

Prevalence of extracorporeal blood purification techniques in critically ill patients before and during the COVID-19 pandemic in Egypt

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Background: Extracorporeal blood-purification techniques are frequently needed in the pediatric intensive care unit (PICU), yet data on their clinical application are lacking. This study aims to review the indications, rate of application, clinical characteristics, complications, and outcomes of patients undergoing extracorporeal blood purification (i.e., by continuous renal replacement therapy [CRRT] or therapeutic plasma exchange [TPE]) in our PICU, including before the coronavirus disease 2019 (COVID-19) pandemic in 2019 and during the pandemic from 2020 to 2022.

Methods: This study included children admitted for extracorporeal blood-purification therapy in the PICU. The indications for TPE were analyzed and compared to the American Society for Apheresis categories.

Results: In 82 children, 380 TPE sessions and 37 CRRT sessions were carried out children, with 65 patients (79%) receiving TPE, 17 (20.7%) receiving CRRT, and four (4.8%) receiving both therapies. The most common indications for TPE were neurological diseases (39/82, 47.5%), followed by hematological diseases (18/82, 21.9%). CRRT was mainly performed for patients suffering from acute kidney injury. Patients with neurological diseases received the greatest number of TPE sessions (295, 77.6%). Also, the year 2022 contained the greatest number of patients receiving extracorporeal blood-purification therapy (either CRRT or TPE).

Conclusions: The use of extracorporeal blood-purification techniques increased from 2019 through 2022 due to mainly autoimmune dysregulation among affected patients. TPE can be safely used in an experienced PICU. No serious adverse events were observed in the patients that received TPE, and overall survival over the 4 years was 86.5%.

Key Words: acute kidney injury; blood component removal; child; continuous renal replacement therapy; COVID-19; humans; pandemics; plasma exchange

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INTRODUCTION

The pediatric intensive care unit (PICU) is principally concerned with treating children with critical illness. The primary goal of essential pediatric treatment is not only to reduce the mortality rate, but also to improve the quality of life [1]. As continuous renal replacement therapy (CRRT) is an extracorporeal blood-purification technique [2], it is recommended to be used

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in the PICU for renal and non-renal indications [3]. CRRT can resolve inflammatory mediators, modify the immune function, and regulate oxygenation [4]. Furthermore, a recent suggestion was made that CRRT be administered to critically ill patients to support different organs, including those with coronavirus disease 2019 (COVID-19) suffering from sepsis and multi-organ system failure (MOSF) [5]. There are a limited number of pediatric studies describing the demographic characteristics and outcomes of critically ill pediatric patients receiving CRRT, as it is a complex extracorporeal blood-purification therapy requiring high levels of knowledge, practice, and resources [6]. Therapeutic plasma exchange (TPE) is another extracorporeal blood-purification procedure with established efficacy in several diseases [7] that removes pathological intravascular auto-antibodies, immunocomplexes, and high-molecular-weight substances such as cryoglobulin [8]. The American Society for Apheresis (ASFA) published an updated list of indications for TPE in 2019 [9] however, while ample studies have been performed in adults, there are insufficient data available across other age groups. Although the principles of TPE are similar in adults and children, there remain technical obstacles in children, such as problems in setting up vascular access and extracorporeal blood volume distribution [10]. TPE is now used to treat many disorders, including thrombotic microangiopathies, sepsis-related multiple organ failure and neurological diseases [9].

The novel coronavirus (severe acute respiratory syndrome coronavirus 2), first identified in Wuhan, China, in late 2019, rapidly evolved and led to a pandemic by the first quarter of 2020, as indicated by the increase in the number of cases and the rapid geographical spread. Moreover, this virus can activate a severe critical illness state in some patients, marked by respiratory failure, circulatory shock, sepsis, or other organ failures, requiring intensive care [11], and it can also lead to various autoimmune and autoinflammatory diseases [12].

We aimed to properly evaluate extracorporeal blood-purification techniques (CRRT and TPE), both during the period before the COVID-19 pandemic in 2019 and during the COVID-19 pandemic from 2020–2022. Accordingly, we described the indications, the rate of application, clinical characteristics, complications, outcomes, and the cost of all patients that required one or both therapies during their PICU stay.

