15th ISFA 2025 World Congress

Extracorporeal Blood Purification for Sepsis; Emerging Role of Apheresis

Ho Chi Minh City Society of Dialysis Therapies (HSDT) Annual Congress
Nalod Hotel, Da Nang City, Viet Nam
December 12-14th, 2025

Rasheed Abiodun Balogun, MBBS(Ib) FACP FASN HP(ASCP) FMCP
Professor of Medicine and Pathology
Regional Medical Director, UVA Ambulatory Dialysis
Medical Director, Apheresis Unit and Extracorporeal Therapies
Division of Nephrology, University of Virginia
Charlottesville, VA

December 13th, 2025. x:x AM –x:xxAM Da Nang

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Disclosure

Relevant Financial Relationships
None

Relevant Non-Financial Relationships
President, International Society for Apheresis
Former Board Member, American Society for Apheresis
Former Member, JCA Special Issue Committee

Slides
Some modified from collaborators in ASFA

Off Label Usage
Any will be identified clearly

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Outline: Innovations in Extracorporeal Blood Purification

At the end of the session; delegates will have/be able to:

1. Give a brief overview of the concept of Destructive Immune Resonance in Sepsis
2. Show innovative plausibility of intervention to alter DIR with Modern Extracorporeal blood purification circuits
3. Recognize Existing Innovative Devices and Evolution of data using Extracorporeal blood purification circuits in Sepsis
4. Review results of relevant Clinical Trials; Improved outcomes? (mortality, convenience)

2025 orld Congress

Debate: Using Extracorporeal Blood Purification Therapies for Sepsis and Immune Dysregulation - CON

Session Title: Critical Care Nephrology: 2021 Update

Rasheed Abiodun Balogun, MBBS(Ib) FACP FASN HP(ASCP)
Professor of Medicine
Medical Director, Apheresis Unit and Extracorporeal Therapies (Apheresis) Program
Division of Nephrology, University of Virginia
Charlottesville, VA

October 25,

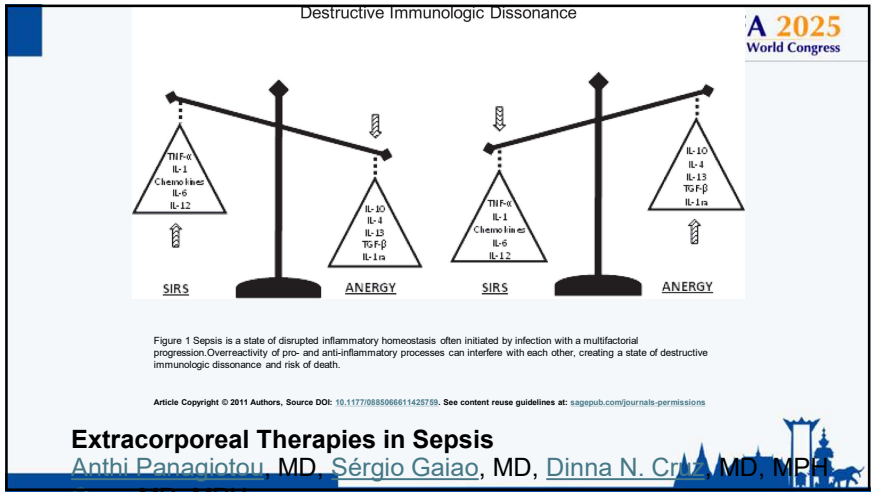


Figure 1 Sepsis is a state of disrupted inflammatory homeostasis often initiated by infection with a multifactorial progression.Overreactivity of pro- and anti-inflammatory processes can interfere with each other, creating a state of destructive immunologic dissonance and risk of death.

Extracorporeal Therapies in Sepsis

Anthi Panagiotou, MD, Sérgio Gaiao, MD, Dinna N. Cruz, MD, MPH

Extracorporeal Circulation

- diversion of blood through an external artificial circuit
- Purpose: blood "purification", gas exchange & correction of metabolic abnormalities
- Circuit hardware: tubing, pump(s), filters/membrane, oxygenator, heat exchange etc….

Stegmayr B, Ramlow W, Balogun RA. Semin Dial. 2012 Mar-Apr;25(2):207-13.

Blood Purification; Size Matters

Molecular Weight kD

Immunoglobulin G
160kDa; 2 LC: 23-25 kDa each; 2 HC:~53 kDa each

BUN	Cr	VitB12	B2-mic	K Lig C	L Lig C	Album	IgG
0.06	0.113	1.355	11.8	25	50	66	160

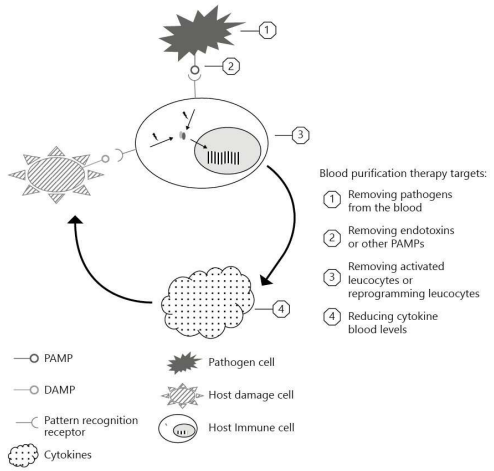
Small Molecules | Middle Molecules | Large Molecules

Hemodialysis: Diffusion Clearance

Hemofiltration: Convective Clearance

Therapeutic Plasma Exchange

Williams ME, Balogun RA. Clin J Am Soc Nephrol. 2014 Jan; 9(1):181-90.



