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Consensus Statement | Critical Care Medicine

Extracorporeal Blood Purification in European Pediatric Intensive Care Units
A Consensus Statement

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Abstract

IMPORTANCE Important advances have been made in extracorporeal blood purification therapies (EBPTs) due to new technologies and biomaterials; however, the lack of established guidelines is a factor in great variability in clinical practice. This aspect is accentuated in pediatric intensive care given the small number of patients with diverse diagnoses treated with EBPT and the technical challenges in treating small children, potentiating the risk of adverse events.

OBJECTIVE To understand what experienced users of EBPT think about its relevant issues, insight that may have implications for the design of future studies, and the application of EBPTs in patient care.

EVIDENCE REVIEW Literature search was conducted using the PubMed and Embase databases between January 1, 2020, and July 15, 2024, and a combination of key medical terms. A panel of experts was formed (composed of 15 authors and pediatric intensivists) to develop a consensus statement using a modified Delphi-based model between 2022 and 2024. The panel's core team drafted the initial questionnaire, which explored EBPT use in pediatric intensive care units (PICUs), including clinical indications for initiating and discontinuing use and outcomes for assessing effectiveness and safety. SurveyMonkey was used in the distribution, completion, and revision of the questionnaire, and findings were analyzed. Panelists were asked to rank answer choices. Numerical value for each ranking was translated to a percentage defining the strength of consensus (>90% agreement from panelists signifying strong consensus; <49% signifying no consensus).

FINDINGS A total of 116 survey responses were received from panelists from 8 European countries. Strong consensus was achieved on 6 of 24 questions and consensus (75%-90% agreement) was reached on 18 of 24 questions. According to the panelists, the continuous renal replacement therapy standard or enhanced adsorption hemofilter and plasma exchange were of interest, representing the most applied EBPTs across various applications. While evidence on hemoadsorption is growing, it remains limited.

CONCLUSIONS AND RELEVANCE This consensus statement on EBPTs in critically ill pediatric patients was developed by an international panel of experts in areas where clinical evidence is still limited. This consensus statement could support pediatric intensivists in bedside decision-making and guide future research on EBPTs in PICUs.

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Introduction

Extracorporeal blood purification therapies (EBPTs) are techniques that use an extracorporeal circuit to remove and/or modulate circulating substances to achieve physiological homeostasis, including support of the function of specific organs and/or detoxification.[1] These techniques include renal replacement therapy, isolated ultrafiltration, hemoadsorption, and plasma therapies.[1]

Important advances in EBPTs have been made in the past decade due to new technologies and biomaterials.[1] The evolution of continuous renal replacement therapy (CRRT) from the initial description to the current technology has allowed the worldwide use of extracorporeal treatments in critically ill patients, moving from single organ support to multiple organ support therapy that later developed to extracorporeal organ support.[2,3] Extracorporeal organ support involves treatments in which blood is withdrawn and manipulated through different circuits using specialized devices and methods alone or combined with other existing techniques, such as CRRT.[3-5]

The use of EBPTs in critically ill patients, particularly those in septic shock, has been suggested as a potential adjuvant treatment. However, its outcome is still controversial.[6-9] Although several encouraging clinical studies in pediatric patients have been reported,[10,11] there is currently a lack of high-quality evidence to support the clinical use of EBPTs.[12-14] The lack of established guidelines is a factor in great variability in clinical practice. This aspect is further accentuated in pediatric intensive care given the small number of patients with diverse diagnoses treated with EBPTs and the technical challenges in treating small children (including vascular access and estimated extracorporeal volume), potentiating the risk of adverse events. The few commercial devices designed for the scope of and the specific technical challenges in pediatric patients limit the clinical practice of EBPTs.[15,16]

Knowing what experienced users of EBPT think about these relevant issues may have implications for the design of future studies and, in due course, may streamline the application of EBPTs in patient care. To improve understanding on this topic, we sought to develop, on behalf of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC), an international expert opinion statement using a modified Delphi-based model across European pediatric intensive care units (PICUs).

Methods

The panel of experts agreed to participate and to publish the collected results. We followed the Accurate Consensus Reporting Document (ACCORD) reporting guideline.[17]

Search Strategy and Selection Criteria

Two of us (G.B. and E.B.), supported by 2 external librarians, electronically searched the literature in the PubMed and Embase databases between January 1, 2020, and July 15, 2024. We used a combination of key medical terms: *extracorporeal blood purification therapies* AND *septic shock*, *extracorporeal blood purification therapies* AND *liver failure*, *extracorporeal blood purification therapies* AND *cardiac by-pass*, *extracorporeal blood purification therapies* AND *cytokine storm syndromes*, *extracorporeal blood purification therapies* AND *rhabdomyolysis*, *extracorporeal blood purification therapies* AND *intoxications* (eMethods in Supplement 1). The search was limited to research in pediatric patients (younger than 18 years) and included randomized clinical trials, observational studies, case series, and case reports (**Table 1**).[10,11,18-39]

Recruitment and Selection of Panel of Experts

Those of us (G.B., A.D., and L.J.S.) who have previously led scientific and academic research in pediatric patients receiving EBPTs conceptualized this project. After ESPNIC endorsement, we identified individuals with relevant expertise in EBPTs and the methods of consensus statements as well as individuals with membership in ESPNIC. We invited them by email to form the panel of experts (hereafter, the panel). The panel was composed of all authors, who are registered nurses in

intensive care or pediatric intensivists currently using EBPT in their clinical practice. These panelists have managed a wide spectrum of clinical indications beyond renal replacement and have led scientific studies on EBPT in pediatric critical care (eTable 1 in Supplement 1).