MATERIALS AND METHODS

This study was approved by the Research Ethics Committee of

KEY MESSAGES

- The use of extracorporeal techniques, including continuous renal replacement therapy and therapeutic plasma exchange (TPE), was rising from the period before coronavirus disease 2019 (COVID-19) era in the year 2019 and during the COVID-19 era in years 2020–2022.
- In 2019, this rise was primarily due to autoimmune dysregulation among affected patients.
- TPE can be safely used in an experienced pediatric intensive care unit.

KasrAlainy Faculty of Medicine, Cairo University (N-85-2023). Due to its retrospective design, informed consent was waived.

We conducted a retrospective observational study using data collected from patient files over 4 years (2019–2022). We included all patients who received extracorporeal blood-purification therapy, including TPE and CRRT, in our PICU. Among 1,192 patients identified, 82 who underwent extracorporeal blood-purification therapy were studied as shown in Figure 1. Their age ranged from 1 month to 14 years, and the following data were collected from medical records: admission diagnosis, clinical characteristics, urinary output, signs of overload, mechanical ventilation, inotropic support, number of sessions, PICU length of stay, and outcome. TPE indications were categorized according to ASFA categories, as follows: category 1, disorders where apheresis is considered as first-line management; category 2, disorders where apheresis is considered as second-line management; category 3, disorders in which the optimum role of apheresis therapy is not yet established; and category 4, disorders where published evidence demonstrates

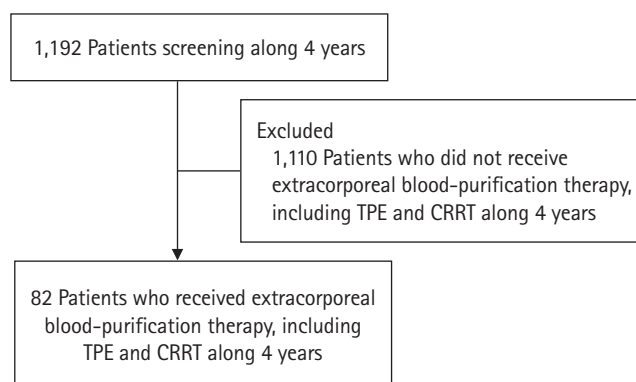


Figure 1. Flowchart of studied patients. TPE: therapeutic plasma exchange; CRRT: continuous renal replacement therapy.

or suggests apheresis to be ineffective or harmful [9]. The extracorporeal blood-purification procedures were carried out according to the protocol of our hospital, including proper vascular access (double lumen hemodialysis catheter). The jugular vein was chosen as the preferred vascular access route, catheter size was selected according to body weight (7.0–10.0 F), and anticoagulation of the tube was performed with either citrate or heparin according to the clinical condition of each patient. Heparin was administrated at a dosage of 5–25 IU/kg/hr based on the activated partial thromboplastin time. Laboratory examinations (complete blood count, electrolytes, and coagulation profile) and continuous monitoring of cases were completed. Prismaflex (Gambro Prismaflex machine, Baxter) was the device used in TPE. The filter used was a membrane plasma separator (TPE 1000 for children up to 15 kg or TPE 2000 for children ≥ 15 kg). The target treatment volume for each TPE was 1–1.5 times the plasma volume,

where plasma volume = $0.065 \times \text{body weight (kg)} \times (1 - \text{hematocrit})$,

and the volume of each plasma exchange was typically 30–50 mL/kg. The replacement fluid used was either albumin or fresh frozen plasma. During CRRT, initiation was determined by the attending physicians according to the clinical situation of the patient and the institutional guidelines. We also gathered technical data, including the information on CRRT initial prescription (i.e., treatment modality, filter type, treatment duration), and minute-by-minute treatment delivery information recorded on the CRRT monitor memory card (e.g., flows, pressures, and machine alarms). During either procedure, patients were observed by an experienced staff member, and the presence of any complications, including circuit complications such as clotting of the filter or intravenous access, and patient complications such as hypothermia, nausea, vomiting, hypotension, hypocalcemia, allergic reactions (itching, urticaria), and bleeding, was recorded.