Extracorporeal Blood Purification Therapies for Sepsis

Monard C. Rimmelé T. Ronco C. C.

Blood Purification
2019, Vol.47, Suppl. 3 May 2019
May 2019

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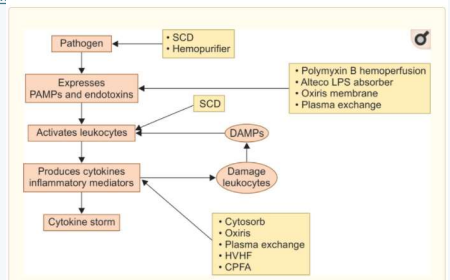
Extracorporeal Therapy in Sepsis 2020

Govil &Kumar Indian J Crit Care Med. 2020 Apr; 24(Suppl 3): S117–S121.



Flowchart 1

Immune response to sepsis and extracorporeal therapies

SCD, selective cytopheretic device; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patters; HVHF, high-volume hemofiltration; CPFA, coupled plasma filtration adsorption

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Table 1. Substances removed by various adsorbers and techniques

Adsorbers	Plasma removal (33)
Polymyxin-B (22–24)	Toxins, free and protein-bound
Endotoxin	Free myoglobin, hemoglobin
T, IL-6, IL-10, PAI-1 activity	Activated complement components
MDS-microspheres (25–27)	Activated coagulation components
Endotoxin	C-reactive protein
TNF-α, IL-1β, IL-6	Cytokines, cytokine-complexes
HELP (29)	Amylase
Endotoxin	Proteases
C-reactive protein	Ghost cells
Fibrinogen	Cell debris
TNF-α	Lysosomal enzymes
BioLogic sorbent (28)	Physiologically essential substances
Cytokines, protein-bound toxins	Plasma exchange
Fresenius adsorber (31)	Removal of adverse products
Endotoxin (LPS), TNF-α	Substitution of essential substances by e.g., plasma from healthy donors

Apheresis as Therapy for Patients with Severe Sepsis and Multiorgan Dysfunction Syndrome

Bernd G. Stegmayr,

Volume5, Issue2
April 2001
Pages 123-127

Table 1. Extracorporeal Blood Purification Techniques in Sepsis.

Technique	Aim	Principle	Reported Results
High-volume hemofiltration (HVHF)	Nonselective removal of inflammatory mediators	Convection	Reduces vasopressor requirements, reduces concentrations of inflammatory mediators in blood, and observed mortality lower than predicted mortality
High cutoff membranes (HCOM)	Nonselective removal of inflammatory mediators	Convection	Reduces vasopressor requirements, high clearance of inflammatory mediators moderates leukocyte proliferation, normalizes PMN phagocytosis
Polymyxin-B column (PMX-F)	Selective removal of endotoxin	Adsorption	Reduces vasopressor requirement, increases blood pressure, ameliorates organ dysfunction, reduces short-term mortality
Coupled plasma filtration adsorption (CPFA)	Nonselective removal of inflammatory mediators	Plasma adsorption	Reduces concentrations of inflammatory mediators in blood, restores leukocyte responsiveness
Cytokine adsorbing columns	Nonselective removal of inflammatory mediators	Plasma adsorption	Reduces cytokine levels, improvement in respiratory parameters
Renal assist device (RAD)	Substitute the filtration, transport, metabolic, endocrine and immunologic functions of the kidney	Cell-based therapy	Ameliorates the cytokine profile, improves calcium, phosphate, urea, and creatinine levels
Extracorporeal immune support system (EISS)	Attenuation of excessive antiinflammatory response	Cell-based therapy	Reduces vasopressor requirement, reduces concentrations of endotoxin and inflammatory markers (eg CRP, procalcitonin) in blood
Leukocyte inhibition module (LIM)	Attenuation of excessive proinflammatory response	Antibody-based therapy	No studies in sepsis

Abbreviations: CRP, C-reactive protein; PMN, polymorphonuclear.

Table 1. Extracorporeal Blood Purification Techniques in Sepsis.

Extracorporeal Therapies in Sepsis

Anthi Papagiotou, MD, Sérgio Gaiao, MD, Dipna N. Cruz, MD, MPH

Seminars in Dialysis

THERAPEUTIC APHERESIS FOR NEPHROLOGISTS

Beyond Dialysis: Current and Emerging Blood Purification Techniques

Bernd Stegmayr,* Wolfgang Ramlow,† and Rasheed A. Balogun‡
*Department of Public Health and Medicine, Umeå University and Division of Nephrology, Department of Internal Medicine, University Hospital, Umeå, Sweden, †Dialysis Center North, Rostock, Germany, and ‡Division of Nephrology, Department of Medicine, University of Virginia Health System, Charlottesville, Virginia

ABSTRACT

Extracorporeal blood purification using various techniques and hardware is a major part of the modern day practice of clinical nephrology. Although the various modalities of hemodialysis and hemofiltration are the most commonly used extracorporeal therapies in clinical nephrology, blood purification using other techniques have become necessary to remove pathogenic, toxic, or waste substances not easily cleared by hemodialysis or hemofiltration due to factors such as molecular size, protein binding, and lipid solubility. The following review is an up to date summary of extracorporeal therapies, beyond hemodialysis and hemofiltration, in current clinical use as practiced by nephrologists and others in the United States and beyond. This comprises therapeutic apheresis (plasma exchange and cytapheresis), plasma adsorption, hemoperfusion, and the bio-artificial devices.

