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Plasma exchange is the hope for critically ill children with life-threatening autoimmune hemolytic anemia

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Abstract

Background Autoimmune hemolytic anemia (AIHA) is a rare disease in children, sometimes associated with acute, life-threatening, rapidly progressive course requiring prompt management. The aim of our study is to describe the role and outcome of plasma exchange in the acute management of pediatric patients with AIHA requiring transfusion and refractory to high doses of corticosteroids.

Methods This was a descriptive retrospective report of all patients admitted to the pediatric intensive care unit (PICU) of Children's University Hospital who received PE for acute intractable AIHA resistant to management with pulse steroids starting from June 2017 to June 2022. The demographic data, vitals, and laboratory investigations at PICU admission and upon discharge were gathered. The number of PE sessions needed for each patient, volume used for exchange, type of replacement, IV access used, complications, and outcome were reported.

Results This series included 19 patients, 10 males, and 9 females, with a median age and weight of 76 months (IQR 18–121), and 20.9 kg. Improvement of the mean hemoglobin was observed from 5.3 ± 1.8 to 9.9 ± 2.6 g/dl at discharge. The average number of PE sessions was 2.4 sessions with no adverse effects encountered. The mean PICU stay was 16.6 days. Mortality occurred in 2 patients (10.5%) due to their primary illness, while 7 patients (36.8%) were in need of further immunotherapy, and 5 patients (28%) showed relapse.

Conclusion PE may be used as a safe and successful therapy in children with severe acute life-threatening AIHA not responding to steroids, or if well-matched PRBCs are unavailable for transfusion.

Keywords Pediatric, AIHA, Plasmapheresis, Steroids, Plasma exchange

Background

Autoimmune hemolytic anemia (AIHA) is a rare condition in children that presents with varying degrees of severity. Acute presentation is typically a life-threatening, rapidly progressing condition that necessitates immediate diagnosis and treatment [15].

The annual incidence of AIHA is predicted to be around 0.8 per 100,000 children under the age of 18 [1]. It can be associated with immune disorders in 53% of cases. It has a modest fatality rate (4%), but if the hemolytic anemia is accompanied by immune thrombocytopenia, the mortality rate rises to 10% [16].

The most prevalent type of AIHA in children is caused by warm-reactive autoantibodies, and it is observed in more than half of AIHA episodes [14]. Cold reactive antibodies result in fewer common variants, such as cold agglutinin syndrome (CAS), and paroxysmal cold hemoglobinuria (PCH). A small percentage of cases are classified as "mixed AIHA" [15].

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Although juvenile CAS has a short duration and is self-limited [15], AIHA caused by warm antibodies has a chronic course and is not predicted to resolve without treatment. Warm AIHA can be fatal because of the severity of the presentation or because it is resistant to treatment and necessitates numerous lines of medication with frequently associated toxicity [5].

Glucocorticoids, usually prednisone, are administered orally as first-line therapy. Depending on the patient's clinical status, intravenous (IV) methylprednisolone may be needed, up to 30 mg/kg/day. Hemolysis reduction, hemoglobin stabilization, and packed RBC transfusion safety are the initial targets. Up to 80% of people respond to steroids within 24–72 h. After hemoglobin stabilization, steroids should be discontinued gradually over 6 months to avoid disease return [15].

For the first time, Burman, and Glader [12] reported clinical improvement in a child with AIHA using Plasma exchange (PE) therapy [12]. Following them, other case reports on the use of PE in children with AIHA were published.

PE can remove antibodies quickly, allowing for safe transfusion, and alleviating persistent hemolysis.

Methods

In this descriptive retrospective study, we included all patients with life-threatening AIHA presented from June 2017 to June 2022, aged 1 month to 14 years old of both sexes, admitted to the critical care unit of Children Cairo University Hospital.

All patients presented with acute hemolysis, as evident clinically by acute pallor and dark-colored urine, and laboratory by CBC, reticulocyte count, and direct antiglobulin test (DAT), with or without the underlying immune disorder, all of them had frequent mismatches or failed to obtain matched PRBCs for transfusion and all had received pulse steroid therapy. The presence of life-threatening acute anemia with organ dysfunction or failure has led us to initiate PE early. Immunosuppressive therapies previously described for AIHA such as cyclophosphamide and Rituximab are not immediately acting [13]. Some patients had failed to respond to IVIG while in others, PE was undertaken first to reduce product removal during the procedure.

Patients maintained isovolaemic during the session through volumetrically controlled filtration, 5% albumin in normal saline for replacement, and PRBCs given as the last part of the replacement. This aimed to remove sufficient antibodies to minimize auto- or alloimmune hemolysis of transfused RBCs with a high-grade mismatch.