Statistical Analysis

Data were subjected to computer-assisted statistical analysis using IBM SPSS ver. 28 (IBM Corp.). Numerical data were summarized as means and standard deviations among parametric data and median, minimum, and maximum values among non-parametric data. Categorical data are presented as frequencies and relative frequencies. The chi-square test was performed to compare categorical data. The Fisher exact test

was used for variables with expected frequencies < 5 [13]. Results were considered significant when $P < 0.05$.

RESULTS

This retrospective observational study collected data from 1,192 patients' files during 2019–2022, and 82 patients (6%) who received extracorporeal blood-purification therapy were analyzed in this investigation. The median age of our patients ($n=82$) was 87 months, and there were 43 men (52 %) and 39 women (47.5%). Sixty-five cases (79%) had received TPE, 17 cases (20.7%) had received CRRT, and four cases (4.8%) had received both therapies. Throughout the 4 years, the number of patients who received extracorporeal blood-purification therapy among the total number of admitted patients in the same year was as follows: 10/328 cases (3%) in 2019, 14/276 cases (5%) in 2020, 20/278 cases (7.1%) in 2021, and 38/310 cases (12.2%) in 2022. As such, the greatest number of patients receiving extracorporeal blood-purification therapy, either CRRT or TPE, was seen in 2022. It was noted that 58.3% of cases ($n=24$) that suffered from acute kidney injury (AKI) and 41.1% of cases ($n=17$) that needed TPE due to autoimmune hemolytic anemia (AIHA) were seen in 2022, while only 4.1% and 11.7% of cases admitted in 2019 met these conditions, respectively, as shown in Table 1. Table 1 also shows 10 of 29 cases (34.4%) that needed TPE due to Guillain-Barré syndrome (GBS) in 2022.

Although the number of patients who underwent extracorporeal blood-purification therapy was 82, the most common two indications for TPE were neurological diseases (39 cases, 47.5%) and hematological diseases (18 cases, 21.9%), as demonstrated in Figure 2. CRRT was mainly performed for patients suffering from complicated AKI, where the main reason was sepsis and MOSF resulting in either fluid overload, anuria, or electrolyte and/or acid-base disturbances. Seventeen patients (70.8%) were diagnosed with AKI due to sepsis and MOSF, and the other seven cases (29.1%) were due to hemolytic uremic syndrome, antibody-mediated rejection after renal transplantation, and systemic lupus erythematosus, representing categories 1–2, as shown in Table 1. According to ASFA classification, from most common to least common, the category breakdown of cases was as follows: category 1, 35/65 cases (53.8%); category 2, 23/65 cases (35.3%); category 3, 1/65 cases (1.5%); and unclassified category, 6/65 cases (9.2%). No category 4 cases were observed, as demonstrated in Table 1.

Four hundred seventeen treatment sessions were carried

Table 1. Distribution of disorders by year

| Cause of admission | ASFA category | Total number | 2019 (n=10) | 2020 (n=14) | 2021 (n=20) | 2022 (n=38) |
|-----------------------------|---------------|------------------|-------------|-------------|-------------|-------------|
| Acute kidney injury | 1–2 | 24 ^{a)} | 1 (4.1) | 2 (8.3) | 7 (29.1) | 14 (58.3) |
| Guillain-Barré syndrome | 1 | 29 | 6 (20.7) | 7 (24.1) | 6 (20.6) | 10 (34.4) |
| Autoimmune hemolytic anemia | 2 | 17 | 2 (11.8) | 3 (17.6) | 5 (29.4) | 7 (41.1) |
| Neuromyelitis optica | 2 | 2 | 0 | 1 (50.0) | 0 | 1 (50.0) |
| Transverse myelitis | Unclassified | 6 | 1 (16.6) | 1 (16.6) | 2 (33.3) | 2 (33.3) |
| Autoimmune encephalitis | 1 | 1 | 0 | 0 | 0 | 1 (100) |
| Sickle cell crisis | 2 | 1 | 0 | 0 | 0 | 1 (100) |
| Myasthenia gravis | 1 | 1 | 0 | 0 | 0 | 1 (100) |
| Snake bite | 3 | 1 | 0 | 0 | 0 | 1 (100) |

Values are presented as number (%).