Delphi-Based Model

The consensus statement was developed using a modified Delphi-based model. The Delphi method is one of the gold standards of consensus statement methods and is used worldwide in all fields, not just medicine. The RAND/UCLA (University of California, Los Angeles) Appropriateness Method

Table 1. Available Scientific Evidence on Extracorporeal Blood Purification Therapies in Pediatric Critical Care by Clinical Indications

Sources by clinical indication	Study type	Outcome	EBPT
Septic shock			
Bottari et al,[10] 2023	Single-center, interventional single-arm trial	VIS; 28-d mortality	CRRT plus hemoadsorption (Cytosorb; CytoSorbents Corp)
Morin et al,[18] 2023	Single-center, prospective observational study	VIS; 28-d mortality	CRRT (Oxiris; Baxter International Inc)
Saetang et al,[19] 2022	Case series	VIS; PELOD score	CRRT plus hemoadsorption (Toraymixin 20R; Toray Industries Inc)
Goldstein et al,[11] 2024	Multicenter, prospective observational study	PELOD score; 28-d mortality	CRRT plus device (Selective Cytophoretic Device; SeaStar Medical Inc)
Siripanadorn and Samransamruajkit,[20] 2023	Retrospective observational study	VIS; PELOD score; lactate and IL-6	CRRT plus hemoadsorption (HA330; Jafron Biomedical Co Ltd)
Liver failure			
Gao et al,[21] 2023	Multicenter retrospective analysis	PELD score; pSOFA score; bilirubin; blood ammonia; IL-6	DPMAS plus half-dose plasma exchange
Lim et al,[22] 2022	Single-center retrospective analysis	Liver function biomarkers; ammonia	High-volume membrane therapeutic plasma exchange
Chowdhry et al,[23] 2023	Single-center retrospective analysis	Liver function biomarkers; ammonia; bridge to transplant; bridge to recovery	Centrifugal plasma exchange
Jackson et al,[24] 2024	Prospective observational study	Liver function biomarkers; ammonia	CRRT plus centrifugal or membrane plasma exchange
Hui et al,[25] 2023	Retrospective analysis	Bilirubin; blood ammonia; PICU mortality	CRRT plus hemoadsorption (CytoSorb); SPAD
Cytokine storm syndromes			
Bottari et al,[26] 2020	Case series	Biomarkers of inflammation; cytokines; PICU mortality	CRRT plus hemoadsorption (Cytosorb)
Bottari et al,[27] 2022	Clinical case study	Biomarkers of inflammation; cytokines	CRRT plus hemoadsorption (Cytosorb)
Bottari et al,[28] 2022	Case series	Biomarkers of inflammation; cytokines; biomarker if cardiac function; LVEF percentage	CRRT plus hemoadsorption (Cytosorb)
Zhang et al,[29] 2022	Clinical case study	Biomarkers of inflammation; cytokines	CRRT
Cardiopulmonary bypass			
Yaroustovsky et al,[30] 2021	Prospective cohort study	Postoperative vasopressor needs; biomarker of inflammation; endotoxin assay; 28-d mortality	CRRT plus hemoadsorption (Toraymixin 05R)
Pace Napoleone et al,[31] 2024	Clinical case study	Biomarker of inflammation; cytokines (IL-6); intra- and postoperative vasopressor needs and hemodynamic improvement	Hemoadsorption (HA60) in cardiac bypass plus hemofilter
Kumar et al,[32] 2022	Clinical case study	Intraoperative vasopressor needs; intraoperative hemodynamic improvement	Hemofilter plus device (Cytosorb) in cardiac bypass
Tirilomis et al,[33] 2021	Clinical case study	Intraoperative vasopressor needs; intraoperative hemodynamic improvement	Device (CytoSorb) in cardiac bypass
Rhabdomyolisis			
Rauch et al,[34] 2022	Case report	CK; myoglobin; kidney function	CRRT plus hemoadsorption (Cytosorb)
Hui et al,[35] 2022	Case report	CK; myoglobin; kidney function	CRRT plus hemoadsorption (Cytosorb and Oxiris)
Padiyar et al,[36] 2019	Case report	CK; myoglobin; kidney function	CRRT plus hemoadsorption (Cytosorb)
Bottari and Guzzo,[37] 2024	Case report	CK; kidney function	CRRT plus hemoadsorption (Cytosorb)
Intoxications			
Corbisier et al,[38] 2024	Case report	Liver function biomarker; kidney function; hemodynamic improvement	CRRT plus MARS
Thery et al,[39] 2022	Case report	Kidney function	CRRT (Oxiris)