The least mismatched available PRBCs were used with no limitation on the degree of mismatch. PRBCs were obtained from hospital blood banks or accredited outsourced services according to availability. All units were collected and the pathogen was tested according to standard laboratory and transfusion medicine techniques. They were ABO compatible and were cross-matched using a card-based procedure noting the degree of mismatch. Subsequent PE sessions were individualized based on response, rebound, and need for further transfusion(s).

Following a documented informed consent for the procedure from the patients' guardians, plasma exchange was done by the membrane plasma separation technique through the GAMBRO Prismaflex machine (SN.PA5870, 2010, Sweden), using the TPE 1000 filter for patients weighting < 10 kg and TPE 2000 filter for those more than 10 kg. One and a half plasma volume exchange session for the first session was done, and then a single plasma volume exchange for those needing further PE sessions. Heparin loading dose of 35 units/kg and maintenance of 15 units/kg was used as anticoagulation.

The medical records of the patients were obtained, and the following data was collected: age, sex, weight, associated comorbidities, steroids and other immunosuppressives used, need for system support (mechanical ventilation, and inotropic medications), vital signs upon admission, PICU length of stay, disease recurrence and outcome. Laboratory investigations such as CBC, reticulocyte count, DAT, indirect antiglobulin test, and liver, and kidney functions upon PICU presentation and at discharging were gathered. Also, the number of PE sessions needed for each patient, volume used for exchange, type of replacement, IV access used, and complications were documented.

The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Cairo University, Registration no.: N-53–2023.

Statistical analysis

Data were tabulated and analyzed using the Statistical Package for Social Science (SPSS) version 21 (SPSS, Armonk, New York: International Business Machines Corporation) and Microsoft Excel version 2013.

Nominal data were expressed as frequencies and percentages. Parametric data were presented as mean and SD, while non-parametric numerical data were presented using median and IQR, and were compared using the Wilcoxon rank-sum test. *P* values less than 0.05 were considered significant.

Results

We reported 19 AIHA cases over the past 5 years (2017–2022), our group included 10 males and 9 females, the median age of our patients was 5.5 years (IQR 1.5–10), and the mean weight was 20.9 kg (IQR 9–30) (Table 1).

Table 1 Characteristics of the studied group of patients and plasmapheresis sessions

Variable		Median	IQR
Age (years)		5.5	1.5–10
Weight (kg)		15.5	9.2–27.2
Associated comorbidities[a]		11	57.9%
Sex[a]	Male	10	52.6%
	Female	9	47.3%
Mechanical ventilation[a]	Yes	3	15.8%
	No	16	84.2%
Complications of PE[a]		1	5.2%
Length of PICU stay (days)		7	4–21
Number of PE sessions needed/patient[a]	1	7	36.8%
	2	6	31.5%
	3	2	10.5%
	> 3	4	20.8%
Recurrence[a]	Yes	5	26.3%
	No	14	73.6%
Mortality[a]	Living	17	89.5%
	Died	2	10.5%

IQR inter-quartile range, *PICU* pediatric critical care, *PE* plasma exchange

[a] Count, percentage

Eleven out of the 19 included patients had associated comorbidities, 3 of them had associated thrombocytopenia (Evan's syndrome), 3 immunodeficiency patients (lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency, severe combined immunodeficiency and hemophagocytic lymphohistocytosis (HLH)), 2 ß thalassemia major, 1 SLE patient, 1 urea cycle defect, and 1 inflammatory bowel disease patient.

Our entire study group had received pulse steroids, and 8 of them (42%) had received IVIG because all were indicated for urgent transfusion with difficulty in obtaining well-matched PRBCs.

Upon PICU admission, all of the 19 patients were tachycardic, and tachypneic for age, and 3 patients needed mechanical ventilation for respiratory support. The mean Hb at presentation was 5.3 ± 1.8 g/dl, mean hematocrit of 18 ± 5.1%, median TLC of 12 (IQR 6.2–16.4) × 10^3/mm^3, median platelets of 234 (IQR 121–343) × 10^3/mm^3, and median reticulocyte count of 10.2 (IQR 4.2–19.9)%. Antiglobulin test was done in 9 patients; positive results were found in 7 of them (77.7%).

The mean number of PE sessions needed in our study group was 2.4 sessions (max of 7 sessions in one patient). Only one patient (5.2%) showed PE session-related complications in the form of hypotension, which was managed with IVFs, and the session was completed successfully. Unfortunately, mortality in our study group was in 2 patients (10.5%), one of them related to his primary disease (SCID) (Table 1).

