrence in the transplanted kidney and death [90, 94]—despite the lack of evidence demonstrating a benefit of TPE in this group [84, 90, 94]. Results of genetic testing are usually not available at the time of presentation, so from a practical standpoint, therapy with TPE must be initiated without this knowledge and can be modified once the results are known, if necessary.

Eculizumab, a monoclonal antibody that inhibits C5 to prevent activation of the terminal complement pathway, was designated an Orphan Medicinal Product in the USA and Europe in 2009 and was approved by the FDA for use in aHUS in 2011. Since 2009, several series of pediatric patients with various complement pathway gene defects and aHUS have reported the successful use of eculizumab in patients

who are treatment naive or who have failed or not tolerated treatment with TPE [95–98]. Eculizumab has also been reported to prevent and treat post-transplant recurrence of aHUS, which is common [90, 97, 99–101]. A prospective, open-label, multicenter clinical trial of eculizumab in pediatric patients with aHUs (<http://clinicaltrials.gov> NCT01193348) is currently in progress. It is a promising treatment for aHUS and may replace TPE as the recommended first line therapy in the next few years.

Other emerging indications

Sepsis with multiorgan failure

Therapeutic plasma exchange has been proposed for use in sepsis to remove endotoxins and the circulating cytokines that drive the inflammatory response. In a study including pediatric patients, a reduction in circulating inflammatory mediators and number of failed organs was observed, but there was no improvement in mortality [102]. Other studies have shown a reduction in endotoxin levels [103], and improved 28-day mortality [104]. The benefit of plasma exchange in severe sepsis with multiorgan failure is currently under investigation in a small study of adult patients (Clinicaltrials.gov NCT01249222).

Technical aspects of pediatric plasma exchange

Therapeutic plasma exchange is an accepted safe and effective therapy in pediatrics; however, automated apheresis machines are designed for use in adults and, therefore, several specific modifications must be considered to ensure safety for use in smaller children.

Techniques

Two automated techniques are available for plasma exchange: centrifugation and filtration. In smaller children, manual exchanges may also be considered to avoid the relatively large extracorporeal volume required for the automated methods if blood products are not available to prime the circuit.

The majority of the evidence for TPE in adults and children has been described with the use of centrifugal methods, although membrane filtration methods may be equally as effective for most indications. In the centrifugal method, blood is removed from the patient, and the blood components are separated by mechanical centrifugation into layers based on density: plasma, buffy coat and red blood cells. Cellular components, which are kept sterile, are returned to the patient with additional replacement fluid.

The patient's plasma is collected into a waste bag and discarded.

Standard membrane filtration is used less frequently in the pediatric setting. It can be performed using hemodialysis or continuous renal replacement therapy equipment with a plasma filter. The transmembrane pressure forces the plasma through the membrane, and cells and platelets are retained in the blood path. The filtration rate is limited, and a smaller portion of plasma is removed, resulting in longer procedure times to achieve the same reduction in the target molecule. Blood components are separated by size in membrane filtration; thus, the size of molecules removed is limited by the size of the pores of the filter. It is a more selective method than centrifugation and leads to less thrombocytopenia compared with centrifugation [47]. In resource-limited countries, membrane filtration may be preferred because of the limited availability of centrifugal equipment and the reliance on a blood bank to supply blood products to avoid hypovolemia during centrifugal plasma exchange [105]. A group in Ottawa, Canada has published methods of plasma exchange using equipment familiar to the pediatric nephrologist: the Baxter BM25 machine, which is typically used for continuous venovenous hemofiltration. Smaller tubing is available for use in pediatrics, and there are two types of plasma filters [106]. This review will focus on centrifugal methods for plasma exchange, which is the most common method used in pediatrics in the USA and the procedure used for most of the trials described in the various 'Indications' sections of this review.

In critically ill children who require other simultaneous extracorporeal therapies (i.e. continuous renal replacement or extracorporeal membrane oxygenation), TPE can be done in parallel or in series with the other therapy [4, 107, 108].