Stegmayr B, Ramlow W, Balogun RA. Semin Dial. 2012 Mar-Apr;25(2):207-13.

Seminars in Dialysis

THERAPEUTIC APHERESIS FOR NEPHROLOGISTS

Septic Shock with Multiorgan Failure: From Conventional Apheresis to Adsorption Therapies

Bernd Stegmayr,*† Emaad M. Abdel-Rahman,‡ and Rasheed A. Balogun‡

*Department of Public Health and Medicine, Umeå University, and Division of Nephrology, Department of Internal Medicine, University Hospital, Umea, Sweden, †Dialysis Center North, Rostock, Germany, and ‡Division of Nephrology, Department of Medicine, University of Virginia Health System, Charlottesville, Virginia

ABSTRACT

Septic shock is often associated with multiorgan failure, a life threatening clinical condition during which there is an imbalance in the proinflammatory and anti-inflammatory cytokines, chemokines, antigens, endotoxins, procoagulant, and anticoagulant factors and also resultant effects of therapeutic intervention like volume overload. Various extracorporeal therapies have shown some positive results as adjunctive therapeutic intervention to traditional antimicrobials in an effort to bring the inflammatory mediators to a homeostatic balance and to improve poor organ perfusion caused by hypotension and thrombosis in the microcirculation. This review focuses on current information on the use of therapeutic apheresis procedures as adjunctive therapy in such clinical situations as well as the exciting prospects for the near future. The sometimes disappointing results of early phase clinical studies may, in some cases, be related to the well known barriers to successful clinical trials in critically ill patients rather than to failure of the novel concept of adjunctive extracorporeal treatment of septic shock. It should be noted that some of the specialized apheresis technologies reviewed in this article are not yet available for clinical use in the United States as they are not yet approved for use by the US Food and Drug Administration.

Stegmayr B, Abdel-Rahman EM, Balogun RA. Semin Dial. 2012 Mar-Apr;25(2):171-75.

Septic Shock with Multiorgan Failure: From Conventional Apheresis to Adsorption Therapies

TABLE 2. Various clinical studies using adsorption techniques in the treatment of sepsis, severe sepsis, and in MODS

Study/adsorber	*n*	Main mode of therapy	Survival (%)	*p*
Polymyxin B				
Tani et al. (36)	37/33c	AdsPmx	54/36	< 0.05
Nemoto et al. (21)	98	AdsPmx	41/11c	< 0.05
Suzuki et al. (37)	24/24c	AdsPmx	75/25c	< 0.05
Vincent et al. (23)	17/19c	AdsPmx	71/72c	ns
Cruz et al. (22)	34/30	AdsPmx	68/47c	< 0.05
Albumin as adsorber				
Staubach et al. (19)	67/76c	Albu adsc		

AdsPmx, adsorption column using group; ns, not significant.

TABLE 3. Various randomized studies using plasma exchange/plasmapheresis in the treatment of severe sepsis and in MODS

Study	*n*	Main mode of therapy	Survival (%)	*p*
Reeves et al. (26)	14/16c	PF	57/50	ns
Busund et al. (27)	54/52c	PE	67/44	0.05
Nguyen et al. (28)	5/5c	PE	100/20	< 0.05

PE, plasma exchange by centrifugation technique; PF, plasma exchange by filtration; c, control.

Septic Shock with Multiorgan Failure: From Conventional Apheresis to Adsorption Therapies

HD is necessary …. severe MOD, including AKI to survive…. uremic solutes, cytokines, chemokines, superantigens, modulators of apoptosis, endotoxins, drugs, and fluid overload.

….. prognosis is poor in severe cases. In the future…. additional approach …….. may be the use of apheresis procedures (centrifugation, filtration or adsorption).

Stegmyr, Abdel-Rahman and Balogun 2012

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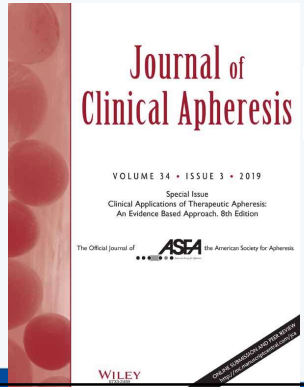
Apheresis Practice Guidelines



- Fact sheets renamed to co-locate similar disorders
- Select fact sheets merged, one fact sheet retired
- Several category recommendations changed based on new evidence or reassessment of existing evidence

J Clin Apher. 2019 Jun;34(3):171-354

DOI: 10.1002/jca.21705

Journal of Clinical Apheresis ASFA WILEY

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue

Anand Padmanabhan[1] | Laura Connelly-Smith[2] | Nicole Aqui[3] | Rasheed A. Balogun[4] | Reinhard Klingel[5] | Erin Meyer[6] | Huy P. Pham[7] | Jennifer Schneiderman[8] | Volker Witt[9] | Yanyun Wu[10] | Nicole D. Zantek[11] | Nancy M. Dunbar[12] |

Guest Editor: Joseph Schwartz[13]

J Clin Apher. 2019;34:171–354. wileyonlinelibrary.com/journal/jca

J Clin Apher. 2019 Jun;34(3):171-354.