Abbreviations: CK, creatine kinase; CRRT, continuous renal replacement therapy; DPMAS, double plasma molecular adsorption system; EBPT, Extracorporeal Blood Purification Therapy; LVEF, left ventricular ejection fraction; MARS, molecular adsorbent recirculating system; PELD, Pediatric End-Stage Liver Disease; PELOD, Pediatric Logistic Organ Dysfunction; PICU, pediatric intensive care unit; pSOFA, pediatric Sequential Organ Failure Assessment; SPAD, single-pass albumin dialysis; VIS, vasoactive-inotropic score.

(RAM) is a modified Delphi method developed by the RAND Institute and UCLA. RAM's advantage over the original Delphi method is that it provides higher-quality answers and an avenue for discussion rounds among the panelists.[40]

A 3-step process was followed. First, based on the literature review, the panel's core team drafted the initial survey questionnaire during the first qualitative round (round 1). These questions explored the most important controversial aspects of EBPTs in pediatric critical care, such as the criteria to initiate and discontinue treatment and the effectiveness and safety end points. The final version of the questionnaire (eTable 2 in Supplement 2) consisted of several specific closed questions on the topic and was divided into 2 sections: (1) main fields of application of EBPTs in PICUs and (2) techniques and devices used in the treatment of pediatric patients.

Second, the questionnaire was sent to the panel using survey software (SurveyMonkey; Symphony Technology Group) (round 2), and the questionnaire findings were analyzed. Third, during a virtual face-to-face meeting (round 3), the panelists were asked to reconsider the round 2 answers and to send their final responses.

The questionnaire was customized using a ranking scale (with the minimum score indicating low priority and the maximum score indicating high priority), wherein respondents were asked to rank answer choices in order of preference. A mean ranking was then calculated for each answer choice, allowing the rapid evaluation of preferred responses. The absolute numerical value (total raw ranking score) for the responses ranked was translated to a corresponding percentage of agreement among panelists that defined the strength of the consensus using the following criteria[41]: more than 90% agreement signified strong consensus, 70% to 89% agreement signified consensus, 50% to 69% agreement signified majority, and less than 49% agreement signified no consensus.

Any survey question or answer choice with clear disagreement or no clear agreement was revised and resent on a subsequent Delphi round, until consensus was reached. All Delphi analyses, including analyses of the results, were conducted between September 2022 and July 2024.

Statistical Analysis

Data were downloaded from SurveyMonkey, and completeness of the responses was checked. Data were analyzed using Stata, version 17.0 (StataCorp LLC). Descriptive data were reported as number and frequency for categorical variables.

Results

The International Survey on Blood Purification in Critically Ill Children (eTable 2 in Supplement 2) received 116 responses from the panelists. The respondents included representatives from 8 European countries (eFigure 1 in Supplement 1).

Pediatric Clinical Indications for EBPTs

The panelists identified 6 clinical indications in the PICU to which EBPTs could be applied: septic shock, cytokine storm syndromes, liver failure, rhabdomyolysis, intoxications, and cardiopulmonary bypass. Cytokine storm syndromes included hemophagocytic lymphohistiocytosis,[42] cytokine release syndrome after advanced immunotherapies,[43] and multisystem inflammatory syndrome.[44] **Figure 1** shows the percentage of priority expressed by the panelists for each clinical indication. For example, panelists gave both septic shock and cytokine storm syndromes 90% priority for EBPT application, whereas cardiopulmonary bypass was given only 30% priority.

Septic Shock

The panelists identified thrombocytopenia associated with multiple organ failure[45] (73%), multiple organ dysfunction syndrome (MODS) (73%), and refractory septic shock[46] (79%) as criteria to initiate EBPTs in patients with septic shock, with a consensus on each criterion (**Table 2**). The clinical condition most commonly detected by the panelists for discontinuing EBPTs in these patients was

hemodynamic improvement associated with a reduced vasopressor requirement, with an 83% consensus (Table 2).

The outcomes proposed for evaluating the effectiveness of EBPTs in patients with septic shock were the reversal of refractory shock,[46] with a strong consensus score of 91%, and a substantial reduction (≥50%) in the vasoactive-inotropic score,[47] with a 78% consensus (**Table 3**). Panelists who were interviewed stated that the most important parameters for ensuring patient safety during treatment were hemodynamic stability within the first 6 hours of initiating EBPTs, which had a strong consensus score of 97%, and incidence of bleeding, with a 74% consensus (Table 3).

Liver Failure

The criteria suggested by the panel for initiating EBPTs in patients with liver failure were hepatic encephalopathy and detoxification, with consensus scores of 88% and 86%, respectively (Table 2). The criteria for discontinuing EBPTs were improvement in both hepatic encephalopathy and serum ammonia, with consensus reaching 89% and 73%, respectively (Table 2).

