THERAPEUTIC PLASMA EXCHANGE IN CRITICALLY ILL CHILDREN: EXPERIENCE OF THE PEDIATRIC INTENSIVE CARE UNIT OF TWO CENTERS IN CHILE

Raul Bustos B, Lilian Hickmann O, Pablo Cruces R, Franco Díaz

PII: S1473-0502(21)00147-6

DOI: https://doi.org/10.1016/j.transci.2021.103181

Reference: TRASCI 103181

To appear in: *Transfusion and Apheresis Science*

Received Date: 26 February 2021

Revised Date: 30 May 2021

Accepted Date: 4 June 2021

Please cite this article as: { doi: https://doi.org/

THERAPEUTIC PLASMA EXCHANGE IN CRITICALLY ILL CHILDREN: EXPERIENCE OF THE PEDIATRIC INTENSIVE CARE UNIT OF TWO CENTERS IN CHILE

Raul Bustos B, MD

Unidad de Cuidado Intensivo Pediátrico, Clínica Sanatorio Alemán y Hospital Guillermo Grant Benavente, Concepción, Chile .

Mail: robustos64@hotmail.com

Lilian Hickmann O, MD

Unidad de Cuidado Intensivo Pediátrico, Hospital Guillermo Grant Benavente, Concepción, Chile.

Mail: lilihickmann@gmail.com

Pablo Cruces R, MD

Unidad de Paciente Crítico Pediatrico, Hospital El Carmen, Maipú, Chile.

Escuela de Medicina Veterinaria, Facultad de Ciencias de la Vida, Universidad Andres Bello, Santiago, Chile.

Mail: pcrucesr@gmail.com

Franco Díaz, MD, MBA.

Unidad de Paciente Crítico Pediátrico, Hospital El Carmen, Maipú, Chile.

Escuela de Medicina, Universidad Finis Terrae, Santiago, Chile

Mail :francodiazr@gmail.com

Abstract

Introduction : Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique used in a wide spectrum of diseases. We aim to review the indications, complications, and outcomes of critically ill children who received TPE and to compare a membrane versus centrifugal method in this cohort.
Methods : A retrospective observational study in two pediatric intensive care units in Chile during eight years (2011–2019) Results: A total of 36 patients underwent 167 TPE sessions (20 centrifugation and 16 membrane-based). The more frequent indications for TPE were autoimmune neurological diseases in 14 cases, renal diseases (9), and rheumatological disorders (5). 58% of children received other immunomodulatory therapy. According to ASFA, 45% of cases were I-II category, 50% to III, and 5% not classified. Response to treatment was complete in 64% (23/36) and partial in 33% (12/36). Complications occurred in 17.4% of sessions, and the most frequent was transient hypotension during the procedure. Overall survival at discharge from the PICU was 92%. Patients who received TPE as a single therapy (n = 26) survived 96%. The clinical outcomes between the two apheresis methods were similar. Survivors had a significantly lower PELOD score on admission (14.5 vs. 6.5, p= 0.004).
Conclusions: TPE is mainly indicated as a rescue treatment in neurological autoimmune diseases refractory to conventional immunomodulatory treatment.
Complications in critically ill children are mild and low. The outcome in children requiring TPE as a single therapy is good, and no differences were observed with centrifugation or membrane method.
Keywords: therapeutic plasma exchange; plasmapheresis; autoimmune encephalitis; Pediatrics

INTRODUCTION

Therapeutic plasma exchange (TPE) is a blood purification technique that removes high molecular weight substances. Elimination of these compounds may help recover homeostasis when these molecules play a significant role in the disease's pathological processes. Some examples are pathogenic autoantibodies, immunocomplexes, cryoglobulins, endotoxins, and cytokines (1).

