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Efficacy of Blood Purification in Paediatric Sepsis and Its Effects on Inflammatory Cytokines: A Systematic Review and Meta-analysis

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ABSTRACT

Continuous blood purification (CBP) has been widely employed in adult sepsis management. However, given the distinct aetiology and host responses in paediatric sepsis compared to adults, the application of CBP in children remains under-researched in high-quality systematic studies, particularly regarding its efficacy in clearing inflammatory cytokines. This meta-analysis aims to evaluate the therapeutic efficacy of CBP in paediatric sepsis patients and its impact on inflammatory cytokines.

This study systematically analysed randomized controlled trials and prospective cohort studies of CBP in paediatric sepsis from January 1990 to October 2025. Studies were retrieved from PubMed, Embase, Cochrane Library, and Web of Science. Outcomes included inflammatory markers and prognostic markers.

This meta-analysis included 6 studies. Pooled results demonstrated that CBP reduced 28-day mortality (OR = 0.57, 95% CI: 0.30 to 1.07), PICU length of stay (OR = −0.06, 95% CI: −1.55 to 1.43), IL-6 (OR = 0.83, 95% CI: 0.14 to 1.53), CRP (OR = 1.26, 95% CI: −16.51 to 19.03), and TNF-α (OR = 1.66, 95% CI: −0.39 to 3.77).

CBP reduced the level of inflammatory markers and improved prognosis, which may provide evidence for the use of CBP in paediatric sepsis patients.

Keywords: Blood purification; Inflammatory cytokines; Meta-analysis; Paediatric sepsis

INTRODUCTION

Sepsis represents a life-threatening disorder of organ function arising from dysregulated host responses to infection, constituting a major health threat in paediatric populations. Globally, paediatric sepsis occurs at an incidence of approximately 22 cases per 100 000 children annually, with a mortality rate ranging from 4% to 50%.[1] The pathophysiological mechanisms of sepsis are complex, with infection-induced excessive inflammatory responses considered the primary pathophysiological mechanism.[2] Consequently, anti-infective therapy and the clearance of inflammatory cytokines and endotoxins are crucial components of sepsis treatment, including antibiotic therapy, fluid resuscitation, and vasoactive drug support. However, these treatments often yield limited efficacy in paediatric sepsis patients.[3,4]

Continuous blood purification (CBP) techniques involve removing pathogenic substances from the patient's blood via an extracorporeal purification device.[5] These include continuous renal replacement

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therapy (CRRT), total plasma exchange (TPE), haemoperfusion (HP), and cytokine adsorption (CA). These techniques have been extensively employed in adult sepsis management, with meta-analyses confirming that CBP significantly reduces mortality rates in adult patients.[6] This suggests CBP represents a viable therapeutic option for sepsis. However, given the differences in infectious aetiology and host responses between paediatric and adult sepsis, although studies have applied CBP to paediatric sepsis treatment, systematic evaluations of its clinical efficacy and effects on inflammatory mediators in paediatric sepsis remain lacking—particularly regarding CBP's impact on inflammatory mediators in paediatric sepsis patients.[7]

This meta-analysis aims to systematically evaluate the clinical efficacy of CBP in paediatric sepsis patients and its impact on inflammatory factors, thereby providing evidence-based medical support for the clinical practice of CBP in treating paediatric sepsis.

