

Extracorporeal blood purification therapy in septic shock patients

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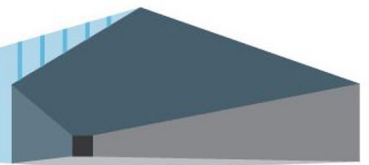


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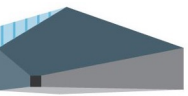
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BaltAnestIC 2023



Disclosure

I have no actual or potential conflict of interest in relation to this presentation.





Prof Claudio Ronco



MD Alessandra Brendolan



IRRIV team



Why blood purification is appealing in sepsis?

Sepsis is the most common cause of multiorgan failure¹

Multiorgan failure is common final pathway for mortality during sepsis^{1,2}



ORIGINAL

Sepsis-associated acute kidney injury in the intensive care unit: incidence, patient characteristics, timing, trajectory, treatment, and associated outcomes. A multicenter, observational study



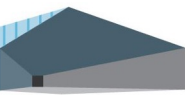
Kyle C. White^{1,2,3*}, Ary Serpa-Neto^{4,5}, Rod Hurford¹, Pierre Clement⁶, Kevin B. Laupland^{3,6}, Emily See^{7,8,9,10,11}, James McCullough¹², Hayden White^{13,14}, Kiran Shekar^{2,3,15}, Alexis Tabah^{2,3,16}, Mahesh Ramanan^{2,17,18}, Peter Garrett^{5,19}, Antony G. Attokaran^{2,20}, Stephen Luke^{21,22}, Siva Senthuran^{22,23}, Philippa McIlroy²⁴ and Rinaldo Bellomo^{4,8,9,25} on behalf of the Queensland Critical Care Research Network (QCCRN)

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- A retrospective multicenter (12 ICU) cohort study
- Out of 84,528 admissions, 13,451 met (18%) the **Sepsis Associated acute kidney injury (SA-AKI)** criteria (SA-AKI is AKI occurring within 7 days of the diagnosis of sepsis)
- SA-AKI hospital mortality was 18% and SA-AKI was independently **associated with increased:**
 - length of ICU
 - length of hospital stay
 - hospital mortality
 - ICU mortality.

1. White, K.C., Serpa-Neto, A., Hurford, R. et al. Sepsis-associated acute kidney injury in the intensive care unit: incidence, patient characteristics, timing, trajectory, treatment, and associated outcomes. A multicenter, observational study. *Intensive Care Med* 49, 1079–1089 (2023). <https://doi.org/10.1007/s00134-023-07138-0>

2. Vincent J-L, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. *Crit Care*. (2019) 23:196. doi: 10.1186/s13054-019-2478-6



Why blood purification is appealing in sepsis?

The **typical trigger** of sepsis is **bacteremia** or **viremia** or **fungemia**

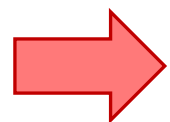


Endotoxin; viral DNA or RNA, mycotoxins



Alarmins (High mobility group box I protein (HMGB1))

They all imply that **blood is the «carrier» the toxic state** leading to multiorgan failure.



Thus, **removing toxins from blood** under such circumstances makes **biological and clinical sense**