ASFA: American Society for Apheresis.

a) Only 7 patients received therapeutic plasma exchange.

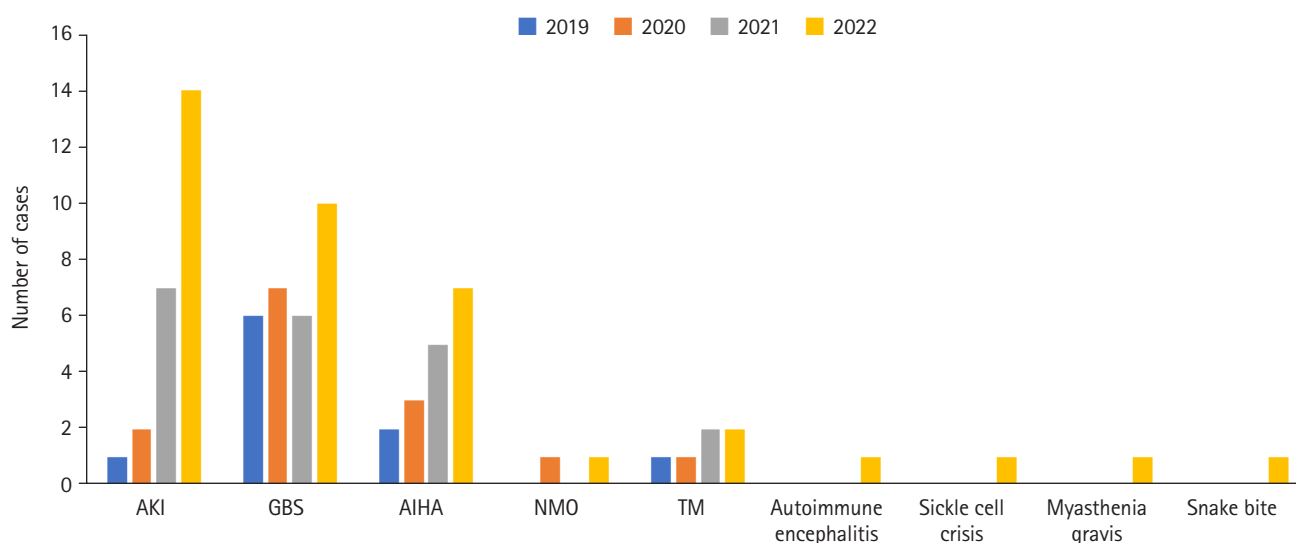


Figure 2. The distribution of each disorder along the 4 years (n=82). AKI: acute kidney injury; GBS: Guillain-Barre syndrome; AIHA: autoimmune hemolytic anemia; NMO: neuromyelitis optica; TM: transverse myelitis.

out among the 82 cases, including 380 TPE sessions and 37 CRRT sessions, as shown in Table 2. Children with neurological disorders (295, 77.6%) underwent the greatest number of TPE sessions. Twenty-two of 128 sessions (17.8%) were CRRT sessions, and these sessions were all performed in 2022, while there were no sessions performed in 2019. Regarding the critical support needed for patients on admission, a total of 20/82 cases (24%) required mechanical ventilators, including 10 cases (50%) in 2022 compared to just four cases in 2019. Overall, 9/82 cases (10.9%) required inotropic support, including seven in 2022 compared to zero in 2019, as shown in Figure 3.

Most of our patients, 92.6% (76/82), had started extracorpo-

real blood-purification therapy on admission, while four began on the second day, one patient on the fourth day, and one patient after 10 days; this kind of late-onset is usually attributed to difficulty with establishing vascular access, unavailability of procedure requirements (e.g., filter, albumin, plasma), or the trial of another line of treatment. Five patients (6%) had complications during their CRRT session in the form of clotting of the filter (one patients) and cardiac arrest (four patients). In contrast, 93.5% of patients (n=77) did not develop any complications, including all patients receiving TPE.