MATERIALS AND METHODS

Literature Search Strategy

This study was conducted according to standard meta-analysis methodology. Databases including PubMed, Embase, Cochrane Library, and Web of Science were searched from January 1990 to October 2025. Search terms included combinations of keywords such as: "paediatric sepsis"[MeSH Terms] AND ("blood purification"[All Fields] OR "CRRT"[All Fields] OR "plasma exchange"[All Fields] OR "haemoperfusion"[All Fields] OR "cytokine adsorption"[All Fields]); (2) "paediatric sepsis"[MeSH Terms] AND ("IL-6"[All Fields] OR "TNF-α"[All Fields] OR "CRP"[All Fields] OR "galactooligosaccharides"[All Fields] OR "synanthrin"[All Fields]); (3) "septic shock in children"[MeSH Terms] AND ("blood purification"[All Fields] OR "CRRT"[All Fields] OR "plasma exchange"[All Fields] OR "haemoperfusion"[All Fields] OR "cytokine adsorption"[All Fields]); (4) "septic shock in children"[MeSH Terms] AND ("IL-6"[All Fields] OR "TNF-α"[All Fields] OR "CRP"[All Fields] OR "galactooligosaccharides"[All Fields] OR "synanthrin"[All Fields]); (5) "paediatric sepsis"[MeSH Terms] AND ("randomized controlled trial"[All Fields] OR "prospective cohort"); (6) "septic shock in children"[MeSH Terms] AND ("randomized controlled trial"[All Fields] OR "prospective cohort").

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Patients: aged ≤ 18 years with sepsis; (2) Intervention and control: blood purification/CRR/plasma exchange/haemoperfusion/ cytokine adsorption versus routine treatment; (3) Outcomes: inflammatory markers (IL-6, CRP, TNF-α) and prognostic markers (28-day mortality, PICU stay); (4) Study design: randomized controlled trials or prospective cohort studies; (5) Language: English; (6) Publication period: January 1990 to October 2025.

Exclusion criteria: (1) Duplicate publications; (2) Case reports; (3) Animal or in vitro studies; (4) Studies lacking full text or key data; (5) Conference abstracts, commentaries, reviews, meta-analyses, guidelines, or consensus statements.

Data Extraction

Two dedicated staff members independently conducted searches and data extraction. Data were extracted using Excel spreadsheets and verified by a third reviewer. Extracted data included: study details (title, first author, publication year, sample size, study design type); patient characteristics (age, sepsis severity, comorbidities); treatment methods (CBP type, treatment parameters, duration); and outcome measures (organ function markers, inflammatory markers, prognostic markers).

Quality Assessment

During literature screening, two dedicated staff members independently conducted a secondary screening of articles against inclusion and exclusion criteria. Discrepancies were resolved through joint review of full texts and consensus-based decision-making. Where agreement could not be reached, a third party was consulted for assessment. Quality assessment of included randomized controlled trials was conducted using Cochrane assessment items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other biases.

Cohort study quality was assessed using the Newcastle-Ottawa Scale (NOS), categorized as low quality (0–3 points), moderate quality (4–6 points), and high quality (7–9 points). Non-randomized studies were evaluated using the Non-Randomized Studies Methodological Index (minors) criteria, with a maximum score of 24 points.[8]

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Statistical Analysis

Literature information was recorded using Excel software, with data analysis conducted using RevMan 5.3 and StataSE 15.0 software. Quantitative data were expressed as ($x \pm s$) with 95% confidence intervals (CI); dichotomous data were presented as odds ratios (OR) with 95% CI, with results displayed in forest plots. Heterogeneity was assessed using the Q statistic, *p* value, and I^2 statistic. $I^2 \leqslant 50\%$ and $p>0.05$, indicating homogeneity among included studies, a fixed-effect model was employed; otherwise, a random-effects model was used. Meta-regression analysed sources of heterogeneity. Sensitivity analyses were conducted by sequentially excluding individual studies to assess the robustness. For outcomes with fewer than 10 included studies, publication bias assessment was not performed. RevMan 5.3 software was employed to assess the quality of randomized controlled trials (RCTs), generating risk of bias plots and risk of bias summary plots. For continuous outcomes, comparisons were based on change-from-baseline values (baseline minus 72 hours after treatment). When data were reported as medians and interquartile ranges, means and standard deviations were estimated using the method described by Wan et al; for categorical outcomes, original event counts were used. $p<0.05$ was defined as statistically significant.

RESULTS

Study Characteristics and Quality Assessment

The initial screening identified 2 031 potentially relevant publications. After excluding 1 701 duplicates, 330 studies remained. Following review of titles and abstracts, 314 studies were excluded, leaving 70. After full-text review, 64 studies were excluded, leaving 6. 6 studies evaluated the clinical efficacy of CBP combined with conventional therapy versus conventional therapy alone. Ultimately, ten studies were included in this meta-analysis (Figure 1), encompassing a total of 603 paediatric sepsis patients. Table 1[9–14] summarizes the characteristics of studies comparing CBP combined with conventional therapy versus conventional therapy alone.