Access

Most children will require a double-lumen, central venous catheter for plasma exchange. In children older than 10 years of age or weighing >30 kg, discontinuous therapy may be considered. For the latter, only one access site is required, and blood is withdrawn, processed and then reinfused through the same port. Continuous therapy, during which simultaneous withdrawal and infusion occur, is preferred in smaller children to avoid the large shifts in intravascular volume that are necessary for discontinuous therapies. Continuous plasma exchange requires two access ports. In some adolescents with adequate veins, TPE can be performed through two large-gauge peripheral intravenous lines, if the child is able to be still with both arms extended for the duration of the procedure. Based on our experience, a 17-gauge steel dialysis needle can be used to draw blood, and an 18-gauge short angiocath can be used to return cells and replacement fluid to the patient. Other groups have reported the use of even smaller needles (18-

gauge to draw and 22-gauge to return) [47]. Children weighing <30 kg require larger central access to achieve adequate blood flow rates to supply the cell separator without collapse of the patient's vessel. The catheters used are the same as those used for pediatric hemodialysis and have the advantage of being stiff enough to tolerate the negative pressure of the apheresis machine without collapse and large enough to allow for adequate blood flow rates, which may be as high as 2 mL/kg/min [109]. Because blood flow rates are lower than those necessary for hemodialysis, a smaller catheter can be used than would be necessary for hemodialysis, and we often place 9 French catheters in our adolescent and adult patients. When using a double-lumen catheter, blood is drawn from the proximal port and returned through the distal port to limit potential recirculation. The internal jugular vein is the preferred site of access; femoral catheters limit mobility and may have increased rates of infection, while subclavian catheters are at higher risk of mechanical failure and long-term vascular stenosis. If a longer duration of treatment is expected, a tunneled cuffed catheter should be placed, although temporary catheters can be used for emergent or single procedures if necessary. To date there have no studies reporting the use of arteriovenous (AV) fistulas or grafts for plasma exchange, although permanent surgical vascular access should be considered for patients who require long-term therapy (i.e. years).

Catheter-related complications are common in pediatric apheresis patients. In one series of pediatric apheresis patients, most of whom had tunneled central access for their procedures, catheter-associated thrombosis occurred in 12.4 % of patients (1.7 % of procedures) and infection (positive blood culture) occurred in 16.1 % of patients (2.1 % of procedures) [110]. This rate of infection (antibiotic course given) is lower than that reported for pediatric hemodialysis patients with indwelling central venous catheters (9 % of procedures) [111]. Infection rates can be reduced by hand-washing and diligent exit site care with chlorhexidine [112].

Sedation

For the rare child who is very anxious and cannot remain calm and cooperative even with reassurance and distraction provided by their family member(s) and sensitive staff, sedation is possible with benzodiazepines and antihistamines can be used [4].

Extracorporeal blood volume

The most important adaptation to ensure safety of plasma exchange in smaller children is modification of the treatment to avoid complications of the relatively large extracorporeal blood volume necessary to use the automated apheresis equipment. The blood volume removed acutely from the child at the initiation of plasma exchange is the equivalent of the volume

of the circuit, including the centrifuge, associated tubing and blood warmer. Blood volumes for commonly used equipment are included in Table 3. In addition, there is an obligatory red cell mass that is retained in the machine during the procedure to allow for separation of the blood components. This obligatory extracorporeal volume ranges from 200 to 400 mL depending on which machine is used and can represent a significant percentage of the patient's total blood volume [113]. Patient blood volume can be estimated by using pediatric formulae [114, 115] or sex-specific formulae developed in adults, which are determined by height and weight (Table 4) [116]. If the extracorporeal volume exceeds 10–15 % of the patient's blood volume, measures must be taken to avoid hypotension and acute blood loss anemia, and resultant impaired oxygen delivery [47]. By comparison, for a 70-kg adult male, 400 mL (the largest circuit) represents about 8 % of total blood volume (Table 4).

To avoid hypotension and acute blood loss anemia associated with relatively large extracorporeal volume, the circuit can be primed with packed red blood cells (PRBC) diluted to a hematocrit of 35 % with normal saline. After priming with saline, the centrifuge chamber is filled with donor blood. The saline prime is then diverted to the waste bag, and the return line is filled with donor blood [47]. While dilution is standard practice, a recent abstract reported ten children who received TPE with PRBC priming without dilution who did not develop polycythemia or volume overload [117].

With blood priming, successful plasma exchange has been reported in children weighing as little as 3.2 kg [118]. Most centers do not have a lower weight limit, although some use a lower weight limit of 5 or 10 kg for initiating TPE [119].