TPE requires an extracorporeal circuit to separate the blood into its components, then they are modified by interaction with a centrifuge or filter and returned to the patient. TPE is especially useful when the substances to be removed are large, higher than 15000Da, and have a long half-life (2). TPE is challenging in children due to the usual technical difficulties of extracorporeal therapies and the lack of consensus regarding indications, dose, frequency, therapy goals, and exposure to blood components at a young age. Some of these limitations

are especially important in developing countries, given the deficiency of technologies, human resources, and its high cost in a stressed budget health system.

With these thoughts in mind, we designed this study to review the indications -according to 2019 American Society for Apheresis (ASFA) guidelines (3) – complications and outcomes of critically ill children that received TPE in a pediatric intensive care unit (PICU) of two tertiary centers in Latin America. The secondary aim was to compare a membrane vs. centrifugal method of TPE in this cohort.

PATIENTS AND METHODS

This study is a retrospective chart review of critically ill children admitted to PICUs in two tertiary centers of Concepción, Chile, over eight years (from August 2011 to September 2019). Both units are polyvalent, with a total capacity of 16 beds, taking care of medical and surgical pediatric patients, except for congenital heart defects surgery and pediatric ECMO support. The local ethics committee approved the study, and informed consent was waived because of its retrospective nature. Patients younger than 18 years old admitted to PICU for TPE were included.

Demographic data, diagnoses, pediatric risk index of mortality scale (PRISM III), and pediatric logistic organ dysfunction (PELOD 2) were collected at admission. Mechanical ventilation (MV), vasoactive drugs (VAD) and renal replacement therapy (RRT) requirement and duration, immunomodulatory therapy received, PICU length of stay, and complications

of the technique and outcome expressed as mortality during PICU stay were also recorded. The indications for TPE utilization were recorded and compared with ASFA indication categories (3).

The procedure was performed with two methods: a centrifugal system COBE Spectra (TerumoBCT,Lakewood,CO, USA) at PICU Clínica Sanatorio Aleman and the membrane system, Prismaflex™ (Baxter, Minneapolis, USA) in the PICU of Hospital Guillermo Grant Benavente. With the membrane system, a Prismaflex™ TPE 1000 set (0.15 m^2 filter with 73 mL circuit blood volume) was used for the children under 15 kg, while Prismaflex™ TPE 2000 set (0.35 m^2 filter with 125 mL circuit blood volume) was used for children over 15 kg. ACD–A was used as anticoagulation in the centrifugal system and heparin in the membrane system, aiming for an activated clotting time (ACT) of 150–180 s.

A double lumen hemodialysis catheter (Mahurkar™, Medtronic, Minneapolis, USA) was obtained exclusively for TPE. The catheter was inserted in the internal jugular, subclavian, or femoral vein. Catheter size was selected based on body weight: 7.0F catheter for ≤10 kg, 8.0F catheter for 10 to 20 kg, 9.0 to 10.0F catheter for 20 to 50 kg, and 11.0F catheter for >50 kg. The estimated plasma volume (EPV) was adjusted according to the formula EPV=80 × weight (kg) × (1 - Ht)/100. We aimed to exchange 1–1.5 times the EPV (3). In children < 10 kg in whom the extracorporeal volume exceeded 10% of their total blood volume, the circuit was primed with cross-matched packed red blood cells before the start of TPE.

To mitigate citrate toxicity, we use a 1 mL/kg/hr drip of 20 mg/mL calcium gluconate in normal saline solution, adjusted as necessary for symptoms and/or low (<1.0 meq/L) ionized calcium

The selected replacement solution was fresh frozen plasma in patients with thrombotic microangiopathy (TMA), hemophagocytic lymphohistiocytosis (HLH), or macrophage activation syndrome (MAS), while 5% albumin is used as replacement for neurological diseases and intoxications. The efficacy of the technique was determined using the criteria of Panglialonga et al., which are based on clinical and laboratory parameters according to the pathology (4).

Procedural complications were classified as circuit complications (clotting, malfunction) and complications related to the patient (hypotension, anaphylaxis, hypocalcemia).