A total of 2 cohort studies were included, assessed using the NOS scale, of which were high-quality studies (Table 1).[9–14] 2 non-randomized controlled trials were included, with MINORS scores of 13 and 12, respectively. 2 randomized controlled trials were included. Results from the Cochrane risk of bias tool are presented in the risk of bias plot (Figure 2) and risk of bias summary (Figure 3).

Comparison of Clinical Efficacy between CBP Plus Routine Treatment and Routine Treatment

Regarding prognostic markers, five studies[9, 11, 12, 13, 14] were included in the analysis of 28-day mortality; the test group demonstrated an average reduction of 0.57 in 28-day mortality compared to the control group (OR = 0.57, 95% CI: 0.30 to 1.07) (Figure 4A). Three studies[9,10,11] were included in the analysis of PICU stay, PICU stay (OR = −0.06, 95% CI: −1.55 to 1.43) (Figure 4B). Regarding inflammatory markers (IL-6, CRP, TNF-α), four studies[9,11,12,13] were included in the analysis of IL-6, the test group demonstrated an average reduction of 0.83 in IL-6 compared to the control group (OR = 0.83, 95% CI: 0.14 to 1.53) (Figure 4C), two studies[10,12] were included in the analysis of CRP, CRP (OR = 1.26, 95% CI: −16.51 to 19.03) (Figure 4D), four studies[9,11,13,14] were included in the analysis of TNF-α, TNF-α (OR = 1.66, 95% CI: −0.39 to 3.77) (Figure 4E). Heterogeneity tests are presented in Table 2. Meta-regression suggested that age contributed substantially to the heterogeneity in PICU length of stay, whereas sex appeared to be an important source of heterogeneity for IL-6 and TNF-α (Table 3).

Sensitivity Analysis and Publication Bias

Sensitivity analysis was conducted to assess the impact of individual studies on the meta-analysis results, achieved by sequentially excluding single studies (Table 4), demonstrating robust findings. As fewer than ten studies were included in this meta-analysis, no assessment of publication bias was performed.

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Table 1. Characteristics of studies comparing CBP plus routine treatment and routine treatment

Author	Year	Design	Country	Intervention	N	Male/female	Age	Blood flow rate, mL/kg/min	Ultrafiltration rate, mL/kg/h	Membrane/adsorbent type	Anticoagulation dosage, UI/kg/h	Duration of CBP	MODS, %	PRISM III score	Outcomes	Quality assessment	GRADE framework quality
Miao H[9]	2019	C	China	CBP	136	77/59	33 (12–65) m	4-6	50	AN69	NR	45 h (26–83 h)	63.2%	17 (16–19)	28-day mortality, PICU stay, TNF-α, IL-6	8	High
				Con	136	63/73	35 (19–64) m						55.9%	16 (15–19) points			
Aygün F[10]	2019	NR	Turkey	CBP	47	24/23	2 y (2 d–17.83 y)	5–20	37	AN69	5–25	34.0 h (8–189 h)	61.7%	28 (5–56)	PICU stay, CRP	13	Moderate
				Sta	121	62/59	1 y (3 d–17.5 y)						35.5%	20 (3–65)			
Cui Y[12]	2018	C	China	CBP	16	6/10	54 (3–144) m	4–6	35–50	NR	5–20	8 h (31–70 h)	NA	14 (10–20)	28-day mortality, PICU stay, TNF-α, IL-6	7	High
				Sta	11	7/4	12 m						NA	13 (10–18)			
Li L[13]	2014	NR	China	CBP	30	15/15	1.45 y	3~5	35	AN69	5-10	48 h	NA	NA	28-day mortality, IL-6, CRP	12	Moderate
				Sta	17	11/6	1.50 y						NA	NA			
Ning B[15]	2020	RCT	China	CBP	25	14/11	3.1±2.2 y	3	30	AN69	NR	NR	NA	20.3±1.7	28-day mortality, TNF-α, IL-6	NA	NA
				Sta	22	12/10	2.6±2.0 y						NA	19.7±2.1			
Yuan YH[18]	2014	RCT	China	CBP	20	13/7	4.3±0.7 y	3-8	100-250	polysulfone	10-25	36–72 h	NA	NA	28-day mortality, TNF-α	NA	NA
				Sta	22	14/8	4.0±0.9 y						NA	NA			