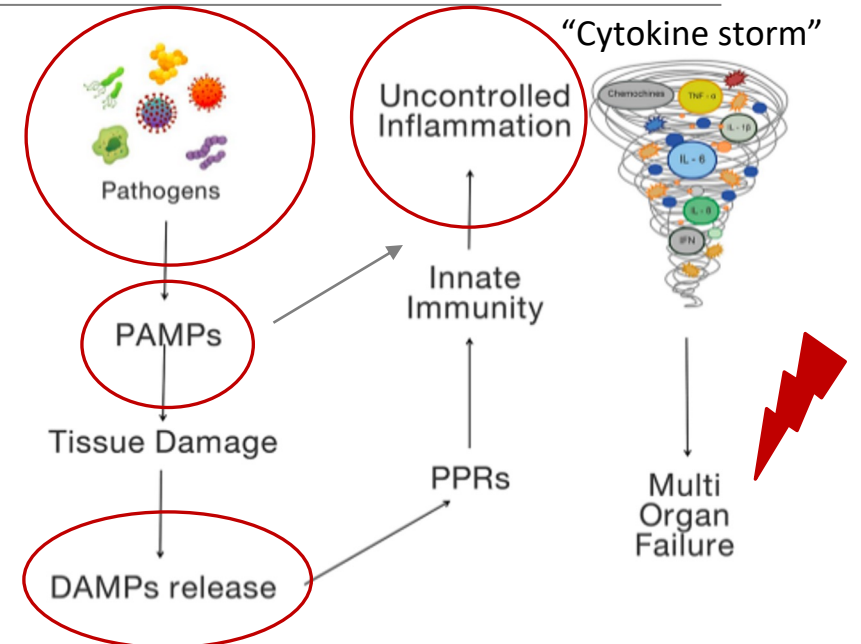
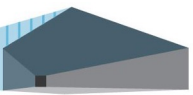