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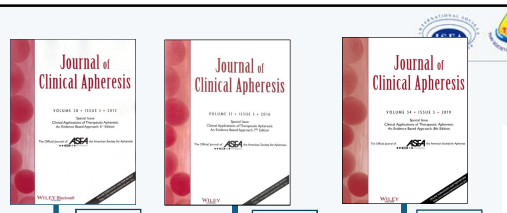
Category Definitions: 2019

Category	Description
I	Disorders for which apheresis is **accepted as first-line therapy**, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is **accepted as second-line therapy**, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum **role of apheresis therapy is not established**. Decision making should be individualized.
IV	Disorders in which **published evidence demonstrates or suggests apheresis to be ineffective or harmful**. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

J Clin Apher. 2019 Jun;34(3):171-354.



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2023

Journal of Clinical Apheresis

The Official Journal of ASFA the American Society for Apheresis

Volume 38, Number 2, 2023

Special Issue

Clinical Applications of Therapeutic Apheresis: An Evidence Based Approach. 9th Edition

J Clin Apher. 2023 Apr;38(2):77-278

APHERESIS PRACTICE GUIDELINES

c. Laura Connely-Smith

2023 Special Issue Highlights

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c. Nancy Dunbar

- 91 diseases/conditions , 166 indications

TABLE 1 Category and grade recommendations for therapeutic apheresis.

Disease/condition	Indication	Procedure	Category	Grade	Page
Acute disseminated encephalomyelitis	Steroid refractory	TPE	II	2C	95
Acute inflammatory demyelinating polyradiculoneuropathy	Primary treatment	TPE	I	1A	97
		IA	I	1B	
Acute liver failure	Acute liver failure	TPE-HV	I	1A	99
		TPE	III	2B	
	Acute fatty liver of pregnancy[a]	TPE	III	2B	
Acute toxins, venoms and poisons	Mushroom poisoning	TPE	II	2C	101
	Envenomation	TPE	III	2C	
	Other[a]	TPE/RBC exchange	III	2C	

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ASFA Guidelines Fact Sheets 2016, 2019, 2023

2016

SEPSIS WITH MULTIORGAN FAILURE

Journal of Clinical Apheresis 31:149–338 (2016)

Incidence: 300/100,000/yr (US)		**Procedure** TPE	**Recommendation** Grade 2B	**Category** III
No. of reported patients: >300	**RCT** 4(194)	**CT** 5(155)	**CS** 12(231)	**CR** 11

PADMANABHAN ET AL.

2019

SEPSIS WITH MULTIORGAN FAILURE

J Clin Apher. 2019;34:171–354.

Incidence: Severe sepsis in adults 300/100,000/yr (US); 8% prevalence in pediatric intensive care		**Procedure** TPE	**Recommendation** Grade 2B	**Category** III
# reported patients: >300	**RCT** 4(194)	**CT** 6(215)	**CS** 16(1,216)	**CR** NA

CONNELLY-SMITH ET AL.

2023

SEPSIS WITH MULTIORGAN FAILURE

J Clin Apher. 2023 Apr;38(2):77–278.

Incidence: severe sepsis in adults 300/100,000/year (United States); 8% prevalence in pediatric intensive care

Indication	**Procedure**	**Category**		**Grade**	
	TPE	III		2A	
# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Sepsis*	TPE	5 (234)	7 (295)	NA	NA
Sepsis, COVID-19 related	TPE	1 (87)	6 (359)	NA	NA

*excluding sepsis due to COVID-19

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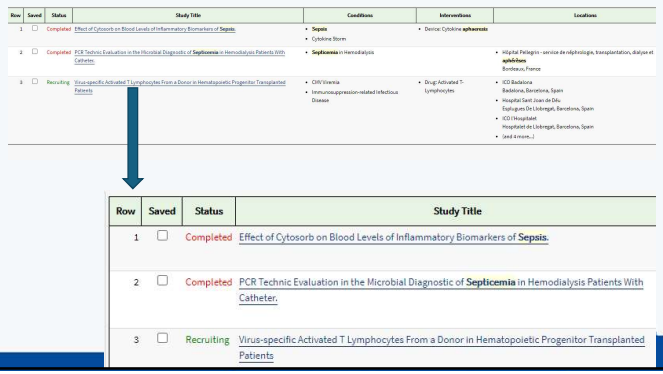
ClinicalTrials.gov October 9, 2021 Sepsis and Apheresis



Row	Saved	Status	Study Title
1	☐	Completed	Effect of Cytosorb on Blood Levels of Inflammatory Biomarkers of **Sepsis**.
2	☐	Completed	PCR Technic Evaluation in the Microbial Diagnostic of **Septicemia** in Hemodialysis Patients With Catheter.
3	☐	Recruiting	Virus-specific Activated T Lymphocytes From a Donor in Hematopoietic Progenitor Transplanted Patients

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ClinicalTrials.gov July 16, 2025 Sepsis and Apheresis