Hypotension is common in pediatric plasma exchange patients, occurring in 14 % of procedures, and fluid boluses are required in almost 5 % of procedures. Identifiable risk factors for hypotension include low patient weight, young age, renal disease, absence of blood primer and hypocalcemia [110]. Whether the patient can tolerate the removal of a large red cell mass without any compromise of their oxygen delivery must be determined based on the clinical circumstances, including volume status, cardiovascular status and hematocrit prior to the procedure.

Table 3 Obligatory extracorporeal volume of equipment for continuous pediatric plasmapheresis

Plasmapheresis equipment	Obligatory extracorporeal volume of equipment (mL)
Baxter BM25 plus filter	Neonatal: 85–100 Pediatric: 101–116
Cobe spectra	170
Cobe Optia	185
Fenwal Amicus	160

Table 4 Equations to estimate total blood volume in children

Equations	Blood volume
Russel 1949 [114]	
Weight (kg)	Blood volume (mL)
3–10	$58.2 \times \text{weight (kg)} + 42$
10–20	$82.7 \times \text{weight (kg)} + 17$
20–30	$95.7 \times \text{weight (kg)} - 274$
Nadler 1962 [115]	
Sex	Blood volume (mL)
Male	$0.3669 \times \text{height (m)}^3 + 0.03219 \times \text{weight (kg)} + 0.6041$
Female	$0.3561 \times \text{height (m)}^3 + 0.03308 \times \text{weight (kg)} + 0.1833$
Geigy scientific tables 1970 [116]	
Age	Mean blood volume per weight (mL/kg)
24 h	83
3 months	87
6 months	86
1 year	80
6 years	80
10 years	75
15 years	71
Adult men	71
Adult women	70

Hypothermia may also result as a consequence of large extracorporeal volume. A blood warmer, which requires an additional 20–50 mL of extracorporeal volume, can be used to prevent hypothermia in small children.

Anticoagulation

Regional anticoagulation with sodium citrate has been used for TPE in children for over a decade. Citrate chelates free ionized calcium to prevent activation of the clotting cascade in the extracorporeal circuit. Citrate is preferred to other types of anticoagulation because it is safe, relatively cheap and rapidly cleared in patients with normal hepatic function [120, 121].

The anticoagulant infusion rate is set relative to the blood flow rate, with a goal to achieve adequate anticoagulation of the circuit without inducing systemic toxicity. The manufacturer sets a default blood flow:anticoagulation ratio of 10–14:1. We typically use a ratio of 13–14:1 because patients with renal disease clear systemic citrate slower than patients with normal renal function [121]. To avoid systemic hypocalcemia, calcium chloride (8 g/L of normal saline) is infused into a return line at 0.4-fold the anticoagulant infusion rate, based on protocols developed for pediatric continuous renal replacement therapy. Calcium gluconate (20 mg/mL) at an infusion rate of 1 mL/kg/h can also be used.

Symptoms of citrate toxicity, including paresthesias, abdominal symptoms and headaches are another common adverse event in pediatric apheresis. Young children are often unable to communicate early symptoms of hypocalcemia, so frequent monitoring of serum ionized calcium and adjustment of the calcium infusion rate to maintain serum ionized calcium at levels of >1 mEq/L is recommended. For patient's receiving fresh frozen plasma (FFP) for replacement fluids, there may be an increased incidence of metabolic alkalosis and an increased calcium infusion requirement during the procedure due to a higher citrate load [122].

Unfractionated heparin anticoagulation has also been used for pediatric plasma exchange, with a target activated clotting time of 180–210 s. Multiple factors that contribute to a higher bleeding risk, including decreased coagulation factors and platelets, make heparin a less frequently utilized choice.

Determinants of substance removal/TPE prescription

The appropriate apheresis prescription depends on the characteristics of the pathogenic molecule that is targeted for removal. These characteristics include its volume of distribution, its equilibrium between the plasma space and the extravascular and intracellular compartments, and its rate of synthesis and catabolism. The volume of plasma processed, the frequency of therapy and the duration of therapy are modified to achieve maximum removal of the pathogenic molecule.

