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Review Article

Hemoadsorption in pediatric critical care: current insights and future perspectives"

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Short Title: Hemoadsorption in pediatric critical care

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Abstract

Background:

Hemoadsorption (HA) is increasingly recognized as a valuable extracorporeal blood purification technique in paediatric intensive care. Although initially developed for adult patients, HA's application in paediatric critical care, particularly for conditions such as septic shock, liver failure, and rhabdomyolysis, has gained significant attention due to promising clinical outcomes.

Summary:

HA has demonstrated efficacy in managing paediatric septic shock by reducing vasopressor requirements and lowering inflammatory markers. In liver failure, HA complements continuous renal replacement therapy (CRRT) by removing albumin-bound toxins and cytokines, mitigating systemic inflammation. Emerging evidence also supports HA as a rescue therapy in rare paediatric conditions like rhabdomyolysis and acute intoxications, preventing organ damage and reducing morbidity. Despite its benefits, HA in paediatrics presents technical challenges, including concerns over extracorporeal circuit volumes, vascular access, and anticoagulation. Paediatric-specific devices, such as the HA60, BS80 and PMX-05R, are addressing these limitations by offering lower priming volumes suitable for small children. Recent studies have highlighted improvements in hemodynamic stability, cytokine reduction, and organ function, reinforcing HA's potential as a critical adjuvant therapy. This review underscores the evolving landscape of HA in paediatric critical care, advocating for further research to optimize its application across diverse clinical scenarios.

Key Messages:

- HA shows significant promise in paediatric septic shock, liver failure, and rhabdomyolysis.
- Technical advancements are expanding HA's applicability to neonates and small infants.
- More multicentre studies are needed to establish HA's role in reducing mortality and improving quality of life post-PICU.

Introduction

Hemoadsorption techniques rely on the adsorption of specific solutes circulating in the bloodstream that are implicated in pathological processes. This is achieved by passing blood or plasma through dedicated cartridges containing adsorbent surfaces within an extracorporeal circuit (ADQI). Improved biocompatibility and safety, along with a broad range of clinical applications, have contributed to the increasing adoption of hemoadsorption in clinical practice and a growing body of scientific literature, primarily in adult settings [1]. In this context, evidence supporting the use of hemoadsorption (HA) in paediatric intensive care is also expanding [2]. However, current scientific literature suggests that its application could further broaden in the coming years [3]. One of the major limitations of HA in paediatric settings is the increased risk of adverse events due to the unique physiological characteristics of paediatric patients, the scarcity of paediatric-specific devices, and the frequent reliance on adult equipment. On the other hand, promising clinical results HA has emerged as an effective adjuvant therapy in paediatric sepsis, in liver failure and in other minor indications as rhabdomyolysis and acute intoxication [4-8].

This is a narrative review aiming to analyse the technical challenges associated with the application of this extracorporeal technique in paediatric patients, highlighting their unique characteristics compared to adults. Additionally, it will provide an up-to-date overview of the existing clinical experiences. A comprehensive search of the PubMed, Embase, Web of Science, and Scopus databases between August 2014 and May 2024. The search was restricted to studies involving paediatric patients (younger than 18 years) and included randomized clinical trials, observational studies, case series, and case reports.

Main Text

Technical challenges in critically ill children

There are currently numerous clinical studies in which HA has been applied to neonates, small infants, and children showing encouraging clinical results with no major adverse events reported [9] [10] [11]. However, it is important to consider the safety rules related to the use of the extracorporeal circuit in children [12] [13].

The priming volume of extracorporeal circuits should be carefully evaluated, as the amount of blood that remains in the extracorporeal circuit predisposes children to hypotension, haemodilution, and high risk of cardiac arrest. Indeed, some studies report the combination of HA with ECMO or cardiac bypass even in neonates and low-weight children [11], but it is important to note that the presence of a high-flow cardiac pumps capable of pumping large volumes of bloods at a sufficient rate to maintain systemic perfusion, temporarily take-over the role of the heart. Safety limitations require even greater attention if the patient is using HA exclusively or in combination only with CRRT with pumps designed to pump blood at lower flow rates than ECMO. It should be emphasized that the authors made similar considerations about the safety of extracorporeal volumes in the context of continuous renal replacement therapy (CRRT) to prevent associated risks [14]. In addition, the extracorporeal volume, resulting from the combination of the circuit and devices, inevitably impacts haemodilution, particularly regarding the stability of haemoglobin levels, platelet counts, and coagulation factors, which are now recognized as safety outcomes by the authors [3]. Thus, the ideal safe extracorporeal volume (≤10% of the patient's total blood volume) must be calculated in advance concerning the priming volume of the extracorporeal circuit, potentially used in combination with the CRRT haemofilter and circuit lines. Priming of the extracorporeal circuits with packed red blood cells, or when this is not possible, administration of the same (bypass system) to the patient during priming should always be considered.