Statistical analysis was performed by Statistical Package for Social Sciences for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as median (interquartile range), and categorical data are expressed as proportions. Comparisons among continuous variables were performed with the Wilcoxon signed-rank test. Significance was set at $p < 0.05$.

RESULTS

167 TPE sessions on 36 patients were analyzed during the study period. The demographic and clinical characteristics of the patients included are shown in Table 1. Five children were younger than two years old. 58% of patients received MV, 44% VAD, and 9 (25%) RRT. RRT modalities were hemofiltration in four patients, peritoneal dialysis in three patients, and hemodialysis in two patients. Immunomodulatory therapy was prescribed before or after TPE in 21 (58%) children. Drugs for immunomodulation were methylprednisolone in 19 patients, immunoglobulin in 18 patients, rituximab in 4 patients, cyclosporine in two patients, eculizumab, and cyclophosphamide in one patient each.

Twenty children received TPE using a centrifuge technique and 16 using a membrane technique. Patients who underwent TPE with membrane technique had lower PELOD scores

at admission than centrifuge technique, without other clinical or demographic differences. When comparing both methods, there were no significant differences in MV duration, PICU length of stay, use of renal replacement, and mortality (Table 2).

The indications for TPE, ASFA category, and the response to therapy are shown in Table 3. According to ASFA classification, 12 (33%) patients corresponded to category I, 4 (11%) to category II, and 18 (50%) to category III. Two (5,5%) patients were not categorized since their diagnoses are not included in the 2019 ASFA guidelines.

The autoimmune encephalitis etiology was Anti-N-Methyl D-Aspartate (NMDA) antibodies in four cases, anti-thyroid peroxidase antibodies (AntiTPO) in 1 child, and 1 case in which the autoimmune panel was negative. Three children had atypical hemolytic uremic syndrome (HUS) and three Shiga toxin-producing Escherichia coli (HUS-STEC).

Three children had septic shock and Thrombocytopenia–Associated Multiple Organ Failure (TAMOF), triggered by *Streptococcus pneumoniae* meningitis, *Klebsiella pneumoniae* sepsis, and fulminant influenza (H3N2) infection. TPE was combined with hemofiltration in two of those cases.

A patient presented with severe rhabdomyolysis due to intentional ingestion of selective serotonin reuptake inhibitors (citalopram and paroxetine). In this case, maximum CK was 109.000 IU, and TPE and hemodialysis were used alternately.

The unclassified group corresponded to two children: a patient with *purpura fulminans* with low plasma protein C and S activities secondary to varicella infection. This case presented a favorable clinical outcome. The other case was a child with enterovirus-related acute flaccid myelitis in which the TPE did not change the clinical course.

For the whole group, response to TPE according to Paglialonga et al. (4) criteria were 64% (23/36) complete and 33% (12/36) partial.

Procedural complications are shown in Table 4. Complications of TPE occurred in 29 of the 167 (17.4%) TPE sessions. Arterial hypotension that required a fluid bolus administration and an increase in VAD dose was observed in 12 procedures, 5 in membrane and 7 in centrifugal system. None of these complications led to a discontinuation of the therapy. An anaphylactic reaction to plasma was reported in a child with Guillain-Barré syndrome, and one case of transfusion-related acute lung injury was observed in membrane system. Nine filters clotted prematurely, all in the membrane system (Prismaflex™). Six catheter dysfunctions were observed, 3 in each group, requiring the placement of another catheter.

Thirty-three children (92%) survived PICU discharge. Three patients died, all in the group of children who received centrifuge TPE. Deceased patients had a PELOD 2 score at admission significantly higher than those who survived (14.5 vs. 6.5, $p = 0.0041$). The causes of death were not related to the TPE procedure: one patient with refractory shock four days after the TPE procedure, one patient due to fulminant liver failure with severe brain edema and subsequent cerebral herniation, and one child with *Trichosporum* sepsis after liver transplant. 78% of children that received RRT survived PICU discharge.