C: cohort; CBP: continuous blood purification; Con: conventional; NA: not available; NR: non-randomized controlled trial (for study design) or not reported (for data); RCT: randomized controlled trial; Sta: standard.

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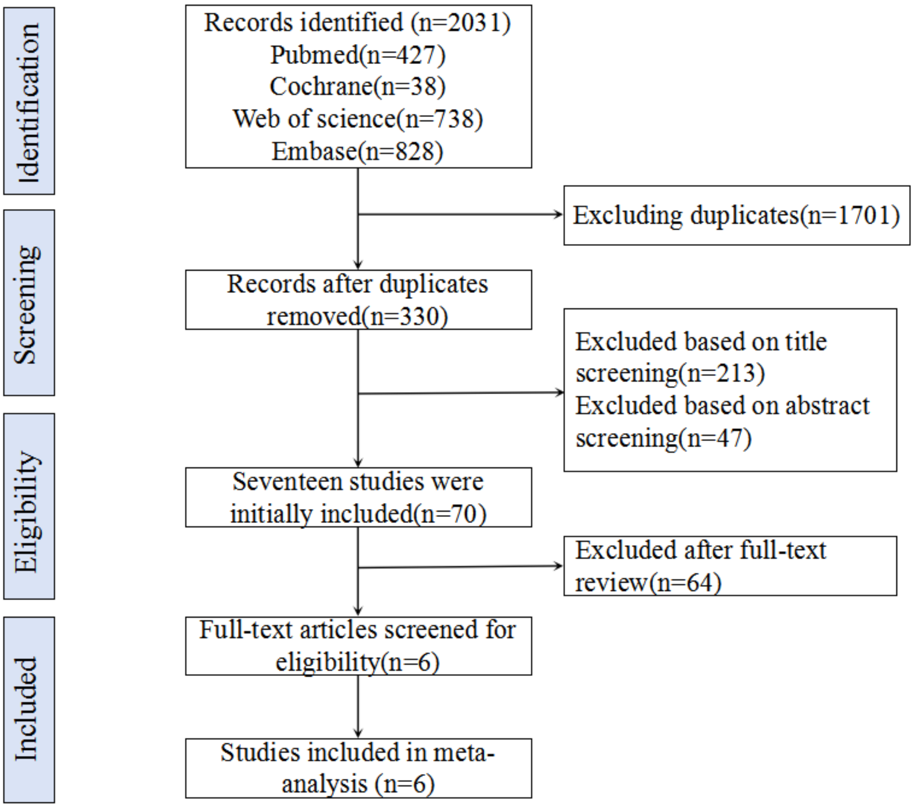