	Study Title	NCT Number	Status	Conditions	Interventions	Sponsor	Study Type
1	Safety, Tolerability and Performance of the NucleoCapture Device in the Reduction of Circulating CfDNA/NETs in Subjects with **Sepsis**	NCT05647096	Not yet recruiting	• **Sepsis** • Respiratory Failure	• Device: NucleoCapture device	Santersus AG	Interventional
2	Effect of Cytosorb on Blood Levels of Inflammatory Biomarkers of **Sepsis**.	NCT04226430	Completed	• **Sepsis** • Cytokine Storm	• Device: Cytokine apheaeresis	University of Gazia mep	Observational
3	Pro-inflammatory Cytokines Profile and Mortality Rate of Critically Ill Septic Patients Following Plasmapheresis	NCT01249222	Unknown status *	• Severe **Sepsis**	• Procedure: plasmapheresis • Other: plasmapheresis	Tehran University of Medical Sciences	Interventional
4	NADPH Oxidase Correction in mRNA-transfected Granulocyte-enriched Cells in Chronic Granulomatous Disease (CGD)	NCT05189925	Recruiting	• Chronic Granulomatous Disease • Infection			
5	Virus-specific Activated T Lymphocytes From a Donor in Hematopoietic Progenitor Transplanted Patients	NCT04018261	Completed	• CMV Viremia • Immunosuppression-related Infectious Disease			
6	Therapeutic Plasma Exchange in Septic Shock: a Pilot Study	NCT05093075	Recruiting	• Septic Shock			
7	A Vaccine (CMV-MVA Triplex Vaccine) for the Enhancement of CMV-Specific Immunity and the Prevention of CMV Viremia in Patients Undergoing Haploidentical Hematopoietic Stem Cell Transplant	NCT07020533	Not yet recruiting	• Accelerated Phase Chronic Myeloid Leukemia, BCR-ABL1 Positive • Acute Lymphoblastic Leukemia • Acute Myeloid Leukemia • 9 more			

	Study Title	NCT Number	Status	Conditions	Interventions	Sponsor	Study Type
1	Safety, Tolerability and Performance of the NucleoCapture Device in the Reduction of Circulating CfDNA/NETs in Subjects with **Sepsis**	NCT05647096	Not yet recruiting	• **Sepsis** • Respiratory Failure	• Device: NucleoCapture device	Santersus AG	Interventional
2	NADPH Oxidase Correction in mRNA-transfected Granulocyte-enriched Cells in Chronic Granulomatous Disease (CGD)	NCT05189925	Recruiting	• Chronic Granulomatous Disease • Infection	• Biological: gp91 Grans	National Institute of Allergy and Infectious Diseases (NIAID)	Interventional
3	Therapeutic Plasma Exchange in Septic Shock: a Pilot Study	NCT05093075	Recruiting	• Septic Shock	• Other: Therapeutic Plasma Exchange	University of Manitoba	Interventional
4	A Vaccine (CMV-MVA Triplex Vaccine) for the Enhancement of CMV-Specific Immunity and the Prevention of CMV Viremia in Patients Undergoing Haploidentical Hematopoietic Stem Cell Transplant New	NCT07020533	Not yet recruiting	• Accelerated Phase Chronic Myeloid Leukemia, BCR-ABL1 Positive • Acute Lymphoblastic Leukemia • Acute Myeloid Leukemia • 9 more	• Procedure: Biospecimen Collection • Other: Electronic Health Record Review • Procedure: Haploidentical Hematopoietic Cell Transplantation • 5 more	City of Hope Medical Center	Interventional

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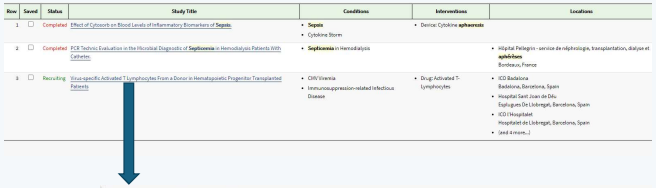
ClinicalTrials.gov October 9, 2021
Sepsis and Extracorporeal



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ClinicalTrials.gov October 9, 2021
Sepsis and "Extracorporeal" All Phases, All Time

- Sepsis and Extracorporeal Results 45 all time
- Suspended or Terminated: 2
- Completed: 17
- Completed + Has Results: 3

Row	Saved	Status	Study Title	Conditions
1	☑	Completed Has Results	Inflammatory Cytokine Quantification in Infants	• Sepsis • Congenital Diaphragmatic Hernia • Neonatal Cardiopulmonary Failure
2	☑	Completed Has Results	Safety and Efficacy of Polymyxin B Hemoperfusion (PMX) for Septic Shock	• Septic Shock • Endotoxemia
3	☑	Completed Has Results	The Effects of Polymyxin-B Protects on Sepsis Induced Kidney Dysfunction: a Randomized Clinical Trial	• Gram-Negative Bacterial Infections • Sepsis

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ClinicalTrials.gov July 16, 2025
Sepsis and "Extracorporeal" All Phases, All Time

- Sepsis and Extracorporeal Results 93 all time (from 45)
- Completed -

None Selected | Download | Save | RSS

	Study Title	NCT Number	Status	Conditions	Interventions	Sponsor	Study Type
1	S.A.F.E.BT System: **Extracorporeal** Treatment With DIAPACT CRRT	NCT01312675	Terminated	• Severe **Sepsis**	• Device: S.A.F.E.BT	B. Braun Medical Inc.	Interventional
2	Imipenem/Cilastatin/Relebactam PK in ECMO	NCT04493151	Completed	• **Sepsis**	• Drug: Imipenem, Cilastatin and Relebactam	Joseph L. Kuti, PharmD	Interventional
3	Inflammatory Cytokine Quantification in Infants	NCT01155830	Completed	• **Sepsis** • Congenital Diaphragmatic Hernia • Neonatal Cardiopulmonary Failure		University of Utah	Observational
4	The Effects of Polymyxin-B Protects on **Sepsis** Induced Kidney Dysfunction: a Randomized Clinical Trial	NCT00490477	Completed	• Gram-Negative Bacterial Infections • **Sepsis**	• Device: Polymyxin -B fiber hemoperfusion system	University of Turin, Italy	Interventional
5	Safety and Efficacy of Polymyxin B Hemoperfusion (PMX) for Septic Shock	NCT01046669	Completed	• Septic Shock • Endotoxemia	• Device: TORAYMYXIN PMX-20R (PMX cartridge) • Other: Standard medical care for septic shock	Spectral Diagnostics (US) Inc.	Interventional