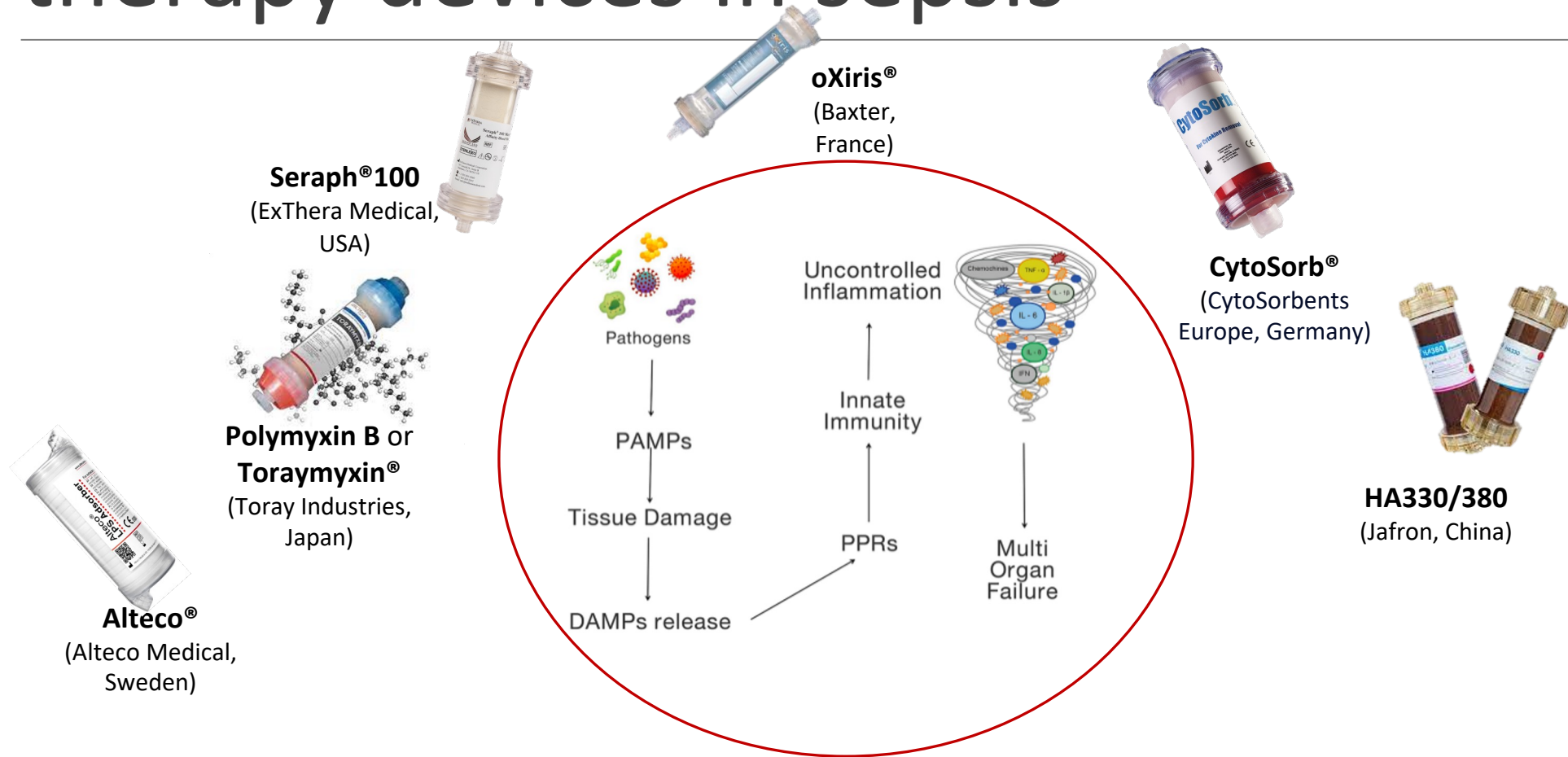
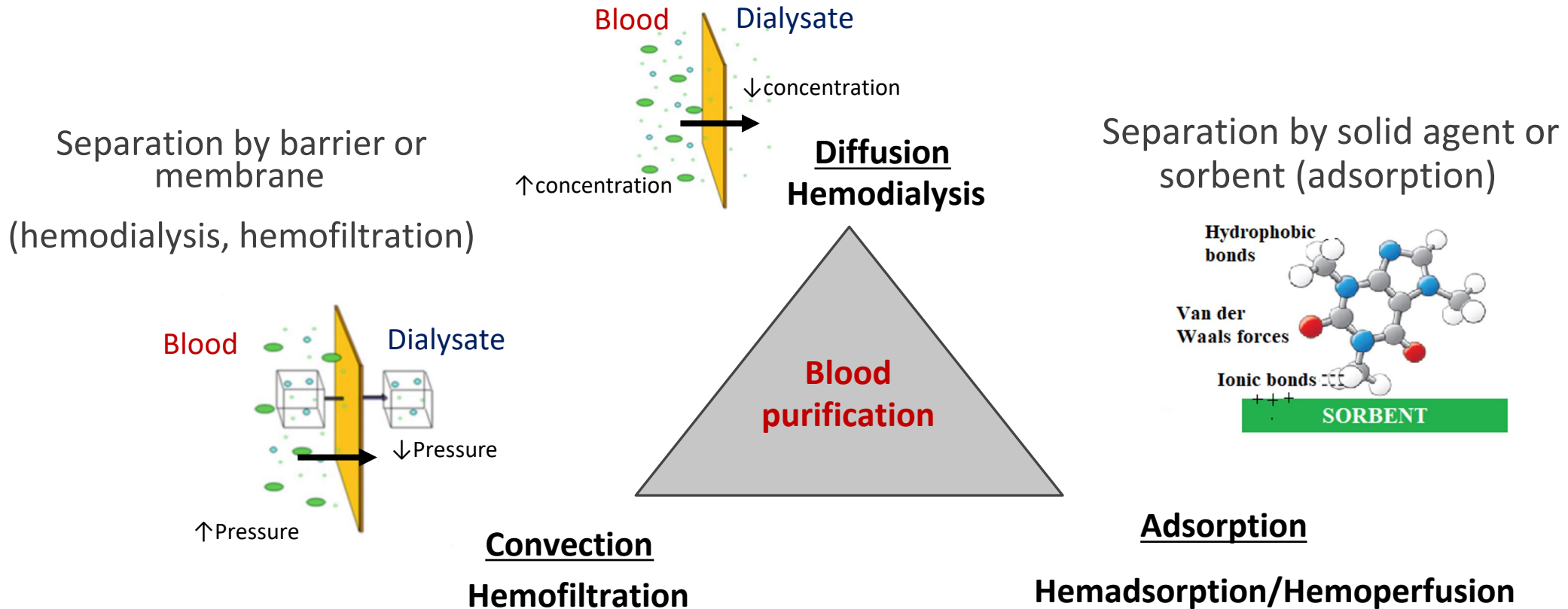