Figure 1. The flowchart of studies selection

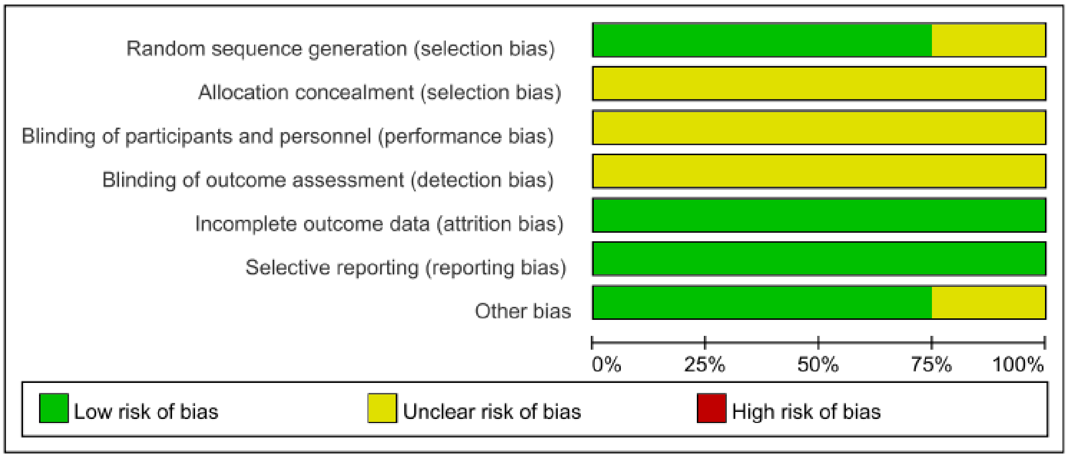

Figure 2. Risk of bias graph

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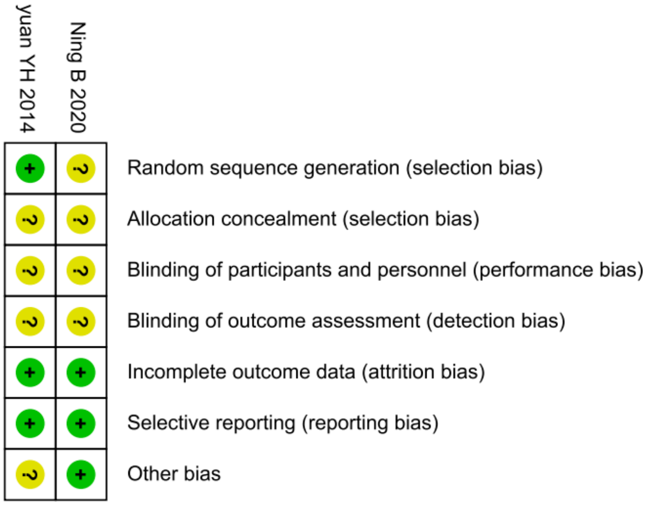