The mean PICU length of stay was 16.6 days. Seventeen patients showed favorable improvement with mean Hb at discharge of 9.9 ± 2.6 mg/dl and hematocrit of 30.1 ± 8.7% (Table 2). Seven patients (36.8%) at discharge were in need of further immunotherapy to maintain remission by immunomodulators: mycophenolic acid (3 patients), azathioprine (2 patients), rituximab (1 patient), and sirolimus (1 patient). Unfortunately, 5 patients (28%) showed disease recurrence months later after discharge (Table 1, Fig. 1).

Discussion

Pediatric AIHA is a rare hematological disorder that may be severely life-threatening, requiring systems support, and aggressive and rapid management [15].

Unfortunately, the presence of autoantibodies in the serum of some pediatric patients fails to achieve a good response even with intravenous pulse steroids to induce remission and to get well-matched PRBCs for transfusion. Previous research on adult patients showed that the use of PE therapy may be effective at treating AIHA. This is achieved through removing autoimmune antibodies from the intravascular space [3]. However, pediatric data on the use of PE in AIHA patients is almost lacking due to the rarity of these cases.

Warm antibody AIHA (w-AIHA) is the most common AIHA type in the pediatric population, and it

Table 2 Comparison between laboratory investigations of the studied group at presentation and at discharge

		Median	IQR	*p* value*
Hemoglobin (g/dl)	Admission	5.5	4.0–6.4	0.002
	Discharge	9.8	8.0–11.6	
Hematocrit (%)	Admission	17.0	13.7–19.3	0.003
	Discharge	30.3	27.1–34.3	
Total leucocytic count (× 10^3/mm)	Admission	12.0	6.2–16.4	0.003
	Discharge	5.6	3.0–13.3	
Platelets (× 10^3/mm)	Admission	234	121–343	0.096
	Discharge	169	86–207	
ALT (U/L)	Admission	44	32–47	0.388
	Discharge	31	19–55	
Albumin (mg/dl)	Admission	3.8	3.6–4.1	0.080
	Discharge	3.8	3.4–4.3	
BUN (mg/dl)	Admission	38.5	29.0–50.5	0.033
	Discharge	15.5	11.0–31.0	
Creatinine (mg/dl)	Admission	0.5	0.4–0.6	0.062
	Discharge	0.4	0.3–0.5	

IQR Inter-quartile range, *ALT* Alanine aminotransferase, *BUN* Blood urea nitrogen

* Wilcoxon rank-sum test

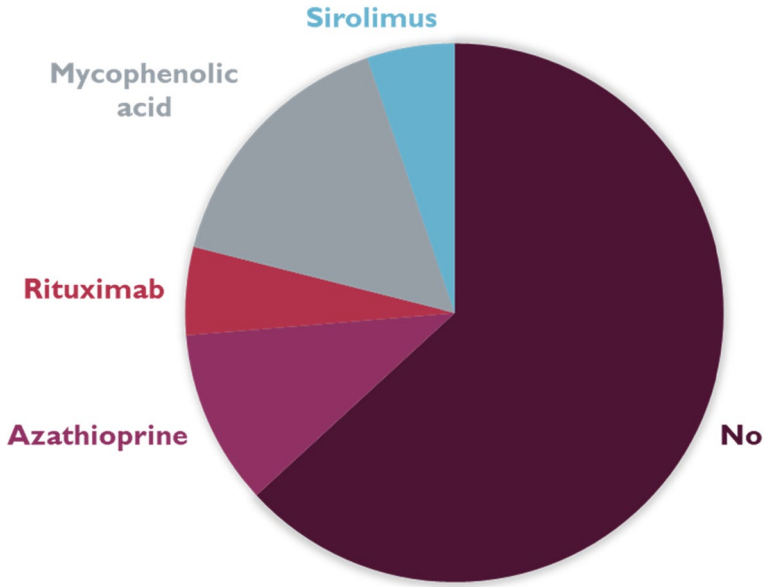

Fig. 1 Immunosuppressive treatment other than steroids used at discharge from the PICU

is classified as a category II recommendation for PE according to the latest American Society of Aphaeresis (ASFA) guidelines. However, cold agglutinin disease (CAS) and paroxysmal cold hemoglobinuria (PCH) are responsible for the less frequent, more resistant forms of the disease with the optimal role of apheresis therapy is not well established and decisions in those patients need to be individualized (ASFA Category III). In addition, a small subset of cases is recognized as mixed AIHA, with serological work-up revealing findings of both AIHA types [9, 15].