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level
The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, MD, MSc; Sean M. Bagshaw, MD, MSc; Massimo Antonelli, MD; Debra M. Foster, BSc; David J. Klein, MD, MBA; John C. Marshall, MD; Paul M. Palevsky, MD; Lawrence S. Weisberg, MD; Christa A. Schorr, DNP, MSN, RN; Stephen Trzeciak, MD, MPH; Paul M. Walker, MD, PhD; for the EUPHRATES Trial Investigators

JAMA Network

From: **Effect of Targeted Polymyxin B Hemo**
Elevated Endotoxin Level: The EUPHRATES

JAMA. 2018;320(14):1455-1463. doi:10.1001/jama.

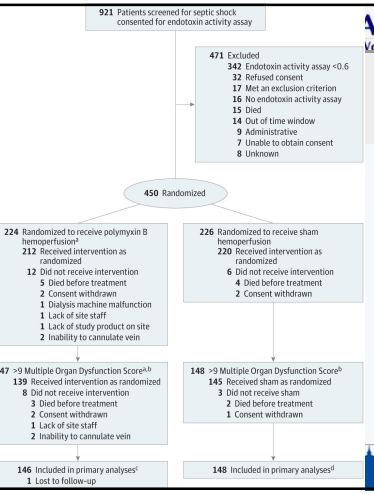

Figure Legend:

Patient Recruitment, Randomization, and Flow of t

[b]Protocol adjusted following interim analysis to enro
Dysfunction Score of more than 9.

[c]Primary analyses also included all participants ran

[d]Primary analyses also included all participants ran

JAMA Network

From: **Effect of Targeted Polymyxin B Hemo**
Elevated Endotoxin Level: The EUPHRATES

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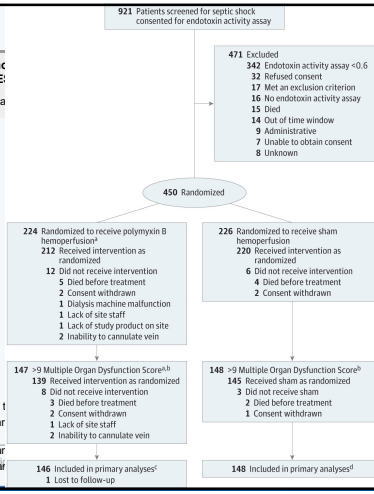

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Patient Recruitment, Randomization, and Flow of t

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JAMA Network

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From: **Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial**

JAMA. 2018;320(14):1455-1463. doi:10.1001/jama.2018.14618

Table 2. Summary of the Primary End Point of 28-Day Mortality for All Participants and for Patients With MODS of More Than 9

	No./Total (%)		(95% CI)		
	Polymyxin-B Hemoperfusion	Sham	Risk Difference	Risk Ratio	*P* Value[a]
All Participants	84/223 (37.7)	78/226 (34.5)	3.15 (−5.73 to 12.04)	1.09 (0.85 to 1.39)	.49
>9 MODS[b]	65/146 (44.5)	65/148 (43.9)	0.60 (−10.75 to 11.97)	1.01 (0.78 to 1.31)	.92

[a] *P* values were calculated by χ^2 and were unadjusted.

[b] Multiple Organ Dysfunction Score (MODS)–measure of altered organ function in acutely ill patients using 6 organ systems with weighted scores (0, normal; 4, severe) of each organ system (MODS range, 0-24). A higher score is associated greater burden of organ dysfunction. A MODS of 9 to 12 points has a hospital mortality of approximately 50%. Prior to the protocol amendment, the MODS score was calculated at baseline (time of randomization to the initiation of the study treatment). After the amendment, MODS of more than 9 was included at the time of screening, prior to randomization.

Table Title:

Summary of the Primary End Point of 28-Day Mortality for All Participants and for Patients With MODS of More Than 9[a]P values were calculated by χ^2 and were unadjusted.

[b] Multiple Organ Dysfunction Score (MODS)–measure of altered organ function in acutely ill patients using 6 organ systems with weighted scores (0, normal; 4, severe) of each organ system (MODS range, 0-24). A higher score is associated greater burden of organ dysfunction. A MODS of 9 to 12 points has a hospital mortality of approximately 50%. Prior to the protocol amendment, the MODS score was calculated at baseline (time of randomization to the initiation of the study treatment). After the amendment, MODS of more than 9 was included at the time of screening, prior to randomization.