Figure 3. Risk of bias summary

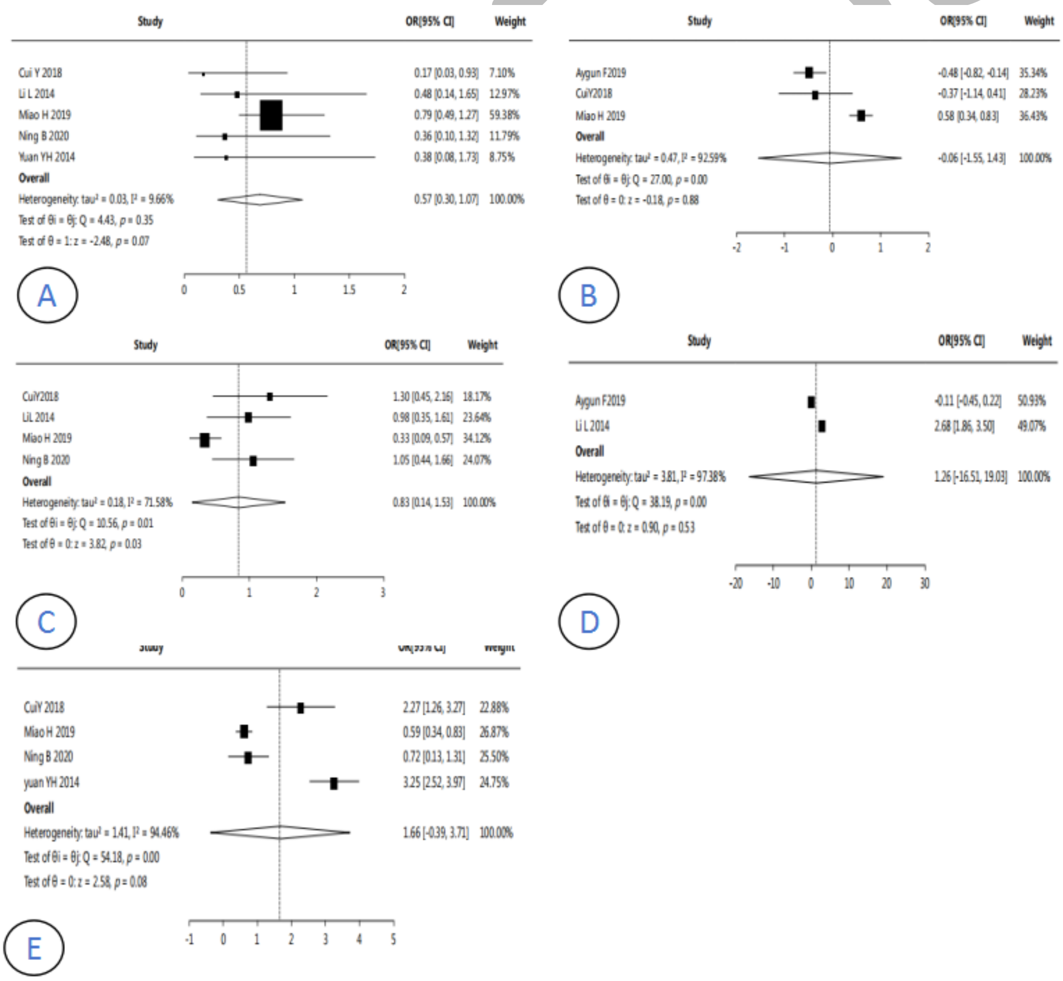

Figure 4. Forest plots regarding 28-day mortality, PICU stay, IL-6, CRP, PCT, and TNF-α. Note: (A) Forest plots regarding 28-day mortality, (B) Forest plots regarding PICU stay, (C) Forest plots regarding IL-6, (D) Forest plots regarding CRP, (E) Forest plots regarding TNF-α

Table 2. Heterogeneity tests

Item	Q	*p*	tau² value	I² (%)	H	Lower 95% limit	95% Upper Limit	H²
28-day mortality	4.427	0.351	0.034	9.66	1.05	1.00	2.31	1.11
PICU stay	27.003	<0.001	0.470	92.59	3.67	2.33	5.79	13.50
IL-6	10.556	0.014	0.184	71.58	1.88	1.11	3.16	3.52
CRP	38.188	0.010	3.811	97.38	6.18	3.90	9.80	38.19
TNF-α	52.182	<0.001	1.408	94.46	4.25	3.00	6.01	18.06

Table 3. Meta-regression

Item		Regression coefficient	SE	Z	*p*	Lower 95% limit	95% Upper Limit
PICU stay	Age	−1.039	0.259	−4.015	<0.001	−1.546	−0.532
	Gender	−0.727	0.651	−1.116	0.264	−2.003	0.549
IL-6	Age	1.641	0.422	3.888	0.069	0.814	2.468
	Gender	1.231	0.240	5.123	<0.001	0.760	1.702
TNF-α	Age	1.658	4.149	0.400	0.689	−6.473	9.789
	Gender	2.343	1.027	2.281	0.023	0.329	4.356

Table 4. Meta-analysis results for Sensitivity analysis and publication bias

Outcomes	OR/Hedges' effect size	Lower limit of 95% CI	Upper limit of 95% CI	*z*	*p*	*I²*
28-day mortality	0.568	0.301	1.071	−2.406	0.095	0.00
PICU stay	−0.061	−1.553	1.430	−0.117	0.876	92.59
IL-6	0.834	0.140	1.529	−3.823	0.023	71.58
CRP	1.258	−16.513	19.029	0.900	0.534	97.38
TNF-α	1.664	−0.336	3.713	2.581	0.082	94.46

DISCUSSION

This meta-analysis systematically incorporated 6 studies, using clinical efficacy (28-day mortality, PICU stay) and inflammatory markers (IL-6, CRP, TNF-α) as core indicators, to quantitatively evaluate the clearance effect of CBP on inflammatory markers in paediatric sepsis and its impact on clinical outcomes. Results indicate that CBP is associated with reduced levels of IL-6, CRP, and TNF-α in paediatric sepsis patients, along with decreased short-term mortality risk, but may prolong PICU stay.