A proper **vascular access** allowing the **target blood flow** are required to ensure adequate HA performance. These technical requirements must be balanced with careful attention to the hemodynamic impact at the time of **patient connection**, especially when the therapeutic indication for extracorporeal therapy is associated with hemodynamic instability.

Lower blood flows in the paediatric population, in accordance with the child's weight, in association with the increased resistance induced by the column in the circuit, especially when combined with a dialysis haemofilter, may predispose to complications such as circuit clotting [3]. Recently, the

authors have evaluated circuit coagulation as one of the main safety outcomes in the paediatric population undergoing extracorporeal purification techniques [3]. There are currently no clinical studies evaluating the impact of **anticoagulation** in the treatment of paediatric patients undergoing HA. The most recent clinical experiences refer to the use of regional anticoagulation with citrate as an alternative to heparin in the methods section [4][6].
Finally, similarly to the adult population, one of the safety endpoints in the paediatric population is the unintended removal of molecules such as antimicrobials. Recent experiences have shown that, even in paediatrics, the impact of adsorption columns differs from that of other devices, such as the CRRT haemofilter, and clinical protocols to optimize patient care should consider also the interference that all such therapies have with drugs and antibiotic in particular [15].

Table 1 provides a summary of the extracorporeal volume (percentage) calculated according to the priming volume of the main HA devices used in paediatric intensive care and in relation to the average weight of paediatric patients by age group and the cut-off for safe extracorporeal volume (<10%). PV=priming volume.

Hemoadsorption in Paediatric Septic Shock

Septic shock remains one of the most studied clinical indications for hemoadsorption (HA), though current guidelines do not recommend its use in paediatric septic shock. However emerging evidence suggests that HA can be an effective treatment for refractory paediatric septic shock (4). The unique characteristics of paediatric patients may present technical challenges but can enhance the effectiveness of HA in removing target mediators.
The first clinical case of HA using CytoSorb® in paediatric septic shock occurred in 2016, involving a 12-year-old girl with acute leukaemia and refractory septic shock [16]. Since then, multiple studies, including clinical cases and observational research, have explored HA's role in paediatric septic shock. Notably, in 2023, a major interventional study demonstrated the efficacy of CytoSorb® in reducing vasopressor load and 28-day mortality in paediatric patients with septic shock [4].
Toraymixin® (PMX), used for treating Gram-negative infections, has also been adapted for paediatric use with smaller cartridges such as PMX-01R and PMX-05R [17]. Clinical experiences in newborns and small infants in Japan have shown positive results with polymyxin B-immobilized fibres for septic shock treatment [17]. Subsequent researches using PMX-5R have shown improved hemodynamic and clinical outcomes in paediatric septic shock patients [18] [19].
Additionally, a prospective observational study of HA330 with continuous renal replacement therapy (CRRT) in 12 children with septic shock reported significant reductions in inflammation markers and improved clinical scores [20]. Recently, the HA60 cartridge has become available for smaller children, featuring a lower priming volume and showing potential for reducing inflammatory mediators and removing toxins.
The Selective Cytopheretic Device (SCD), an immunomodulatory treatment, has also been used in paediatric patients. Early studies in critically ill children with acute kidney injury (AKI) and multiorgan dysfunction have shown promising results, with significant survival rates and improved kidney function after treatment [21].
In summary, while hemoadsorption remains an evolving treatment modality in paediatric septic shock, recent studies support its potential benefits in improving patient outcomes, particularly in cases of refractory septic shock and multiorgan dysfunction [4] [21]. Further research and clinical trials are needed to refine its use and explore new devices tailored to the paediatric population.
Table 2 provides a comprehensive overview of the most recent clinical studies using hemoadsorption in paediatric population [4,18,19,20-27]