DISCUSSION

In this study, we described TPE use in a heterogeneous population of critically ill children. The procedures were well tolerated without significant complications. Clinical response to the patient's treatment and outcomes was good, despite the fact that more than half of patients were with life support therapies, like MV and VAD. The most frequent causes for TPE were autoimmune neurologic and renal diseases. Interestingly, TPE is considered a first-line treatment in one-third of the analyzed children according to the underlying diagnosis and ASFA I classification. Most of the patients were classified ASFA III, therefore TPE role use has not been well established in those diseases (3).

Unlike patients with general diseases, there is still limited experience for the use of TPE, specifically in critically ill children. Plasmapheresis use has been extended to many pediatric disorders, and the frequency of TPE in children has been steadily increasing over the last years. The indications TPE and outcomes of children vary according to the patient's age and complexity of the centers. Sik G. et al. analyzed 135 patients that received plasmapheresis over five years. Patients were younger than our cases, and the most frequent diagnoses were sepsis with multiorgan failure, hematological diseases, and autoimmune neurologic disorders (5). Cortina G. et al. described 48 patients over eight years in a high complexity PICU. Hematologic disorders, solid organ transplantation, and neurologic disorders were the most frequent indications (6). TPE was performed with membrane technique in both series, and the most frequent complications were related to circuit clotting and catheter dysfunction. TPE with membrane technique has the advantage that it can be easily combined with other extracorporeal therapies and is usually the choice in sicker patients. In our study, the PELOD score was higher in patients who received plasmapheresis with the centrifuge system, so it

can be challenging to select each patient's appropriate technique, considering hemodynamic instability, renal failure, hematologic and coagulation abnormalities. Similar to our findings, in both series the patients who died presented a greater multiorgan involvement upon admission.

The main indication for TPE in our study was neurological immune disorders, and the response to the treatment was complete in 86% of cases. This is in accordance with the emerging consensus for early prescription of TPE, even as first-line therapy, in association with steroids and immunoglobulins in autoimmune neurological disease (7-10). All ASFA I neurological diseases in our cohort, specifically autoimmune encephalitis and Guillain Barré syndrome, had an excellent clinical response. Although TPE is an important tool in the acute stabilization of neuroimmune diseases, it does not modify the underlying process and clinical course. Therefore, TPE and other first-line therapies should not delay the escalation to second-line therapies when indicated (11-12).

The second most frequent indication for TPE in our series was renal diseases, and all had a partial response to treatment, even considering that 2 cases were ASFA I category. HUS-STEC with neurological involvement had the highest frequency. Although HUS is usually cataloged as renal disease, some of the pathophysiologic mechanisms fit in hematologic disorders. In this way, HUS-STEC mortality is associated with neurological complications and not only due to renal failure and renal support requirement (13). TPE could theoretically allow the elimination of Shiga toxins, pro-inflammatory cytokines, and prothrombotic factors. However, robust data to support TPE use in HUS and its efficacy is scarce. A recent review, consistent with ASFA guidelines, places the indication for TPE in category III and concludes that the efficacy of TPE in this scenario is still uncertain (14).

Interestingly, half of the patients that received TPE corresponded to ASFA III, and half of them had a complete response to treatment. The cases with a complete response to treatment were TAMOF, MAS, acute liver failure, and poisoning.

TAMOF is an inflammatory phenotype induced by sepsis and multiple organ dysfunction in children, which can be identified clinically by thrombocytopenia and multiple organ failure (15). These patients have a deficient disintegrin and metalloproteinase activity with thrombospondin type 1 motif (ADAMTS-13), elevated von Willebrand factor (VWF) activity, and the presence of ultra-large VWF plasma. TPE could exert its effect by removing inflammatory mediators, reducing antifibrinolytic molecules, replenishing anticoagulant proteins, and restoring the activity of ADAMTS-13 (16). In our cohort, all patients that received TPE due to TAMOF responded to treatment. This is in accordance with some observational data that described a decrease in organ failures and mortality in children with TAMOF treated with TPE (17). Despite these promising results, TPE user in any disease related to sepsis is exceptionally used in children. For instance, it is not even mentioned in the 2020 Sepsis Survival Campaign guidelines (18).