Research

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JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level

The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, MD, MSc; Sean M. Bagshaw, MD, MSc; Massimo Antonelli, MD; Debra M. Foster, BSc; David J. Klein, MD, MBA; John C. Marshall, MD; Paul M. Palevsky, MD; Lawrence S. Weisberg, MD; Christa A. Schorr, DNP, MSN, RN; Stephen Trzeciak, MD, MPH; Paul M. Walker, MD, PhD; for the EUPHRATES Trial Investigators

CONCLUSIONS AND RELEVANCE Among patients with septic shock and high endotoxin activity, polymyxin B hemoperfusion treatment plus conventional medical therapy compared with sham treatment plus conventional medical therapy did not reduce mortality at 28 days.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01046669

Intensive Care Med (2008) 34:1638–1645
DOI 10.1007/s00134-008-1124-6

ORIGINAL

OpenAccess

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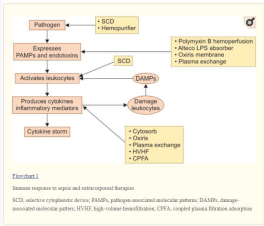
Polymyxin-B hemoperfusion inactivates circulating proapoptotic factors

Extracorporeal therapy with PMX-B reduces the proapoptotic activity of the plasma of septic patients on cultured renal cells. These data confirm the role of apoptosis in the development of sepsis related ARF.

Extracorporeal Therapy in Sepsis 2020

Govil &Kumar Indian J Crit Care Med. 2020 Apr; 24(Suppl 3): S117–S121.



Significant progress has been made ……but till date no conclusive evidence has emerged to support a routine use of any of these modalities as an adjunct to standard sepsis care.

Govil & Kumar
April 2020

Post Hoc Analysis; Selection Selection Selection

Intensive Care Med (2018) 44:2205–2212
https://doi.org/10.1007/s00134-018-5463-7

ORIGINAL

CrossMark

Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein[1*], D. Foster[2], P. M. Walker[2], S. M. Bagshaw[3], H. Mekonnen[4] and M. Antonelli[5]

EUPHRATES Trial Findings

Trial Overview

EUPHRATES was a large randomized controlled trial involving trial involving 450 septic shock patients with high endotoxin high endotoxin activity.

Primary Outcome

No significant 28-day mortality reduction was observed in the observed in the overall patient population receiving PMX receiving PMX hemoadsorption.

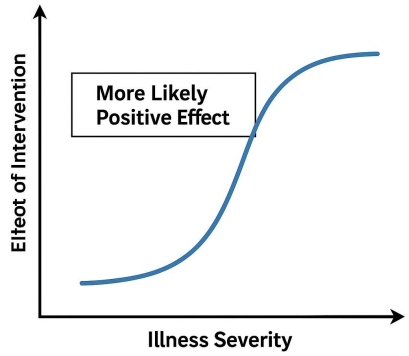
Subgroup Benefits

Patients with MODS > 9 and EAA 0.6-0.89 had a 16% higher 16% higher survival rate with PMX treatment.

Additional Clinical Improvements

PMX therapy improved mean arterial pressure and increased increased ventilator-free days among treated patients. patients.

Post Hoc Analysis; Selection Selection Selection



TIGRIS Trial Results

Topline results released on **August 12**, on **August 12, 2025**

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Trial Design and Population

TIGRIS was a Phase 3 U.S. study targeting 157 adults 157 adults with endotoxic septic shock using strict using strict criteria.

Primary Endpoint Results

The trial showed an 8.3% absolute and 18% relative relative reduction in 28-day mortality with PMX therapy. with PMX therapy.

Long-term Outcomes

90-day mortality was 17.4% lower in PMX group with a group with a benefit probability over 99%, confirming 99%, confirming efficacy.

Clinical Significance

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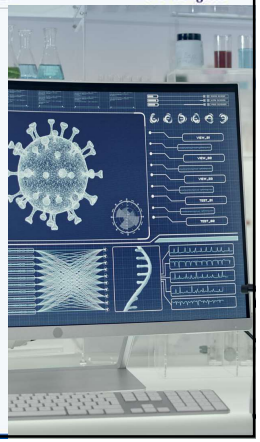
Background and Purpose of Trials



Purpose of Trials

TIGRIS and EUPHRATES trials evaluated Polymyxin B Hemoadsorption therapy for endotoxic therapy for endotoxic septic shock patients.

Trial Design Differences

EUPHRATES covered a broad septic shock population while TIGRIS focused on patients with on patients with specific endotoxin activity levels.

Hypothesis and Rationale

Removing endotoxin may improve survival in septic shock by targeting its critical role in disease its critical role in disease progression.

Innovative Statistical Approach

TIGRIS used Bayesian methods with prior EUPHRATES data to enhance trial power and power and interpretation.

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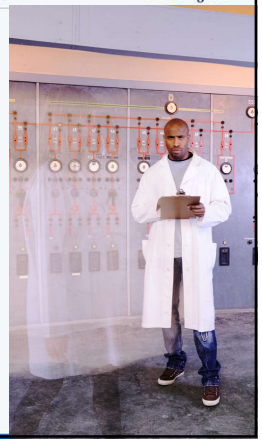
Study Design and Patient Selection



EUPHRATES Trial Overview

EUPHRATES was a multicenter randomized controlled trial enrolling septic shock patients using septic shock patients using standard severe sepsis criteria.

TIGRIS Inclusion Refinement

TIGRIS refined inclusion to patients with specific EAA levels and organ dysfunction scores for dysfunction scores for targeted PMX therapy benefit.

Bayesian Trial Design

TIGRIS used Bayesian design combining new data and prior evidence to improve efficacy improve efficacy evaluation of PMX treatment.

Treatment Protocol

PMX treatment involved two hemoperfusion sessions spaced 24 hours apart to maximize to maximize endotoxin removal safely.

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Endpoints and Statistical Approach

Primary and Secondary Endpoints
The primary endpoint was 28-day all-cause all-cause mortality; secondary endpoints endpoints included 90-day mortality and and hemodynamic improvements.