Hemoadsorption in paediatric liver failure

Paediatric acute liver failure (PALF) is a devastating condition with a high morbidity and mortality: key contributors to mortality in PALF are the inflammatory state, cerebral oedema, and

sepsis with multiorgan failure. These complications occur secondary to spread of cytokines and chemokines into the systemic circulation as the accumulation of toxins such as ammonia. Extracorporeal therapies including CRRT and extra-corporeal liver support system is increasingly applied in PALF. CRRT achieves clearance of small molecules including ammonia and urea and promotes survival in PALF. Despite its advantage, CRRT is not effective in removing larger albumin-bound molecules including bilirubin and cytokines. HA as newer extracorporeal immunomodulatory therapies, working on the principle of hemoadsorption, can potentially target the cytokine release and intractable inflammation in PALF and albumin bound toxins [28] [29]

Jafron® HA and BS series (Jafron® Biomedical Co., Ltd, China) are a group of cartridges with a porous resin made of double cross-linked styrene-divinylbenzene copolymers (HA series) and polystyrene divinylbenzene anion exchange resin (BS series), widely used in China [1] [30]. Recently, two small cartridges, HA60 and BS80, become available for low weight children. Clinical indications are also different, HA60 can reduce inflammatory mediators and remove medium and large toxins whereas BS80 is specifically indicated for adsorption of bilirubin and bile acids. In particular, plasma adsorption with BS series cartridge has been used in combination with a plasma separator or as double plasma molecular adsorption system (DPMAS). The DPMAS modality uses, in a 2 hours session, a plasma filter to separate plasma combined with two types of adsorbents, the ion exchange resin (BS) specific for bilirubin and the microporous resin (HA) to remove toxic metabolites and inflammatory mediators. The DPMAS can improve jaundice and encephalopathy of liver failure but not coagulation disorders [31] [32]. For this reason, combining plasma exchange and the DPMAS can overcome the limitations of the 2 techniques [31] [32]. In a small series of 5 paediatric patients with acute liver failure (PALF) secondary to mushroom poisoning, the combination of PE and DPMAS was effective in reducing bilirubin, removing inflammatory mediators and improving blood coagulation as a bridge to recovery or transplantation [33]. Conversely, in a prospective Chinese study comparing children with PALF randomly assigned to PE or DPMAS, the DPMAS group had significantly greater reduction of total bilirubin, interleukin-6 and tumour necrosis factor and shorter duration of ICU stay than the PE group [34]. In these groups of patients, BS330 and HA330 were employed for DPMAS with the risk of hemodynamic instability related to the use of adult equipment [34]. More recently in a multicentre retrospective observational study enrolling 115 paediatric patients with acute liver failure admitted in PICU, Gao Q. et al reported on the use of mini-DPMAS using HA60 and BS80 [5]. The authors compared full dose PE versus DPMAS plus half-dose PE showing a reduce plasma consumption without obvious adverse event. The effective rate of decline for total bilirubin, blood ammonia and IL-6 were significantly higher in DPMAS + PE. No difference in 28-day mortality has been found between the two groups [5].

The role of Cytosorb in PALF have been reported as well. In-vitro study has demonstrated that the strong hydrophobicity of the Cytosorb may break the albumin-bilirubin bonding, rendering bilirubin removable by the device. The application of the cartridge has been reported inside case report of critically ill children with MOF and liver failure [9] [24], but also in a clinical case of a 6 years old boy affected by liver failure treated with CytoSorb in combination with CRRT highlighting the synergy between the two extra-corporeal techniques: ammonia and hydrophilic bile acids should be readily removable by diffusion or convection-based dialysis techniques including CRRT, whereas the removal of hydrophobic bile acids or albumin-bound bilirubin are removable by CytoSorb hemoadsorption [35]. The most important study on Cytosorb in PALF is a retrospective analysis of 6 critically ill children (median age 9.3) comparing HA with Cytosorb, SPAD and Plasma ex-change [39]. This study showed as, measuring Bilirubin blood levels pre and post cartridge the saturation equilibrium of Cytosorb was 12 hours. The liver enzymes showed improvement in all children receiving HA. A patient also showed improvement of hepatic coma with regain of conscious level. None of the children required liver transplantation [36].