In pediatric liver failure, the outcomes considered appropriate for assessing the effectiveness of EBPTs in promoting spontaneous liver regeneration included substantial improvement of liver synthetic biomarkers (82%), reversal of shock (68%), and substantial reduction of inflammatory biomarkers and serum ammonia (68%), with a consensus to majority agreement (Table 3). The main safety measures followed by the panelists during EBPTs were hemodynamic stability at the start of EBPT, with a strong consensus (92%), and incidence of bleeding (83%) and platelet counts variations after the initiation of EBPT (71%), with all 3 reaching consensus (Table 3).

Cardiopulmonary Bypass

The main indications for initiating EBPTs during or after cardiopulmonary bypass were low cardiac output syndrome (80%) and systemic inflammatory response syndrome indicated by elevated inflammation biomarkers (76%), with consensus among the panelists (Table 2). The primary criterion for discontinuing EBPTs after cardiopulmonary bypass was hemodynamic improvement, with a strong consensus score of 94%. The main outcome recommended for assessing the effectiveness of EBPTs in patients was the reversal of shock, with an 87% consensus (Table 3). For assessing safety, the outcomes considered appropriate were hemodynamic stability at the start of EBPT, reaching a strong consensus score of 92%, and incidence of bleeding, with an 81% consensus (Table 3).

Figure 1. Panelist-Expressed Priorities Regarding Application of Extracorporeal Blood Purification Therapies (EBPTs) Across Clinical Indications

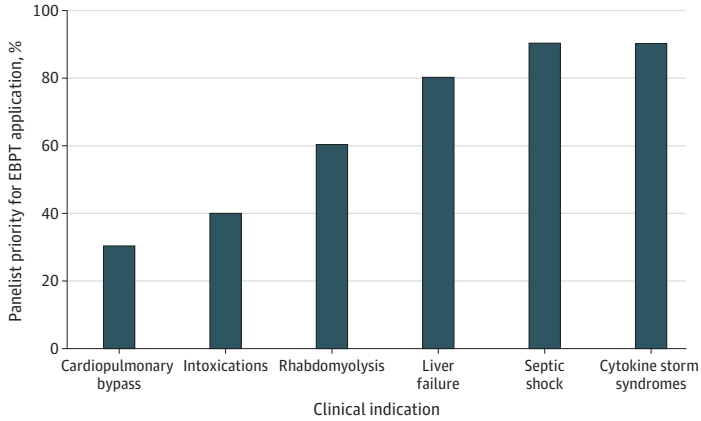


Table 2. Clinical Indications for Initiating or Discontinuing Extracorporeal Blood Purification Therapies by Clinical Condition

Indication	Panelist agreement score, %	Total raw ranking score
Indications to initiate EBPTs		
Septic shock (ranking scale: 1-8)		
Refractory septic shock	79[a]	5.5[a]
TAMOF	73[a]	5.13[a]
MODS	73[a]	5.13[a]
Fluid overload	68	4.75
AKI	64	4.5
Hyperlactatemia and metabolic acidosis	61	4.25
Septic shock	50	3.5
Conventional inflammatory biomarkers	46	3.25
Liver failure (ranking scale: 1-7)		
Hepatic encephalopathy	88[a]	6.14[a]
Detoxification	86[a]	6.0[a]
MODS	61	4.29
Cardiovascular dysfunction	49	3.43
Fluid overload	49	2.86
Septic shock	39	2.71
AKI	37	2.57
Cardiopulmonary bypass (ranking scale: 1-7)		
Low cardiac output syndrome	80[a]	5.6[a]
Systemic inflammatory syndrome (increase in inflammation biomarkers)	76[a]	5.3[a]
Fluid overload	71[a]	5.0[a]
MODS	61	4.3
Ischemia-reperfusion injury (hyperlactatemia and vasoplegia)	51	3.6
AKI	43	3.0
Endocarditis	14	1.0
Cytokine storm syndromes (ranking scale: 1-4)		
Cardiovascular dysfunction	81[a]	3.25[a]
MODS	75[a]	3.0[a]
Conventional inflammatory biomarkers	53	2.13
Advanced biomarkers of inflammation (cytokines)	40	1.63
Intoxications (ranking scale: 1-5)		
Time elapsed since toxin exposure	75[a]	3.75[a]
Pharmacokinetic of the toxic agent	75[a]	3.75[a]
MODS	54	2.7
Cardiovascular dysfunction	50	2.5
AKI	44	2.2
Rhabdomyolisis (ranking scale: 1-4)		
Blood levels of CK	82[a]	3.3[a]
AKI	62	2.5
MODS	54	2.17
Blood levels of myoglobin	50	2.0
Indications to discontinue EBPTs		
Septic shock (ranking scale: 1-6)		
Cardiovascular improvement	83[a]	5.0[a]
Improvement in MODS	62[a]	3.7
Fluid overload improvement	62	3.7
Vasoactive drug doses	58	3.5
Reduced systemic inflammatory biomarkers	43	2.6
Improvement in metabolic markers (lactate)	38	2.3