Clearance of Inflammatory Mediators Constitutes the Core Mechanism by Which CBP Improves Outcomes

The pathophysiological core of sepsis is the infection-triggered "cytokine storm". IL-6 and TNF-α, as upstream pro-inflammatory factors, activate downstream inflammatory pathways, leading to massive release of inflammatory mediators that cause vascular endothelial injury, capillary leakage, and multiple organ dysfunction.[15,16] Due to incomplete organ development, children exhibit heightened sensitivity to inflammatory responses. Furthermore, differences in infectious

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pathogens compared to adults contribute to greater disease complexity. Our findings indicate that CBP significantly reduces post-treatment IL-6 and TNF-α levels (OR of 0.83 and 1.66, respectively). CBP clears excess inflammatory mediators from the circulation via adsorption and ultrafiltration mechanisms, thereby interrupting the cascade of inflammation. This represents a core mechanism for improving clinical outcomes. As markers of systemic inflammatory response, changes in CRP levels reflect the degree of inflammation control.[17] This study demonstrates that blood purification significantly reduces CRP (OR of 1.26).

CBP Reduces 28-day Mortality but Does not Shorten PICU Stay

A key finding of this meta-analysis indicates that CBP confers a significant advantage in reducing 28-day mortality in paediatric sepsis patients (OR = 0.57), but did not shorten the duration of PICU stay in paediatric patients (OR = −0.06). CBP reverses the pathological progression of sepsis by clearing inflammatory mediators, reducing circulating levels of IL-6, CRP, PCT, and TNF-α, thereby interrupting the inflammatory cascade and mitigating organ damage caused by this cascade. This ultimately lowers the short-term mortality risk in paediatric patients. However, CBP therapy relies on extracorporeal circulation equipment, potentially increasing the need for secondary treatments. Furthermore, CBP necessitates more intensive organ function monitoring, and paediatric patients may present with more complex baseline conditions, potentially delaying treatment response. Consequently, paediatric septic patients undergoing CBP may require longer hospital stays, and CBP may not meaningfully reduce PICU stay.[18]

Although CBP did not demonstrate a significant advantage in PICU length of stay, the reduced mortality is of greater clinical value. However, given the limited number of studies included in this review, this conclusion requires further validation through high-quality RCTs to provide robust clinical evidence supporting the use of CBP in paediatric sepsis management.

Comparison with Previous Studies and Health Economic Considerations

Compared to previous meta-analyses, this study possesses distinct advantages: firstly, it strictly included paediatric populations, avoiding interference from adult data; secondly, it centred on key inflammatory markers (IL-6, CRP, TNF-α), yielding more targeted conclusions; thirdly, it quantified sources of heterogeneity via meta-regression rather than relying solely on subgroup *p* values, enhancing conclusion reliability.

However, the health economics of CBP warrant attention, as the technique is extremely costly and labour-intensive. Furthermore, while this study's meta-regression analysis of CBP treatment demonstrated significant short-term benefits in reducing 28-day mortality risk, the long-term cost-effectiveness remains to be further evaluated.

Significant heterogeneity was observed in certain outcome measures. Although meta-regression analysis partially explained this variability, some sources of heterogeneity remain unexplained. The included studies lacked long-term prognostic data, precluding assessment of CBP's impact on the long-term outcomes of paediatric sepsis patients. The small number of included studies, combined with the inherent limitations of incorporating non-randomized controlled trials (non-RCTs), cohort studies, and non-RCT research, necessitates caution in drawing causal inferences.

CBP effectively clears core inflammatory mediators such as IL-6 and TNF-α, reducing 28-day mortality in paediatric sepsis patients, but may prolong PICU stay duration.