Our cohort's rheumatological pathologies were Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS). The mainstays of treatment of primary and infection-associated secondary HLH are immunomodulation and immunosuppression, with different combinations of agents, including immunoglobulins, steroids, cyclosporin A and Etoposide (19). Treatment in non-responders is challenging, and mortality has been reported between 30% and 80% (20). There are some reports of successful use of TPE for HLH and MAS. The rationale for using TPE in these disorders includes removing toxic substances related to organ failure (particularly liver failure) and suppressing the hyperinflammatory syndrome secondary to cytokine storm. One small RCT study showed

promising results of a combination of TPE with other conventional treatments for infection-associated secondary HLH. TPE combined with methylprednisolone or IVIG therapy had better survival compared to TPE and dexamethasone or cyclosporine or etoposide or their combinations (100% vs. 50% survival) (21,22). As ASFA guidelines recommend, the role of TPE is still uncertain (ASFA III).

We used TPE in three children with fulminant hepatic failure (FHF) as a "bridge" to transplant. In FHF, TPE can quickly eliminate the toxins and inflammatory mediators responsible for hepatic encephalopathy, hyperdynamic circulation, and decreased systemic vascular resistance. TPE can also restore hemostasis by providing clotting factors and removing activated clotting factors, tissue plasminogen activator, fibrin degradation products, and fibrinogen. A recent meta-analysis concluded that the use of TPE in FHF was associated with a decrease in mortality at 30 and 90 days (23). Specifically, in children with FHF waiting for a transplant, an observational study found that TPE combined with RRT and an albumin-assisted dialysis system resulted in successful liver transplants in 9 out of 15 children (24). Extracorporeal therapies in this setting are still being explored, so strong data to support them are lacking.

Finally, poisonings caused by drugs or toxic substances with high protein affinity are good candidates for TPE, like the case reported in our cohort. A few case reports and clinical series have been published (25-26), but the information is still scarce in children and adolescents. A recent report of 14 children with severe poisonings showed promising results in multiple and single poisonings with amitriptyline, carbamazepine, with clinical recovery in 13 patients (27).

We observed a similar frequency of complications described in previous reports. It is important to note that the reported complications in critically ill children are different from

programmed plasmapheresis. Besides hypertension and hypotension, replacement-related complications, like allergic reactions and other symptoms like nausea and dyspnea, might be underreported in the PICU (28). On the other hand, critically ill children might present more frequently circuit complications and clotting. These complications have been reported in series of small children with membrane system technique. In our cohort, we did not find a higher frequency of complications in infants, but clotting issues of the filter was observed only in membrane system (5,29,30). Our data cannot recommend one method over another. Although our current practice is to prefer the membrane system in critically ill children older than 1 year old without requirement of CRRT.

Among the limitations of our study, due to its retrospective design, it is subject to this type of studies' usual pitfalls. The small sample size prevents subgroups comparisons, because a type II error cannot be ruled out. In most centers worldwide, there is a lack of standardization in the indication, prescription, and number of TPE sessions, which in most cases are decided by the PICU team. This is the case of the PICUs analyzed in this study. With the lack of a control group and the simultaneous treatments of the diseases, it is difficult to attribute some patients' functional improvement as an exclusive effect of the TPE treatment. We believe that the high frequency of ASFA category III cases in our cohort probably reflects the lack of evidence in children and the evolving clinical indications for TPE over the last years, despite the periodic updates in the ASFA guidelines.