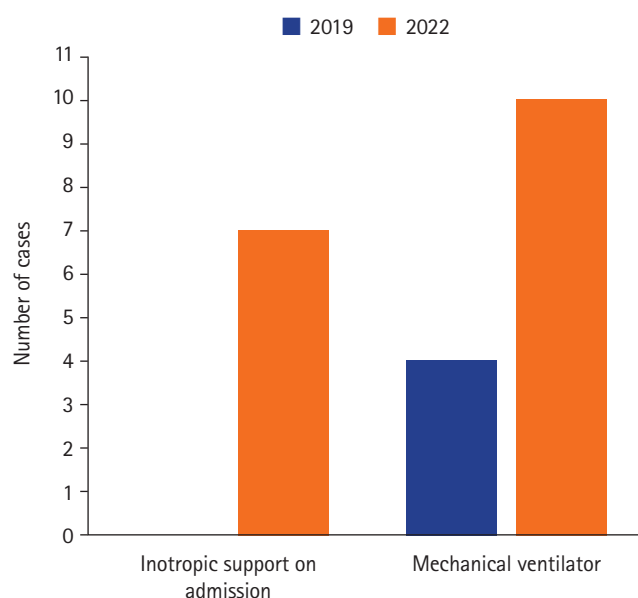
Ten days was the median length of stay in the PICU. Only 11 of 82 cases (13.4%) died; of these, nine had sepsis and MOSF

Table 2. Number of sessions done including TPE and CRRT in each year

| Cause of admission | 2019 | 2020 | 2021 | 2022 |
|-----------------------------|-----------|-----------|-----------|-----------|
| Acute kidney injury | 3 (3.2) | 4 (6.8) | 30 (24.6) | 34 (26.6) |
| Guillain-Barré syndrome | 69 (73.4) | 41 (69.5) | 64 (52.5) | 61 (47.7) |
| Autoimmune hemolytic anemia | 10 (10.6) | 4 (6.8) | 18 (14.8) | 14 (10.9) |
| Neuromyelitis optica | 5 (5.3) | 5 (8.5) | 0 | 9 (7.0) |
| Transverse myelitis | 7 (7.5) | 5 (8.57) | 10 (8.2) | 10 (7.8) |
| Autoimmune encephalitis | 0 | 0 | 0 | 5 (3.9) |
| Sickle cell crisis | 0 | 0 | 0 | 1 (0.8) |
| Myasthenia gravis | 0 | 0 | 0 | 4 (3.1) |
| Snake bite | 0 | 0 | 0 | 4 (3.1) |
| Total | 94 (100) | 59 (100) | 122 (100) | 128 (100) |

Values are presented as number (%).

TPE: therapeutic plasma exchange; CRRT: continuous renal replacement therapy.

**Figure 3.** The critical support needed for the patients on admission.

and two had sepsis and respiratory failure. Fifty-four percent of cases died in 2022, while no deaths occurred in 2019. Most of the non-surviving (10/11) cases underwent CRRT; only one of these patients had received TPE. The session cost per patient, including vascular access, filter, albumin, and nurse care, it was 5,800 EGP in the year 2019 compared to 7,890 EGP in the year 2022, and this difference was statistically significant ($P < 0.001$). There was an increase of 36% in the session cost from the year 2019 to the year 2022. Most of the increase was attributed to the cost of vascular access (57%), followed by the price of the albumin (37%), the filter (36%), and the nurse per shift (17.7%).

DISCUSSION

TPE is an extracorporeal blood-purification procedure widely used in various diseases [14]. CRRT is a treatment modality for complicated AKI associated with either fluid overload, electrolyte, and/or metabolic disturbance in critically ill patients [15]. The aim of our work was to study the data of patients admitted to our PICU for extracorporeal blood-purification techniques, describing the indications, the rate of application, clinical characteristics, complications, and outcomes during a period of 4 years (2019–2022) that encompassed the start of the COVID-19 pandemic.

The total number of admitted cases to the PICU in 2019 pre-pandemic was greater than that in other years, and this trend is consistent with findings from other studies like Zee-Cheng et al. [16] and Kanthimathinathan et al. [17]. This is primarily due to the fear of visiting hospitals during the COVID-19 pandemic and the preference for virtual consultations. The year 2022 garnered the greatest number of patients requiring extracorporeal blood-purification techniques, either CRRT or TPE, and this can be explained by establishment of both the global pandemic and vaccination, when almost 651,918,402 cases of COVID-19 had been diagnosed and 13 billion doses of vaccine had been administered [18]. This may suggest that autoimmune diseases may occur after COVID-19 or vaccination for the same condition [12].