(continued)

Table 2. Clinical Indications for Initiating or Discontinuing Extracorporeal Blood Purification Therapies by Clinical Condition (continued)

Indication	Panelist agreement score, %	Total raw ranking score
Liver failure (ranking scale: 1-7)		
Hepatic encephalopathy improvement	89[a]	6.2[a]
Improvement in serum ammonia	73[a]	5.1[a]
Improvement in liver synthetic biomarkers	60	4.2
Cardiovascular improvement	54	3.8
Improvement in MODS	50	3.5
Improvement in metabolic markers and AKI	46	3.2
Reduced systemic inflammatory biomarkers	21	1.5
Cardiopulmonary bypass (ranking scale: 1-7)		
Hemodynamic improvement	94[a]	6.6[a]
Improvement in MODS	66	4.6
Vasoactive drug doses	61	4.3
Fluid overload improvement	47	3.3
Reduced systemic inflammatory biomarkers	43	3.0
Improvement in metabolic markers	43	3.0
Improvement in AKI	43	3.0
Cytokine storm syndromes (ranking scale: 1-6)		
Hemodynamic improvement	85[a]	5.1[a]
Improvement organ dysfunction	75[a]	4.5[a]
Vasoactive drug doses	63	3.8
Reduced systemic inflammatory biomarkers	46	2.8
Improvement in metabolic markers	38	2.3
Fluid overload improvement	36	2.2
Intoxications (ranking scale: 1-5)		
Blood levels of the toxic agent	80[a]	4.0[a]
Hemodynamic improvement	74[a]	3.7[a]
Improvement in organ function	60	3.0
Kidney improvement	42	2.5
Vasoactive drug doses	34	1.7
Rhabdomyolisis (ranking scale: 1-5)		
Blood levels of CK	80[a]	4.0[a]
Kidney improvement	55	3.3
Improvement in MODS	60	3.0
Blood levels of myoglobin	52	2.6
Improvement of metabolic biomarkers	40	2.0

Abbreviations: AKI, acute kidney injury; CK, creatine kinase; EBPT, extracorporeal blood purification therapy; MODS, multiple organ dysfunction syndrome; TAMOF, thrombocytopenia-associated with multiple organ failure.

[a] Consensus reached.

Cytokine Storm Syndromes

For critically ill patients with cytokine storm syndromes, the indications proposed by the panel for initiating EBPTs were cardiovascular dysfunction and MODS, with consensus scores of 81% and 75%, respectively (Table 2). The criteria that reached consensus for discontinuing EBPTs in these patients were hemodynamic improvement (85%) and improvement in organ dysfunction (75%) (Table 2).

The outcomes considered by the panel for evaluating the effectiveness of EBPTs were reversal of shock, with an 82% consensus, and changes in the organ dysfunction score, with a 75% consensus (Table 3). For safety assessment, the outcomes proposed included hemodynamic stability at the start of EBPT, with a strong consensus score of 94%, and incidence of bleeding, with a consensus score of 79% (Table 3).

Intoxications

Regarding pediatric intoxications, the panel proposed the main indications for initiating EBPTs were time elapsed since toxin exposure and pharmacokinetics of the toxins, both with a consensus score of 75% (Table 2). The primary criteria for discontinuing EBPTs were the blood concentration of toxic

Table 3. Outcome for Assessing the Effectiveness and Safety of Extracorporeal Blood Purification Therapies by Clinical Condition

Outcome	Panelist agreement score, %	Total raw ranking score
Outcome for assessing the effectiveness of EBPTs		
Septic shock (ranking scale: 1-10)		
Reversal of refractory shock	91[a]	9.1[a]
Substantial reduction (50%) of VIS	78[a]	7.8[a]
Vasopressor-free days	58	5.8
PICU length of stay	52	5.2
Change in organ dysfunction score	51	5.1
Mechanical ventilation–free days	50	5.0
Mortality at 28 d	48	4.8
Substantial reduction of inflammatory biomarkers	46	4.6
Hospital mortality	38	3.8
Substantial improvement of metabolic biomarkers	33	3.3
Liver failure (ranking scale: 1-9)		
Substantial improvement of liver synthetic biomarkers	82[a]	7.4[a]
Reversal of shock	68	6.3
Change in organ dysfunction score	67	6.1
Substantial reduction of inflammatory biomarkers and serum ammonia	68	6.1
Mortality at 28 d	49	4.4
28-d PICU discharge	45	4.1
Vasopressor-free days	42	3.8
Mechanical ventilation–free days	35	3.2
Hospital mortality	35	3.2
Cardiopulmonary bypass (ranking scale: 1-11)		
Reversal of shock	87[a]	9.6[a]
Renal recovery	66	7.3
Change in organ dysfunction score	66	7.3
Fluid balance and fluid overload improvement	66	7.3
Vasopressor-free days	57	6.3
Hospital mortality	48	5.3
Mortality at 28 d	48	5.3
Mechanical ventilation–free days	42	4.6
Substantial reduction of inflammatory biomarkers and serum ammonia	42	4.6
Substantial improvement of liver synthetic biomarkers	39	4.3
28-d PICU discharge	33	3.6
Cytokine storm syndromes (ranking scale: 1-10)		
Reversal of shock	82[a]	8.2[a]
Change in organ dysfunction score	75[a]	7.5[a]
Vasopressor-free days	56	5.6
Substantial reduction of inflammatory biomarkers	53	5.3
Mechanical ventilation–free days	52	5.2
Substantial improvement of metabolic biomarkers	50	5.0
Mortality at 28 d	47	4.7
28-d PICU discharge	46	4.6
Improvement in fluid balance	45	4.5
Hospital mortality	41	4.1