Our study's strengths are that it includes two centers with heterogeneous diseases and good outcomes using different TPE techniques. It is important to highlight that the analyzed cases were only critically children, mostly with organ support therapies like MV, vasoactive drugs,

or renal replacement therapy. This group of children is poorly described, even in large cohort studies, and represents a significant knowledge gap in pediatric intensive care.

In conclusion, we characterized a cohort of children that received TPE. The main indications for that therapy are severe autoimmune neurological diseases resistant to standard immunomodulatory treatment. Complications due to the procedure were low and mild, and overall outcomes were good. We observed no differences in clinical outcomes according to the technique used.

Credit Author Statement
RB, LH designed the study.
RB, FD and PC wrote the manuscript.
RB, LH collected the data.
All authors reviewed and approved its final version. All authors read and approved the final manuscript.

References

[1] 1.- Haque A, Sher G, Hoda M, Moiz B.Feasibility of pediatric plasma apheresis in intensive care settings.Ther Apher Dial. 2014 ;18:497-501.

[2] 2.-Kaplan AA Therapeutic plasma exchange: a technical and operational review. J Clin Apheresis 2013; 28:3-10

[3] 3.-Padmanabhan A, Connelly-Smith L, Aqui N 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; 34:171-354.

[4] 4.-Paglialonga F, Schmitt CP, Shroff R et al. Indications, technique, and outcome of therapeutic apheresis in European pediatric nephrology units. Pediatr Nephrol. 2015 ;30:103-11.

[5] 5.- Sık G, Demirbuga A, Annayev A, Akcay A, Çıtak A, Öztürk G. Therapeutic plasma exchange in pediatric intensive care: Indications, results and complications. Ther Apher Dial. 2020 ;24:221-229.

[6] 6.-Cortina G, McRae R, Chiletti R, Butt W. Therapeutic Plasma Exchange in Critically Ill Children Requiring Intensive Care. Pediatr Crit Care Med. 2018 ;19:e97-e104.

[7] 7.- Byrne S, Walsh C, Hacohen Y, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. Neurol Neuroimmunol Neuroinflammation 2015; 2: e130

[8] 8.-Suppiej A, Nosadini M, Zuliani L, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: a systematic review. Brain Dev 2016; 38: 613–22.

[9] 9.-Eyre M, Hacohen Y, Lamb K, et al. Utility and safety of plasma exchange in paediatric neuroimmune disorders. Dev Med Child Neurol 2019; 61: 540– 6.

[10] 10.- Savransky A, Rubstein A, Rios MH, Vergel SL, Velasquez MC, Sierra SP, Marcarian G, Alba R, Pugliese AM, Tenembaum S. Prognostic indicators of improvement with therapeutic plasma exchange in pediatric demyelination. Neurology. 2019 ; 93:e2065-e2073

[11] 11.- Eyre M, Hacohen Y, Barton C, Hemingway C, Lim M. Therapeutic plasma exchange in paediatric neurology: a critical review and proposed treatment algorithm. Dev Med Child Neurol 2018; 60: 765– 79.

[12] 12.- Therapeutic plasma exchange in paediatric neuroimmunology: some evidence but more is needed, Developmental Medicine & Child Neurology 2019, 61: 504-5.

[13] .-Manrique-Caballero CL, Peerapornratana S, Formeck C, Del Rio-Pertuz G, Gomez Danies H, Kellum JA. Typical and Atypical Hemolytic Uremic Syndrome in the Critically Ill. Crit Care Clin. 2020 ;36:333-356.

[14] 14.-Keenswijk W, Raes A, De Clerck M, et al. Is plasma exchange efficacious in shiga toxin-associated hemolytic uremic syndrome? A narrative review of current evidence. Ther Apher Dial 2019;23:118–25.