In our study, we have addressed 19 severe pediatric cases of AIHA with impending or actual hemodynamic instability and impending cardiovascular collapse from severe anemia. All patients showed initial failure of response to high doses of steroids (pulse IV methylprednisolone on 30 mg/kg/dose). All patients received PE sessions to be able to transfuse even the least mismatched PRBCs available for the patient (up to 4 + incompatible).

Most of our patients (57.9%) had associated immunological disorders, and this is well reported with cases of w-AIHA. While 40% of w-AIHA in children is idiopathic, underlying disorders leading to secondary w-AIHA most commonly include immunodeficiencies, autoimmune diseases, and infections (mostly viral) [15]. Less frequent causes include malignancies, and previous history of transfusions or transplantation [5].

Three of our patients (15.8%) had Evans syndrome, which accounts for up to 30% of all AIHA in children and is characterized by the presence of at least two immune cytopenias [11, 15]. Children with anemia and thrombocytopenia have remission later than the other children [10].

Forty-two percent of patients had received IVIG, either as an initial line of management with steroids pre-PICU admission with an unsuccessful response or as an adjuvant immunotherapy for patients with incomplete response after PE. This could help to emphasize the role of PE as an initial line of management in those AIHA pediatric patients with impending system collapse without wasting time with other treatment lines, especially when IVIG is not available and or costly.

Although mismatched PRBCs transfusion may be fatal with reported incidences between 5.5% and 30% [8]; no transfusion reactions related to PRBCs transfusion were observed in our study group, even with the use of the least mismatched PRBCs available (up to 4 + incompatible) during the PE sessions.

Relapse was defined as recurrence of anemia, along with hemolysis (i.e., reticulocyte count > 120,000/mm; haptoglobin < 10 mg/dL, indirect bilirubin > 1 mg/dL, lactate dehydrogenase twice normal limits), after having reached a complete response [6]. In our patients, 5 (28%) cases showed recurrence of the hemolytic manifestations months later with further need for PE sessions to control their acute manifestations.

Previously documented 5–eightfold risk of increased mortality in cases with Hb less than 6 g/dL at presentation, multi-treatment, acute kidney injury, Evans' syndrome, and infections [2]. A case series of 13 very severe relapsed/refractory primary AIHA reported a mortality

of 57%, despite treatment including Packed red cell transfusions, pulse steroids, IVIG, rituximab, and plasma-exchange [4]. More recently, 30% mortality was shown in a series of 44 AIHA patients admitted to intensive care unit for severe anemia [7]. In our study, there were two mortalities. One patient with primary AIHA developed several ICU complications, sepsis and died after 88 days of ICU stay. The other had SCID with secondary AIHA and died of severe infection complicating his immunodeficiency.

The retrospective nature of the study, the rarity of this disorder in the pediatric population and the lack of control group was a limiting factor for formulating a standard approach for management of severe acute pediatric AIHA refractory to first line management. However, to the best of our knowledge, we are the first to describe the role and outcome of PE in the acute management of a cohort of pediatric patients with AIHA requiring transfusion and refractory to high doses of corticosteroids rather than single case based reports.

Conclusion

In children with life-threatening acute AIHA, PE can be a life-saving measure, particularly when the condition is difficult to control with pulse steroids and well-matched PRBCs. PE is generally safe, with appropriate facilities and experience. Further large multicenter studies are recommended to formulate a guideline for management for those patients.

Abbreviations

AIHA	Autoimmune hemolytic anemia
ASFA	American Society of Aphaeresis
CAS	Cold agglutinin syndrome
CBC	Complete blood count
Hb	Hemoglobin
HLH	Hemophagocytic lymphohistocytosis
HTN	Hypertension
IV	Intravenous
LRBA	Lipopolysaccharide- responsive and beige-like anchor protein
PCH	Paroxysmal cold hemoglobinuria
PE	Plasma exchange
PICU	Pediatric intensive care unit
PRBCs	Packed red blood cells
SCID	Severe combined immunodeficiency
SLE	Systemic lupus erythematosus
TLC	Total leucocytic count
W-AIHA	Warm antibody AIHA

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Authors' contributions

NE collected the data, YR and FA analyzed and interpreted the data, HB supervised and revised the work, and NE contributed to writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Cairo University, Registration no.: N-53–2023.
All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.
A written informed consent was obtained from the parent and/or legal guardian of all participants.

Consent for publication

Written informed consent for publication was obtained.

Competing interests

The authors declare that they have no competing interests.

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