Hemoadsorption in rhabdomyolysis

Rhabdomyolysis is a clinical and biochemical syndrome determined by the breakdown of skeletal muscles cells and subsequent release of their intracellular content into the bloodstream. In paediatric population, most of the cases are caused by viral myositis or trauma. Other causes include metabolic disorders, strenuous exercise, and drug overdose [37] [38]. Admittance to the paediatric intensive care unit may be needed to prevent and manage rhabdomyolysis complications, specifically acute kidney injury (AKI), occurring in up to 10% of the patients and mostly due to the toxic effects of myoglobin. Therapeutic interventions based on a conservative approach with intravenous fluid therapy, urine alkalinisation and diuretic support is reported to be protective for the kidneys. In the last years extracorporeal therapies and CRRT has gained raising interest in this context as well, especially when integrated with new devices as adsorbing columns, promising results in fact has been showed in removing myoglobin and inflammatory mediators from the bloodstream during acute rhabdomyolysis. Indeed, the pathogenesis of AKI in rhabdomyolysis is multifactorial and related to myoglobin intratubular precipitation but also immune and inflammatory causes with cytokines release effectively removed by adsorption columns. Clinical experiences also in paediatric critical care [6][7] support an early implementation of HA in the presence of severe rhabdomyolysis could potentially prevent the development of AKI, especially in cases of refractoriness to conservative therapy. Extracorporeal therapies, particularly HA, should be tailored to the patient's clinical evolution with tight monitoring of rhabdomyolysis biomarkers. Change of the columns should be performed at an appropriate time for the kinetics of saturation, primarily based on the entity of endogenous muscle breakdown processes rather than on the body weight [6] [7] [39] [40].

Other indications

Over the past 10 years, numerous indications for the use of HA in paediatric critical care have been explored. While significant clinical studies are limited due to the small patient's population, the clinical experiences reported by authors have provided valuable insights into the potential therapeutic benefits of HA, as well as in the method of use. In the context of cytokine storm syndromes, a key 2019 experience highlighted the successful use of CytoSorb as an adjunct therapy for treating cytokine release syndrome (CRS) following CAR T-cell immunotherapy. This case involved a 14-year-old boy with respiratory failure due to inflammatory acute respiratory distress syndrome (ARDS) [41]. The therapeutic regimen used in this clinical experience provided important insights into optimal dosing for modulating the cytokine storm [42]. It also emphasized the importance of timely column changes based on saturation kinetics and immunomodulation [43]. The application of HA in cytokine storm syndromes field has been extended as today to different clinical indications as HLH [44] [45], MIS-C [46], and clinical settings such as paediatric cardiac bypass [47] [11].

Conclusion

Promising results have emerged from clinical studies regarding the application of HA in paediatric critical care. However, the use of these techniques among extracorporeal purification methods remains still limited in the paediatric setting. The benefits that have emerged seem to be supported by the effectiveness of removing target mediators in various clinical indications. These benefits need to be balanced with the need for greater supporting evidence and with the appropriate use in paediatric patients of devices that are often designed for the adult population. There is a need for clinical studies in this field that focus on optimizing the paediatric population sample through the use of registries and multicentre studies across different paediatric intensive care units (PICUs). Additionally, studies should highlight the benefits of these techniques not only in terms of mortality but also in terms of morbidity (quality of life after discharge from the PICU, PICU length of stay, and benefits in preventing organ damage).

Statements

Conflict of Interest Statement

GB received honoraria for lecture by Jafron® and CytoSorbents®. AD and IG have no conflict to declare.

AD was a member of the journal's Editorial Board at the time of submission.

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Author Contributions

GB, AD conceptualized the manuscript. GB written the manuscript with the help pf AD and IG . AD and IG reviewed the manuscript.