Fig.1 Inflammatory cascade and targets for extracorporeal blood purification therapies [EBPT] in sepsis. *DAMPs* damage-associated molecular patterns, *PAMPs* pathogen-associated molecular patterns, *PPRs* pattern-recognition receptors

The targets for blood purification therapy devices in sepsis

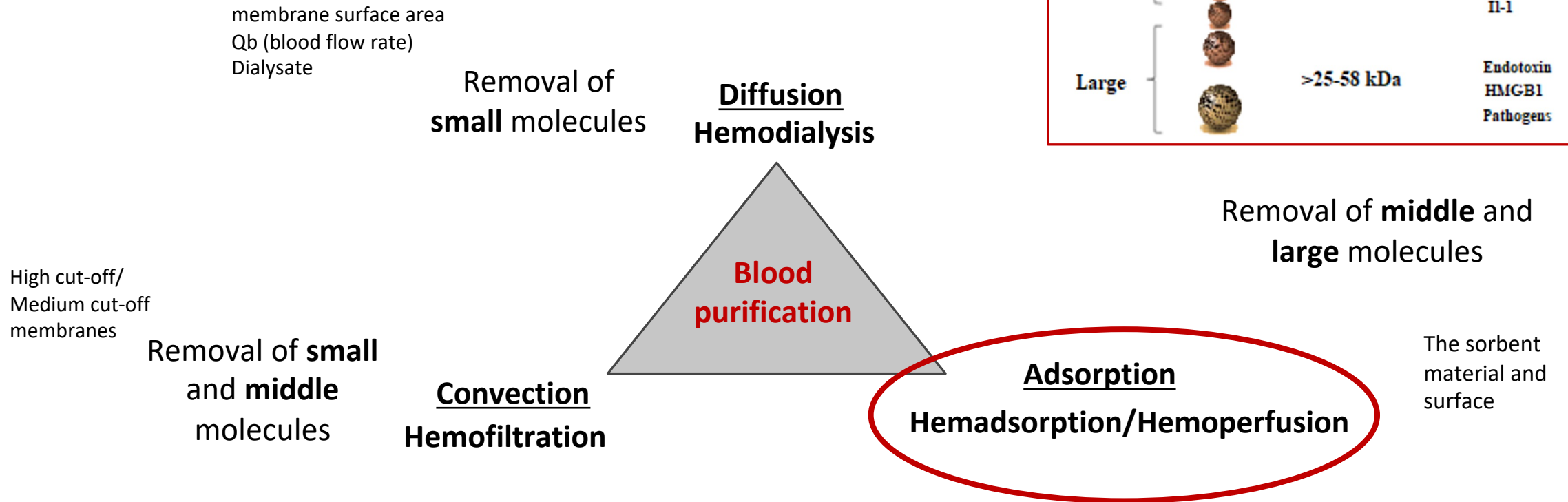


Mass Separation Processes



Mass Separation Processes

Class	Molecular weight	Solute
Small	0.5-15 kDa	Urea Creatinine Vitamin B12 Phosphate
Middle	15-25 kDa	IL-6 TNF-alfa IL-1
Large	>25-58 kDa	Endotoxin HMGB1 Pathogens

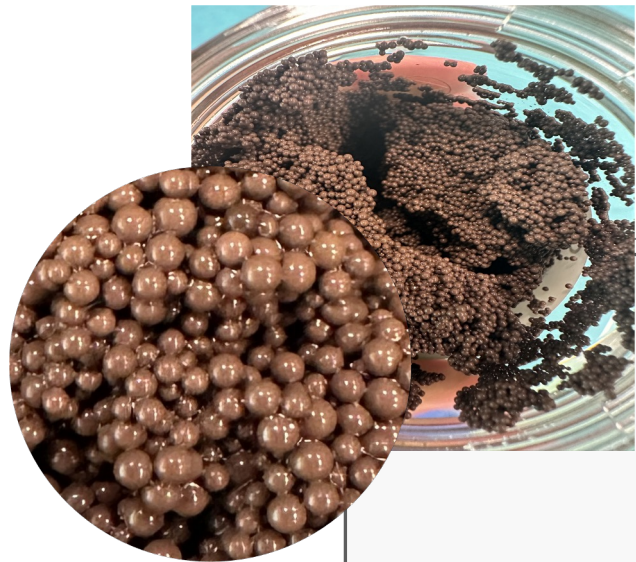


Most inflammatory mediators are middle and large molecules (cytokines, alarmins, endotoxin etc.)

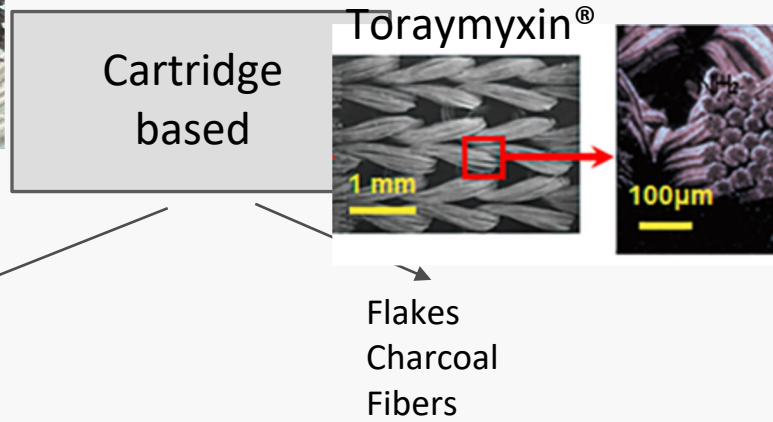


Adsorption is an option for blood purification indicated to remove large middle molecules