Bayesian Statistical Modeling
TIGRIS used Bayesian modeling to integrate integrate prior data and reduce sample size, sample size, improving evidence strength. strength.

Adaptive Decision-Making
Bayesian methods facilitated adaptive decision-adaptive decision-making and nuanced nuanced understanding of treatment effects effects across subpopulations.

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Efficacy Results

FEATURE	EUPHRATES	TIGRIS
Design	RCT, 2:1 PMX vs SOC	Bayesian RCT, 2:1 PMX vs SOC
Population	Septic shock with endotoxemia	EAA 0.60–0.90, MODS >9 or SOFA >11 >11
Sample Size	179 patients	157 patients
28-Day Mortality Reduction	~5% (NS)	8.3% ARR, 18% RRR
Posterior Probability	N/A	>95% (success)
90-Day Mortality	Not primary	17.4% lower with PMX
Safety	Acceptable	Acceptable; no major device events events

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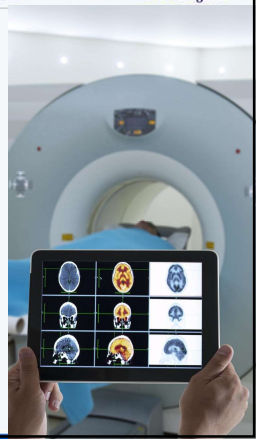
Safety Profile

Acceptable Safety Profiles
TIGRIS and EUPHRATES studies reported no major device-related complications complications with PMX therapy.

Manageable Adverse Events
Common side effects like hypotension and clotting were manageable and did not manageable and did not stop treatment.

Extensive Clinical Experience
Over 360,000 PMX treatments worldwide have shown negligible serious adverse serious adverse events.

Support for Adjunctive Therapy
Favorable safety and efficacy data support PMX as adjunctive therapy for therapy for endotoxic septic shock.



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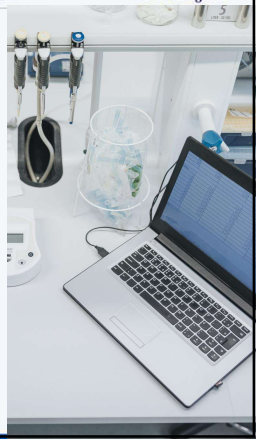
Impact on Clinical Practice

TIGRIS Trial Significance
The TIGRIS trial confirms PMX benefits for septic shock in selected patient groups, supporting patient groups, supporting better treatment strategies.

Targeted Endotoxin Removal
Targeted endotoxin removal via PMX reduces mortality in patients with high endotoxin activity high endotoxin activity and organ dysfunction.

Rapid Diagnostic Integration
Rapid diagnostic tools like Endotoxin Activity Assay allow timely identification of patients for identification of patients for personalized PMX therapy.

ICU Protocol and Training
PMX adoption influences ICU protocols, resource use, and staff training as extracorporeal as extracorporeal therapies gain prominence.



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FDA Approval and Future Directions

TIGRIS Trial Significance
TIGRIS trial met Bayesian success criteria, providing strong evidence of PMX evidence of PMX efficacy and safety for FDA approval.

Regulatory Milestones
PMX received Breakthrough Device designation, accelerating the FDA review and the FDA review and regulatory clearance process.

Future Research and Applications
Focus on post-marketing surveillance, real-world studies, and exploring PMX in exploring PMX in other endotoxin-related conditions.

Innovative Trial Designs
Bayesian trial designs in critical care research offer new methods for evidence methods for evidence generation in high-risk populations.

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Study protocol | Open access | Published: 15 April 2023

EXCHANGE-2: investigating the efficacy of add-on plasma exchange as an adjunctive strategy against septic shock—a study protocol for a randomized, prospective, multicenter, open-label, controlled, parallel-group trial

Sascha David, Christian Bode & Klaus Stahl for the EXCHANGE-2 Study group

Trials **24**, Article number: 277 (2023) | Cite this article

4441 Accesses | **16** Citations | **16** Altmetric | Metrics

Critical Care BMC

Crit Care. 2024 Jan 4;28:12. doi: 10.1186/s13054-023-04795-x

Influence of therapeutic plasma exchange treatment on short-term mortality of critically ill adult patients with sepsis-induced organ dysfunction: a systematic review and meta-analysis

Vladimir Kuklin [1,✉], Michael Sovershaev [2], Johan Bjerner [2], Philip Keith [3], L Keith Scott [4], Owen Matthew Truscott Thomas [5], Wladimir Szpirt [6], Gail Rock [7], Bernd Stegmayr [8]

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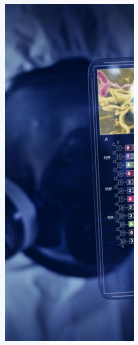
2024 Meta-Analysis and Clinical Implications

Meta-Analysis Overview
Reviewed 20 studies with 937 septic patients comparing standard therapy and plasma exchange outcomes.

Therapeutic Plasma Exchange Benefits
TPE significantly reduced short-term mortality with improved hemodynamics and organ function in sepsis patients.

Subgroup and Technique Insights
Centrifugation techniques outperformed membrane filtration; both COVID-19 and non-COVID-19 patients benefited.

Clinical Implications and Trials
Findings support selective TPE use and highlight need for further trials to optimize sepsis treatment protocols.



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Thank you for listening

- Questions
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Govil & Kumar
April 2020