(continued)

Table 3. Outcome for Assessing the Effectiveness and Safety of Extracorporeal Blood Purification Therapies by Clinical Condition (continued)

Outcome	Panelist agreement score, %	Total raw ranking score
Intoxications (ranking scale: 1-12)		
Change in organ dysfunction score	79[a]	9.5[a]
Reversal of shock	71[a]	8.5[a]
Substantial reduction of xenobiotic blood levels	71[a]	8.5[a]
Renal recovery	59	6.7
Mortality at 28 d	50	6.0
Vasopressor-free days	50	6.0
28-d PICU discharge	47	5.7
Mechanical ventilation–free days	74	5.2
Substantial improvement of metabolic biomarker	43	5.2
Substantial reduction of inflammatory biomarkers of targets organ damage	39	4.7
Hospital mortality	37	4.5
Rhabdomyolisis (ranking scale: 1-9)		
Renal recovery	90[a]	8.1[a]
Substantial reduction of inflammatory CK	89[a]	8.0[a]
Change in organ dysfunction score	84[a]	7.6[a]
Substantial reduction of metabolic biomarkers	75	6.8
Substantial improvement of metabolic myoglobin	64	5.8
Mechanical ventilation–free days	57	5.1
Mortality at 28 d	53	4.8
28-d PICU discharge	48	4.3
Hospital mortality	34	3.1
Outcome for assessing the safety of EBPTs		
Septic shock (ranking scale: 1-9)		
Hemodynamic stability at EBPT initiation by first 6 h	97[a]	8.7[a]
Incidence of bleeding	74[a]	6.7[a]
Hemoglobin variation >20% in first 6 h after EBPT start	62	5.6
Drugs removal with TDM	61	5.5
Platelet counts variation >20% in first 6 h after EBPT start	53	4.8
Incidence of electrolyte imbalance	53	4.8
Circuit survival impact	40	3.6
Loss of nutrients	33	3.0
Incidence of hypothermia	22	2.0
Liver failure (ranking scale: 1-9)		
Hemodynamic stability at EBPT initiation by first 6 h	92[a]	8.7[a]
Incidence of bleeding	83[a]	7.5[a]
Platelet counts variation >20% in first 6 h after EBPT start	71[a]	6.4[a]
Drugs removal with TDM	53	4.8
Hemoglobin variation >20% in first 6 h after EBPT start	49	4.4
Incidence of electrolyte imbalance	46	4.2
Circuit survival impact	44	4.0
Loss of nutrients	28	2.5
Incidence of hypothermia	23	2.1

(continued)

Table 3. Outcome for Assessing the Effectiveness and Safety of Extracorporeal Blood Purification Therapies by Clinical Condition (continued)

Outcome	Panelist agreement score, %	Total raw ranking score
Cardiopulmonary bypass (ranking scale: 1-9)		
Hemodynamic stability at EBPT initiation by first 6 h	92[a]	8.3[a]
Incidence of bleeding	81[a]	7.3[a]
Hemoglobin variation >20% in first 6 h after EBPT start	73[a]	6.6[a]
Platelet counts variation >20% in first 6 h after EBPT start	67	6.0
Drugs removal with TDM	59	5.3
Incidence of electrolyte imbalance	44	4.0
Circuit survival impact	40	3.6
Loss of nutrients	25	2.3
Incidence of hypothermia	14	1.3
Cytokine storm syndromes (ranking scale: 1-9)		
Hemodynamic stability at EBPT initiation by first 6 h	94[a]	8.5[a]
Incidence of bleeding	79[a]	7.1[a]
Hemoglobin variation >20% in first 6 h after EBPT start	67	6.0
Platelet counts variation >20% in first 6 h after EBPT start	61	5.5
Drugs removal with TDM	58	5.2
Circuit survival impact	47	4.2
Incidence of electrolyte imbalance	45	4.1
Loss of nutrients	28	2.5
Incidence of hypothermia	19	1.7
Intoxications (ranking scale: 1-9)		
Hemodynamic stability at EBPT initiation by first 6 h	91[a]	8.2[a]
Incidence of bleeding	85[a]	7.7[a]
Hemoglobin variation >20% in first 6 h after EBPT start	74[a]	6.7[a]
Platelet counts variation >20% in first 6 h after EBPT start	63	5.7
Incidence of electrolyte imbalance	47	4.2
Circuit survival impact	44	4.0
Drugs removal with TDM	41	3.7
Loss of nutrients	28	2.5
Incidence of hypothermia	22	2.0
Rhabdomyolisis (ranking scale: 1-9)		
Hemodynamic stability at EBPT initiation by first 6 h	95[a]	9.5[a]
Incidence of bleeding	86[a]	8.6[a]
Platelet counts variation >20% in first 6 h after EBPT start	65	6.5
Hemoglobin variation >20% in first 6 h after EBPT start	58	5.8
Incidence of electrolyte imbalance	58	5.8
Circuit survival impact	46	4.6
Drugs removal with TDM	41	4.1
Loss of nutrients	26	2.6
Incidence of hypothermia	20	2.0