In our study, there was an increase in the number of neurological cases requiring TPE in 2022 compared to 2019. This trend was also observed by Gigli et al. [19] and Goel et al. [20], who found emerging evidence suggesting an association of GBS after COVID-19 and the occurrence of several other au-

toimmune neurological phenomena. Forty-one percent of the cases ($n=17$) that needed TPE due to severe AIHA were seen in 2022, while only 11.7% of cases were admitted in 2019, and this trend is further supported by results of a study performed by Taherifard et al. [21], which reported that AIHA is a common hematologic autoimmune sequelae resulting from immunological and inflammatory stimulation in the COVID-19. Similarly, Zama et al. [22] concluded that COVID-19 could act as a trigger of new-onset AIHA and must be considered during the pandemic among the viral causes.

Most of our AKI cases suffered from sepsis and MOSE, which was also discovered by Mittal et al. [23], who found that the factors related to renal dysfunction were either reduced tissue perfusion, sepsis, or worsening clinical condition with MOSE. Meanwhile, a study by Chang et al. [24] suggested that sepsis is a primary and significant risk factor for AKI in critically ill patients. We also found that 58.3% of patients ($n=24$) that suffered AKI were seen in 2022, while only 4.1% were seen in 2019, and this finding may be attributed to renal effects of COVID-19, which is an essential marker of disease severity [22].

According to the ASFA classification, categories 1 and 2 contained the largest proportion of cases (89.1%), followed by ASFA category 3 (1.5%), while 9.2% of cases were unclassified; this matches the study by Bustos et al. [14], where category 1 and 2 cases made up the largest proportion. TPE procedures were all performed on the first day of admission in our PICU, and this was beneficial to our cases. Other investigators have also found that early intervention with the procedure could decrease the level of cytokines in the bloodstream, reduce the impairment of organ function, and minimize the mortality rate [25]. Regarding the frequency of sessions, children with neurological disorders received the greatest number of TPE sessions (295, 77.6%), and this represented the most common indication for TPE. These results are in concordance with Bustos et al. [14], where the main indication was immuno-neurological disorders. This study also showed an increase in the number of patients who required mechanical ventilation and vasoactive drugs in 2022 compared to in 2019, and this may be attributed to the severity of illness at PICU admission during the COVID-19 pandemic relative to the period before the pandemic. Similarly, Zee-Cheng et al. [16], suggested that the COVID-19 pandemic negatively affected children's health.

There were no complications documented related to TPE, as in Öztürk et al. [26]. Therefore, the outcome in cases receiving TPE was excellent, indicating its safety in critically ill patients. At the same time, the survival rate declined and the outcome

worsened with an increase in the number of failed systems and the requirement for CRRT, as was also observed by Cortina et al. [27]. Ten of 11 patients who did not survive had received CRRT, while only one had received TPE. However, these deaths were not related to either procedure but to the poor condition of the patients at admission.

CRRT has been recognized as a strong predictor of short-term mortality, particularly when associated with fluid overload and MODS [14]. Many studies, such as Cortina et al. [3], Aygün et al. [2], Miklaszewska et al. [28], and Haga et al. [29], showed high risk of mortality in CRRT cases related to the underlying disease and the severity of illness. Fifty-four percent of the non-surviving cases were seen in 2022, while no mortality was reported in 2019. This is explained by the increased severity of illness and risk of mortality during COVID-19, which is in concordance with results of Zee-Cheng et al. [16].

The use of extracorporeal blood-purification techniques increased from 2019 through 2022 due mainly to the appearance of autoimmune dysregulation among affected patients. TPE can be safely administered in an experienced PICU. CRRT has a poor prognosis in AKI patients resulting from sepsis and MOSE. The cost of an extracorporeal therapy session increased during the study period to almost double.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: HIR. Methodology: AOM. Formal analysis: AOM. Data curation: HIR. Writing-original draft: AOM. Writ-

ing- review & editing: all authors. All authors read and agreed to the published version of the manuscript.

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