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Age group	Average weight (kg)	Estimated Blood Volume (ml)	Safe extra-corporeal Volume (ml) (< 10% blood volume)	Percentage of the extra-corporeal volume according to the pediatric weight and the device applied					
				CytoSorb (PV 150 ml)	HA330 (PV 170 ±30 ml)	HA60 (PV 65±20ml)	BS80 (PV 50±10ml)	CA130 (PV115±20ml)	Efferon LPS NEO (PV 30 ml)
Neonate (0-1 month)	3	240	24	62.5%	71%	27%	21%	48%	12.5%
Infant (1-12 months)	7	560	56	27%	30%	11%	8.9%	20%	5%
Toddler (1-5 years)	12	960	96	15%	17%	6.7%	5%	12%	NA
Child (6-10 years)	20	1600	160	9%	10.6%	4%	3%	7%	NA
Adolescent (11-18 years)	50	4000	400	3.7%	4.2%	NA	NA	NA	NA

Authors	Study Population	Sample size	Treatment Duration and timing	Outcome	Safety
Goldstein S et al (2024)[21]	**Age**: 9.5 (4.3-15.8 ys) **Weight**: 30.3 (16.5-62.1)	22 paediatric patients	CRRT plus Selective Citophoretic Device©	• Organ Dysfunction Score • 28 days mortality	No major adverse events device correlated
Rihar E. et al (2024)[22]	**Age**: 0-75 months (including newborns) **Weight:**1.9 Kg-27 Kg	8 critically ill children (2 out of 8 newborns)	CRRT plus Hemoadsoprtion (Cytosorb©)	• C-RP • Procalcitonin • IL-6 • VIS	• Paediatric patients between 1.9 and 8.5 kilograms no survived. • 3 on 8 patients required VA ECMO for cardiocirculatory instability • Median Vis pre CS: 63; VIS post (six hours) CS 102
Stepanenko SM et al (2024)[23]	**Age**: 26 median (1-159) months	17 critically ill children	Hemoadsorption stand by alone (LPS Neo)	• Vasopressors • PaO_2/FiO_2 • MOF • IL-6 • TNF-alpha • C-RP	• Thrombocytopenia
Bottari et al (2023)[4]	Weight ≥ 10 kilograms	17 paediatric patients	CRRT plus Hemoadsoprtion (Cytosorb©)	• VIS • 28 days mortality	• Thrombocytopenia • No device-related adverse events
Siripanadorn T et al (2023)[20]	Age: 6.5 years median	12 paediatric patients	CRRT plus Hemoadsorption (HA330; Jafron ©)	• Vaso-inotropic score; • Oragan Dysfunction Score • Lactate • Il-6	• No device-related adverse events
Saetang et al (2023)[19]	Age: 99 months (21 days to 167 mo) Weight: median 28 kilograms (10-50 kg)	6 paediatric patients	(Toraymixin 20R©) median 4 hours per session, median 2 session per patient.	• VIS; • Oragan Dysfunction Score (PELOD)	• No device-related adverse events
Steurer et al. (2021)[24]	Age: 7 and 11 months Weight: 7 Kg and 14 Kg	2 paediatric patients	CRRT plus Hemoadsoprtion (Cytosorb©)	• CRP • IL-6 • Vasopressors • SOFA score • Oxygen Index score • Lactate	• No adverse effects related
Bottari et al. (2021)[26]	Age: 11 days – 14 years Weight: mean 17,09 Kg (min 3,13 – max 45)	8 paediatric patients	CRRT plus Hemoadsoprtion (Cytosorb©)	• IL-6 • IL-10. • creatinine • BUN	• None stated
Yaroustovsky (2021)[18]	Age: 9-96 months Weight: 6-22.5 kg	15 paediatric patients	Two session of PMX-05R per patient.	• Endotoxin assay • Procalcitonin • Presepsin • VIS • Oxygen index	• Non stated

Bottari et al (2020)[25]	Age: 1 - 13 yrs Weight: mean 24,25 Kg (min 10 – max 45 Kg)	8 paediatric patients	CRRT plus Hemoadsoprtion (Cytosorb©)	• Inotropes and vasopressors need. • IL-6 and IL-10.	• No adverse effects related
Bottari et al. (2020)[27]	Age: 26 month – 14 yrs Weight: NA	1 paediatric patient	CRRT plus Hemoadsoprtion (Cytosorb©)	• IL-6 • IL-10 • Ferritin	• None stated