Abbreviations: CK, creatine kinase; EBPT, extracorporeal blood purification therapy; PICU, pediatric intensive care unit; TDM, therapeutic drug monitoring; VIS, vasoactive-inotropic score.

[a] Consensus reached.

agents and hemodynamic improvement, with a consensus reaching 80% and 74%, respectively (Table 2).

For evaluating the effectiveness of EBPTs in patients with pediatric intoxications, the outcome considered to be most reliable by the panelists was the change in organ dysfunction score, with a 79% consensus (Table 3). The outcomes recommended for assessing the safety of EBPTs were hemodynamic stability at the start of EBPTs, with a strong consensus score of 91%, and variation in hemoglobin (approximately 20%) after the start of EBPTs, with a consensus score of 74% (Table 3).

Rhabdomyolysis

According to the panelists, the main indication for initiating EBPTs in critically ill pediatric patients with rhabdomyolysis was the plasma concentration of creatine kinase (CK), with a consensus score of 82% (Table 2). Similarly, plasma CK concentration was used as the criterion for discontinuing EBPTs, with a consensus score of 82% (Table 2).

The panel also proposed that the outcomes commonly used to assess the effectiveness of EBPTs in rhabdomyolysis were renal recovery and substantial reduction in CK levels, with consensus reaching 90% and 89%, respectively (Table 3). For safety assessment, the outcomes suggested were hemodynamic stability at the start of EBPTs, with a strong consensus score of 95%, and incidence of bleeding, with an 86% consensus (Table 3).

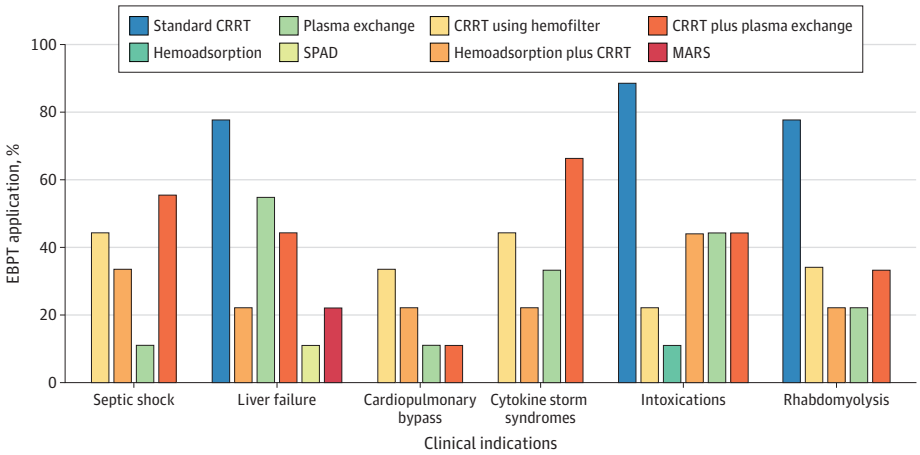
Application of EBPTs

When exploring the application of different types of EBPT among experienced users, we found that the most commonly applied EBPTs were CRRT plus plasma exchange (56%) for septic shock; CRRT, including high-volume hemofiltration, (78%) for liver failure; CRRT using hemofilter with enhanced adsorption properties (33%) for cardiopulmonary bypass; CRRT plus plasma exchange (67%) for cytokine storm syndromes; standard CRRT (78%) for rhabdomyolysis; and standard CRRT (89%) for intoxications (**Figure 2**). eFigure 2 in Supplement 1 shows the distribution of preferences among the panelists regarding the substances commonly used to prime extracorporeal circulation in pediatric patients.

Discussion

We developed a consensus statement on EBPTs in PICUs across Europe. Previous investigators have evaluated practices related to CRRT through a survey.[48] However, before the present initiative conducted on behalf of ESPNIC, the use of EBPTs had not been described across European PICUs.

Figure 2. Application of Extracorporeal Blood Purification Therapies (EBPTs) Across Clinical Indications



CRRT indicates continuous renal replacement therapy; MARS, molecular adsorbent recirculating system; and SPAD, single-pass albumin dialysis.