Volume to process

During each exchange, pathogenic molecules are removed only from the plasma space, such that molecules with a smaller volume of distribution (i.e. IgM) are removed more efficiently than molecules with a larger volume of distribution (i.e. IgG). Molecules that rapidly equilibrate between the plasma space and extravascular and intracellular space can be more efficiently removed as the plasma space is replenished during the treatment. In the simplest model, the relationship between the removal of plasma constituents and volume processed during a treatment with plasma exchange demonstrates exponential decay, such that efficiency is reduced as higher exchange volumes are achieved [123]. When a 1.5-fold plasma volume exchange is performed, 63–72 % of the original plasma components are removed, but extending the procedure beyond 1.5-fold plasma volume does not provide much additional benefit in the removal of the pathogenic molecules (Fig. 1). Because of this, each treatment aims to remove 1- to 1.5-fold the patient's plasma volume. Plasma volume is calculated as:

$$\text{Plasma volume} = \text{Blood volume} (1 - \text{Hematocrit}/100)$$

Fig. 1 The percentage of pathologic substance removed with a single treatment of plasma exchange can be calculated as $\% = e^{-(\text{plasma volume removed}/\text{patient plasma volume})}$

Frequency and duration of treatment

After depletion with TPE, the plasma level of the pathogenic molecule rebounds as it redistributes from the extravascular space back to the plasma space and as ongoing synthesis occurs. The rate and magnitude of rebound is determined by the characteristics of the molecule in question. For example, IgM, which is a large molecule, is distributed mostly in the intravascular space, and therefore the total body level of IgM is efficiently reduced with plasma exchange. This is the case in Waldenström's macroglobulinemia, in which the associated hyperviscosity can be treated effectively with one or two treatments. IgG and IgA, on the other hand, distribute in the extravascular space in addition to the intravascular space, so while IgA and IgG are cleared at a similar rate to that of IgM, they reaccumulate in the plasma space more quickly, and diseases mediated by IgA and IgG thus require more frequent plasma exchange. This has recently been described in mathematical models which are beyond the scope of this article [124]. In addition, synthesis can be modified with concurrent use of immunosuppression in most conditions. For most disease processes, TPE frequency is tapered as the markers of the disease activity improve.

Replacement fluids

The replacement fluids used in children are the same as those used in adults. In aHUS and TTP, FFP is used to replace removed plasma. In other conditions, 5 % albumin alone or a combination of colloid (5 % albumin) and normal saline can be used, usually at a ratio of 2:1 albumin:saline. If frequent (daily) treatments are required or if the patient does not have normal synthesis of coagulation factors (i.e. fibrinogen <100 mg/dL prior to treatment), partial replacement with FFP can be used to restore normal coagulation.

Other complications of plasma exchange

Complication rates in adult series are low at approximately 5 % (excluding transient paresthesias and mild vasovagal events), with higher rates among patients who receive plasma compared with those who do not [125]. Children appear to be at higher risk for complications, including more hypotension, symptomatic hypocalcemia, allergic reactions, severe anemia and catheter infection or thrombosis, affecting up to 55 % of procedures and 82 % of patients. Lower body weight, higher number of procedures and lower hemoglobin were associated with more events [110]. The most common adverse reactions (hypotension secondary to high extracorporeal volume, citrate toxicity and catheter-related complications) are discussed above. There are several other complications that should also be considered, including medication removal, transfusion reactions, removal of beneficial immunoglobulins, and impaired coagulation. These are discussed below.

Medication removal

Medications with a low volume of distribution and which are highly protein bound may be removed by TPE at rates that affect their efficacy. For children undergoing plasma exchange for renal indications, the most important considerations are immunoglobulins, including IVIG, basiliximab and rituximab [126]. Some commonly used antibiotics (cephalosporins, vancomycin) or antiepileptic medications (phenytoin, valproate) may require supplementation or dosing after TPE when possible. On the other hand, corticosteroids, cyclosporine and tacrolimus are only minimally removed by TPE.

Complications of transfusion with human blood products

Complications of transfusion with human blood products introduce additional risks for patients who require blood priming or FFP with the procedure, including transmission of viral infections and transfusion reactions such as hemolysis and acute lung injury. The risk of transmission of viral infections is extremely low in the USA, where blood products are screened extensively. The rate of any non-infectious complication of blood product transfusion is approximately 11 per 1,000 units transfused in a large pediatric population [127]. To avoid transfusion reactions, we typically give acetaminophen (15 mg/kg) and diphenhydramine (1 mg/kg) prior to transfusion. If the patient has had a transfusion reaction in the past, corticosteroids can be used in addition to the above-mentioned prophylactic medications.