[15] 15.-Nguyen TC. Thrombocytopenia-Associated Multiple Organ Failure. Crit Care Clin. 2020 ;36:379-390

[16] 16.-Nguyen TC, Han YY, Kiss JE, et al. Intensive plasma exchange increases a disintegrin and metalloprotease with thrombospondin motifs-13 activity and reverses organ dysfunction in children with thrombocytopenia-associated multiple organ failure. Crit Care Med. 2008;36:2878-87

[17] 17.-Fortenberry JD, Nguyen T, Grunwell JR et al. Therapeutic Plasma Exchange in Children With Thrombocytopenia-Associated Multiple Organ Failure: The Thrombocytopenia-Associated Multiple Organ Failure Network Prospective Experience. Thrombocytopenia-Associated Multiple Organ Failure (TAMOF) Network Study Group. Crit Care Med. 2019 ;47:e173-e18

[18] 18.-Weiss SL, Peters MJ, Alhazzani W et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med. 2020 ;21:e52-e10

[19] 19.-Carcillo JA, Simon DW, Podd BS. How We Manage Hyperferritinemic Sepsis-Related Multiple Organ Dysfunction Syndrome/Macrophage Activation Syndrome/Secondary Hemophagocytic Lymphohistiocytosis Histiocytosis. Pediatr Crit Care Med. 2015; 16:598-600

[20] 20.-Lehmberg K, Nichols KE, Henter JI, et al. consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. 2015;100(8):997-1004

[21] 21.-Demirkol D, Yildzdas D, Bayrakci B, et al. for Turkish Secondary HLH/ MAS Critical Care Study Group. Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/ macrophage activation syndrome: what is the treatment? Critical Care. 2012;16:R52.

[22] 22.-Kinjo N, Hamada K, Hirayama C, Shimizu M. Role of plasma exchange, leukocytapheresis, and plasma diafiltration in management of refractory macrophage activation syndrome. J Clin Apher. 2017; :1–4.

[23] 23.- Tan EX, Wang MX, Pang J, Lee GH Plasma exchange in patients with acute and acute-on-chronic liver failure: A systematic review.World J Gastroenterol.2020; 14:219-245.

[24] 24.- Akcan Arikan A, Srivaths P, Himes RW et Hybrid Extracorporeal Therapies as a Bridge to Pediatric Liver Transplantation. Pediatr Crit Care Med. 2018 ;19:e342-e349.

[25] 25.-Kozanoglu I, Kahveci S, Asma S, Yeral M, Noyan A, Boga C, Ozdogu H.Plamsa-exchange treatment for severe carbamazepine intoxication: a case study. J Clin Apher. 2014;29 :178-80

[26] 26.-Sari I, Turkcuer I, Erurker T, Serinken M, Seyit M, Keskin A. Therapeutic plasma exchange in amitriptyline intoxication: case report and review of the literature Transfus Apher Sci. 2011:45:183-5.

[27] .- Özkale M, Özkale Y. The Role of Therapeutic Plasma Exchange in the Treatment of Childhood Intoxication: A Single-Center Experience. Pediatr Crit Care Med. 2020;21:e998-e995.

[28] 28.-Carter CE, Benador NM: Therapeutic plasma exchange for the treatment of pediatric renal diseases in 2013. Pediatr Nephrol 2014; 29:35–50).

[29] 29.- Cortina G, Ojinaga V, Giner T, et al. Therapeutic plasma exchange in children: One center's experience. J Clin Apher. 2017 ;32 :494-500.

[30] 30.- Duyu M, Turkozkan C. Therapeutic plasma exchange in the pediatric intensive care unit: A single-center 5-Year experience Transfus Apher Sci. 2020;59:102959.

Table 1: Clinical characteristics of children treated with therapeutic plasma exchange included in the study.

TPE: Therapeutic plasma exchange; ASFA: American Society for Apheresis; PRISM: pediatric risk index of mortality; PELOD: Pediatric logistic organ dysfunction; PICU: pediatric intensive care unit; MV: mechanical ventilation; VAD: vasoactive drugs; LOS: length of stay.