Serving as a panel of experts, we followed a modified Delphi approach. The consensus statement was not limited to the main clinical indications, such as septic shock and liver failure; instead, we also explored and addressed potential minor indications for EBPTs, such as rhabdomyolysis and intoxication, to ensure completeness.

According to the responses from the panelists, EBPTs are considered to be a potential adjuvant therapy in pediatric septic shock, particularly refractory septic shock,[46] or in other life-threatening conditions such as MODS and thrombocytopenia associated with multiple organ failure,[45] as previously described.[4] A recent study found that hemodynamic improvement is primarily recognized as an outcome of EBPT effectiveness in septic shock, which is intended as a reversal of septic shock or as a substantial reduction of vasoactive drugs.[49]

Historically, pediatric liver failure has been one of the areas with the most substantial evidence supporting the use of EBPTs.[21-25,50] For liver failure, the panelists identified detoxification as the primary goal of EBPTs, including the improvement of hepatic encephalopathy and the reduction of ammonia level. In pediatric cytokine storm syndrome, MODS has been identified by the panelists as the main condition for EBPTs. This finding is consistent with clinical experiences, suggesting that EBPTs can be effectively used as an adjuvant and salvage treatment for managing cytokine release syndrome associated with organ dysfunction, particularly when pharmacological treatments alone may not fully resolve the clinical manifestations of MODS.[26-29]

Pediatric cardiopulmonary bypass represents a model of systemic inflammation; however, only anecdotal pediatric experiences have been reported regarding the application of EBPT in pediatric cardiopulmonary bypass.[30-32] It has been identified as a potential indication for EBPTs, particularly for managing low cardiac output syndrome, systemic inflammation, and secondary acute kidney injury.[30-33] Growing interest has emerged in recent years regarding the use of EBPTs in pediatric rhabdomyolysis[34-37,51] as supportive therapies aimed at preventing and reversing organs' damage, particularly acute kidney injury, as well as more effectively removing mediators, such as myoglobin and toxins.[38,39]

There is still no consensus on the use of advanced biomarkers for septic shock or myoglobin levels for rhabdomyolysis as the criteria for initiating EBPTs. One potential reason based on current evidence (Table 1) is the limited bedside availability of these biomarkers. There is, however, broad consensus on recognizing hemodynamic stability at the start of EBPTs and the incidence of bleeding as a safety end point. This consensus highlights the importance of accurately estimating the extracorporeal volume in patients undergoing EBPTs in PICUs.

We did not focus our analysis on a specific blood purification device or technique. Instead, we sought to describe the use of various techniques. The standard CRRT, enhanced adsorption hemofilters, and plasma exchange were of particular interest, as they represent the most commonly applied EBPTs across different clinical settings. Although the application of hemoadsorption has been growing in recent years, it remains limited in PICUs, according to our panel.

In terms of future perspectives, although EBPTs hold substantial potential for improving outcomes in critically ill pediatric patients, its implementation in PICUs across Europe has substantial barriers, including challenges in assessing EBPTs' effectiveness and managing the potential complications. It is crucial to identify parameters that can accurately evaluate effectiveness, such as the relationship between the reduction of cytokines or endotoxins and clinical outcomes, as well as when to discontinue EBPT if therapeutic goals are not being achieved. Clear criteria need to be established to assess the futility of these treatments in patients who do not respond to advanced therapies. Furthermore, more technology needs to be adapted explicitly for pediatric patients.

Limitations

The lack of high-quality evidence was the main limitation of this project. For this reason, we did not grade our consensus statement; instead, we reported only the consensus scores based on the ranking responses of the panel on this topic.[41] The option of developing a survey on EBPTs was excluded due to the limited application and clinical expertise in this area across European PICUs.

Conclusions

The purpose of this consensus statement, in the absence of high-quality evidence that supports the development of formal guidelines, was to support pediatric intensivists in bedside decision-making and to guide future research focused on EBPTs in pediatric intensive care. The high level of panel agreement on the clinical indications for EBPTs in the PICU suggests that this practice could be the focus of future studies. The implementation of EBPTs across European PICUs requires targeted research to inform the development of reliable assessment parameters and innovation in pediatric-specific technologies, ahead of high-quality randomized clinical trials. Additionally, a detailed survey of PICU centers all over the world could be the focus of future investigations. By addressing these issues, we can enhance the safety and effectiveness of EBPTs for pediatric patients.

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SUPPLEMENT 1.

eMethods. Research Strategy
eTable 1. Panel List Skills
eFigure 1. Map Showing the Distribution of Panelist Members and PICUs Participating in the Consensus Statement
eFigure 2. Bar Charts Showing the Distribution of Preference on Use of Different Substances to Prime Extracorporeal Circuits for Extracorporeal Blood Purification Therapies in Children

SUPPLEMENT 2.

eTable 2. International Survey on Blood Purification in Critically Ill Children