Removal of immunoglobulins

Therapeutic plasma exchange not only removes pathogenic molecules but also normal immunoglobulins, and immunoglobulin

levels have been demonstrated to be lower in patients undergoing plasma exchange [128, 129]. This does not appear to be associated with a higher rate of infection [128], and levels have been shown to return to baseline after 35 days [129]. Some investigators have suggested that FFP supplementation as part of replacement fluids be used in actively infected plasma exchange patients with IgG levels of <100 mg/dL [130]. In patients undergoing frequent plasma exchange, low-dose IVIG (100–150 mg/kg/dose) infusions have also been used to avoid hypogammaglobulinemia [49].

Depletion of coagulation factors

Levels of coagulation factors are transiently depleted by TPE without FFP supplementation [129]. Most coagulation factors are rapidly synthesized by the liver, and in patients with normal hepatic function, prothrombin time and partial thromboplastin time normalize within 24 h, and fibrinogen normalizes within 48–72 h [129]. Fibrinogen levels should be checked prior to plasma exchange, especially in patients undergoing therapy more frequently than every other day. It is generally agreed that replacement with partial or full volume FFP should be used to avoid bleeding complications if fibrinogen levels are <100 mg/dL prior to a TPE treatment. For patients undergoing TPE in the 48 h before or after surgical procedures, including central venous catheter placement, we recommend replacement with partial or full volume FFP to avoid potential bleeding complications.

Electrolyte abnormalities

There is potential for hypokalemia when the replacement solution used is albumin as it contains a potassium level of <2 mEq/L. Aluminium toxicity has been reported in the past, particularly in patients with impaired renal function due to elevated aluminium content of some albumin preparations. Finally, as discussed above metabolic alkalosis may result from the use of citrate anticoagulation or FFP. Electrolytes should be monitored closely and deficiencies replaced as necessary.

Bradykinin release syndrome

Patients on angiotensin converting enzyme-inhibitors, which inhibit bradykinin breakdown, can develop atypical reactions during plasma exchange because TPE can activate kinins. Reactions can be mild (flushing and hypotension) or rarely can result in anaphylactic reactions, so it is generally recommended that ACE-inhibitors be avoided in patients undergoing plasma exchange [131].

Conclusion

Therapeutic plasma exchange is a safe and effective therapy in children with a variety of renal diseases, but requires specialized care and practitioners experienced in the care of children to meet their specialized needs. More data, especially in children, are necessary to assess the benefit of TPE in these and other renal conditions.

Multiple choice questions (answers appear following the references)

1. Plasma exchange is accepted as a first-line therapy for treatment of these conditions EXCEPT:
 - a) Recurrent FSGS
 - b) Antibody-mediated kidney allograft rejection
 - c) Lupus nephritis
 - d) ANCA-associated rapidly progressive glomerulonephritis and dialysis dependence
 - e) Atypical HUS due to autoantibody to factor H
2. Which of the following complication is NOT associated with citrate anticoagulation
 - a) Hypocalcemia
 - b) Hypotension
 - c) Metabolic alkalosis
 - d) Hypokalemia
 - e) Paresthesias
3. A 10-year-old girl presents with anemia, thrombocytopenia and renal failure. A diagnosis of aHUS is made and plasma exchange initiated. The replacement solution to be used should be:
 - a) Albumin 5 %
 - b) A combination of albumin 5 % and normal saline
 - c) Packed red blood cells
 - d) Fresh frozen plasma
4. A 2-year-old boy (weight 10 kg) is 1-year post-renal transplant. He has evidence of acute antibody-mediated rejection on transplant biopsy. Therapy with automated equipment for plasma exchange is considered. Which of the following statement is TRUE:
 - a) Plasma exchange cannot be performed because he is too young
 - b) A combination of albumin and normal saline can be used for the replacement fluid
 - c) The circuit should not be primed with blood products
 - d) Peripheral venous access can be used for the procedure

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Answers

1c
2d
3d
4b