Variable	Median (IQR)
Age (years)	6 (4, 9)
Weight (kg)	22 (17, 38)
M/F ratio	1:1.2
PRISM III	11 (10, 18)
PELOD 2	7 (4, 11)
TPE sessions, n	167
TPE sessions per patients	5 (3, 6)
Immunomodulation, n (%)	21(58)
MV, n (%)	21 (58)
Vasoactive drugs, n (%)	16 (44)
Renal replacement therapy, n (%)	9 (25)
MV duration (days)	6.5 (4, 11)

VAD support duration (days)	3.5 (2, 5)
PICU LOS (days)	14 (8, 20)
PICU mortality, n (%)	3 (8)

Table 2: Comparison between plasmapheresis centrifuge and membrane technique

TPE: Therapeutic plasma exchange, ASFA: American Society for Apheresis PRISM: Pediatric risk index of mortality, PELOD: Pediatric logistic organ dysfunction, MV: mechanical ventilation, VAD: vasoactive drugs, PICU: pediatric intensive care unit, LOS: length of stay (IQR): Interquartile range

	Centrifuge n= 20	**Membrane n= 16**	**P-value**
Age (years)	6.8 (4, 10)	4.5(3, 6.3)	0.23
Weight (kg)	23 (19, 34)	20.5 (16, 35)	0.70
M/F ratio	1:1.2	1:1	0.66
PRISM III	11 (7.5, 18)	11 (10.5, 18)	0.55
PELOD 2	8 (6.5, 12.5)	4.5 (3.0,6.5)	0.02
ASFA I-II, n (%)	9 (45)	8 (50)	0.37
MV duration (days)	5 (2, 12)	5 (5,5.5)	0.85
VAD duration (days)	2 (0.5, 3.5)	4 (3,4)	0.27
PICU LOS (days)	15 (8.5, 24)	13 (9,155)	0.42
PICU mortality, n (%)	3 (15)	0	0.23

Table 3: Indication for therapeutic plasma exchange, sessions number, disease category according to American Society for Apheresis and response

ASFA: American Society for Apheresis; ADEM: acute disseminated encephalomyelitis; HUS: Hemolytic uremic syndrome; RPGN: Rapidly progressive glomerulonephritis; HLH: Hemophagocytic Lymphohistiocytosis; MAS: Macrophage Activation Syndrome; TAMOF: Thrombocytopenia-Associated Multiple Organ Failure; NC: Not categorized.

Diagnosis	**n (%)**	**TPE sessions**	**ASFA Category**	**Response to treatment**
Neurological disorders	14 (39)	69		12/14 (86%)
Autoimmune encephalitis	6	36	I	Complete
ADEM	3	14	II	Complete
Guillain Barré Syndrome	3	12	I	Complete
Acute Flaccid Myelitis	1	1	NC	No response
Neuromyelitis Optica	1	2	II	Partial
Renal	9 (25)	47		5/9 (55%)
HUS	6	31	III	Partial
RPGN	2	11	I	Partial
Renal Transplant rejection	1	5	I	Partial
Rheumatologic	5 (14)	23		4/5 (80%)
MAS	3	11	III	Complete
HLH	2	12	III	Partial
TAMOF	3 (8)	10	III	Complete

Fulminant liver failure	3(8)	12	III	Complete
Intoxication	1(3)	3	III	Complete
Purpura *fulminans*	1(3)	3	NC	Complete

Table 4. Complications observed for the whole cohort of children analyzed

Complications	**n (%)**
Circuit complications	
Circuit clotting*	9 (5.4)
Access dysfunction	6 (3.6)
Patient complications	
Hypotension	12 (7.1)
Anaphylaxis to fresh frozen plasma	1 (0.6)
Transfusion related acute lung injury	1 (0.6)
Total complications	29 (17.4)

*in the membrane system