STATEMENT OF ETHICS

Not applicable.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

REFERENCES

1. Schlapbach LJ, Watson RS, Sorce LR, Argent AC, Menon K, Hall MW, et al. International Consensus Criteria for Pediatric Sepsis and Septic Shock. Jama-J Am Med Assoc. 2024;331(8):665-74.
2. Jarczak D, Kluge S, Nierhaus A. Septic Hyperinflammation-Is There a Role for Extracorporeal Blood Purification Techniques? Int J Mol Sci. 2024;25(6):3120.
3. Nishida O, Nakamura T, Nakada T, Takahashi G, Masuda Y, Tsubouchi H, et al. Granulocyte and Monocyte Adsorption Therapy in Patients With Sepsis: A Feasibility Study. Artif Organs. 2025;49(5):852-63.
4. Liu JP, Wang XW, Qie LP. Disease indicators for sepsis and analysis of sepsis treatment in children using the continuous blood purification technique. Genet Mol Res. 2015;14(2):5685-93.
5. Bottari G, Guzzo I, Marano M, Stoppa F, Ravà L, Di Nardo M, et al. Hemoperfusion with Cytosorb in pediatric patients with septic shock: A retrospective observational study. The International Journal of Artificial Organs. 2020;43(9):587-93.
6. Feng S, Cui Y, Zhou Y, Shao L, Miao H, Dou J, et al. Continuous renal replacement therapy attenuates polymorphonuclear myeloid-derived suppressor cell expansion in pediatric severe sepsis. Front Immunol. 2022;13:990522.
7. Nishizaki N, Hirano D, Miyasho T, Obinata K, Shoji H, Shimizu T. Evaluation of urinary IL-6 in neonates with septic shock treated with polymyxin B-immobilized fiber column. J Japan Pediatric Society. 2017;59(9):1032-3.
8. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. Anz J Surg. 2003;73(9):712-6.
9. Miao H, Shi J, Wang C, Lu G, Zhu X, Wang Y, et al. Continuous Renal Replacement Therapy in Pediatric Severe Sepsis: A Propensity Score-Matched Prospective Multicenter Cohort Study in the PICU. Crit Care Med. 2019;47(10):e806-13.
10. Aygün F, Varol F, Durak C, Talip Petmezci M, Kacar A, Dursun H, et al. Evaluation of Continuous Renal Replacement Therapy and Therapeutic Plasma Exchange, in Severe Sepsis or Septic Shock in Critically Ill Children. Medicina (Kaunas, Lithuania). 2019;55(7):350.
11. Cui Y, Xiong X, Wang F, Ren Y, Wang C, Zhang Y. Continuous hemofiltration improves the prognosis of bacterial sepsis complicated by liver dysfunction in children. Bmc Pediatr. 2018;18(1):269.
12. Li L, Gong H, Wang Y, Zhang Y, Zhang C, Pan G, et al. A multicenter prospective clinical study on continuous blood purification in treating childhood severe sepsis. Zhonghua Er Ke Za Zhi = Chinese Journal of Pediatrics. 2014;52(6):438-43.
13. Ning B, Ye S, Lyu Y, Yin F, Chen Z. Effect of high-volume hemofiltration on children with sepsis. Transl Pediatr. 2020;9(2):101-7.
14. Yuan Y, Yuan Y, Xiao Z, Zhang H, Fan J, Zhang X, et al. Impact of continuous blood purification on T cell subsets in children with severe sepsis. Zhongguo Dang Dai Er Ke Za Zhi = Chinese Journal of Contemporary Pediatrics. 2014;16(2):194-7.
15. Sahin EG, Guvenc KB, Can YY, Durak C, Varol F, Guven S. Continuous Renal Replacement Therapy in Pediatric Sepsis and MIS-C: Comparative Efficacy of Oxiris and Conventional Filters. Artif Organs. 2025:10-1111.
16. Tomar A, Kumar V, Saha A. Peritoneal dialysis in children with sepsis-associated AKI (SA-AKI): an experience in a low- to middle-income country. Paediatr Int Child H. 2021;41(2):137-44.
17. Ryazanova D, Tobylbayeva Z, Mironova O, Kakenov E, Sazonov V. Comparison of CytoSorb and Jafron HA330 Hemoadsorption Devices in Pediatric Oncological Patients with Sepsis: Retrospective Observational Study. J Clin Med. 2024;13(24):7694.
18. Kimmel JD, Lacko CS, Delude RL, Federspiel WJ. Characterizing accelerated capture of deoligomerized TNF within hemoadsorption beads used to treat sepsis. J Biome Materials Res. 2011;98(1):47-53.