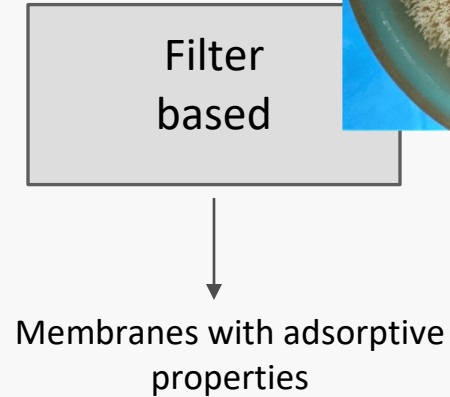
ive Therapies for sepsi



HA380



oXiris®

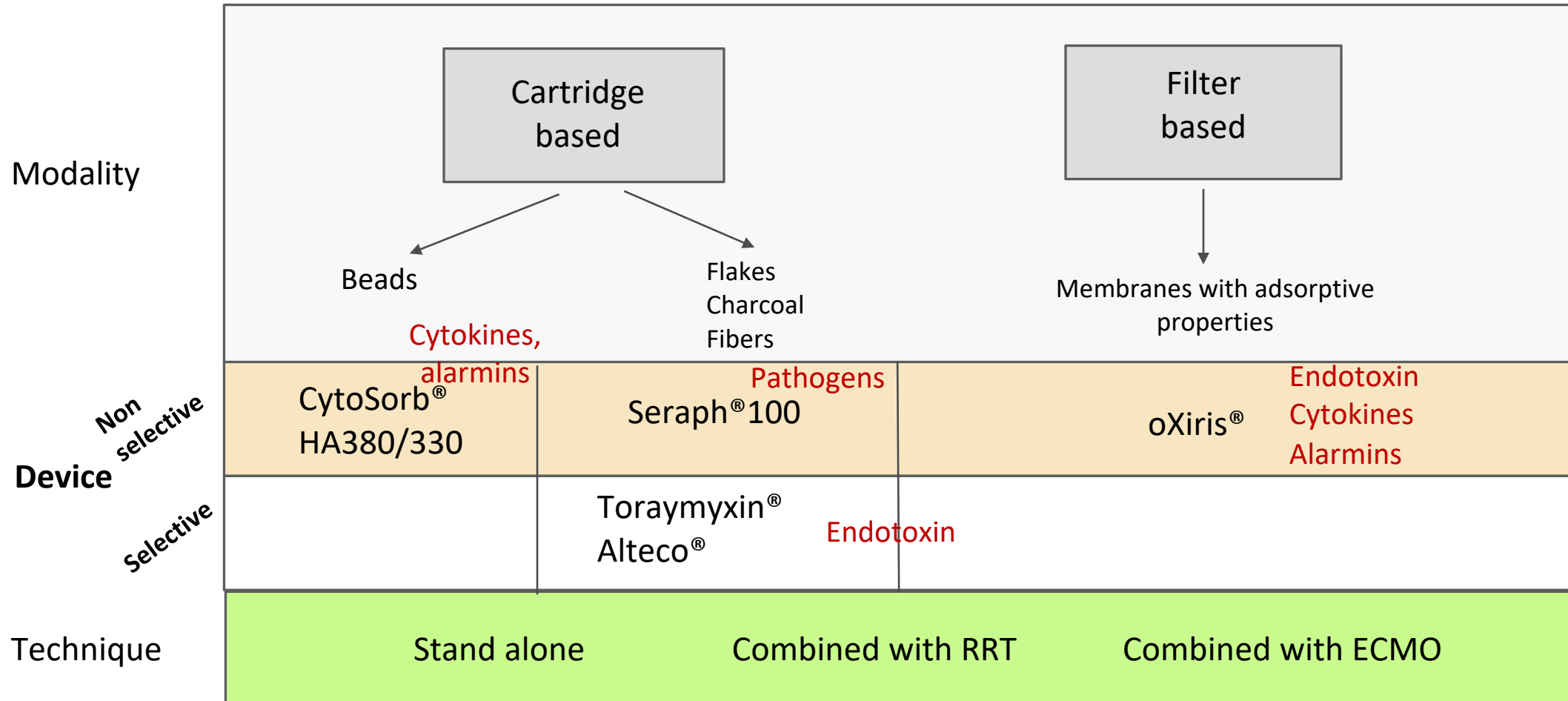


Non selective
Device

Selective

	CytoSorb® HA380/330	Seraph® 100	oXiris®
		Toraymyxin® Alteco®	
Technique	Stand alone	Combined with RRT	Combined with ECMO

Adsorptive Therapies for sepsis



Adsorptive Therapies for sepsis

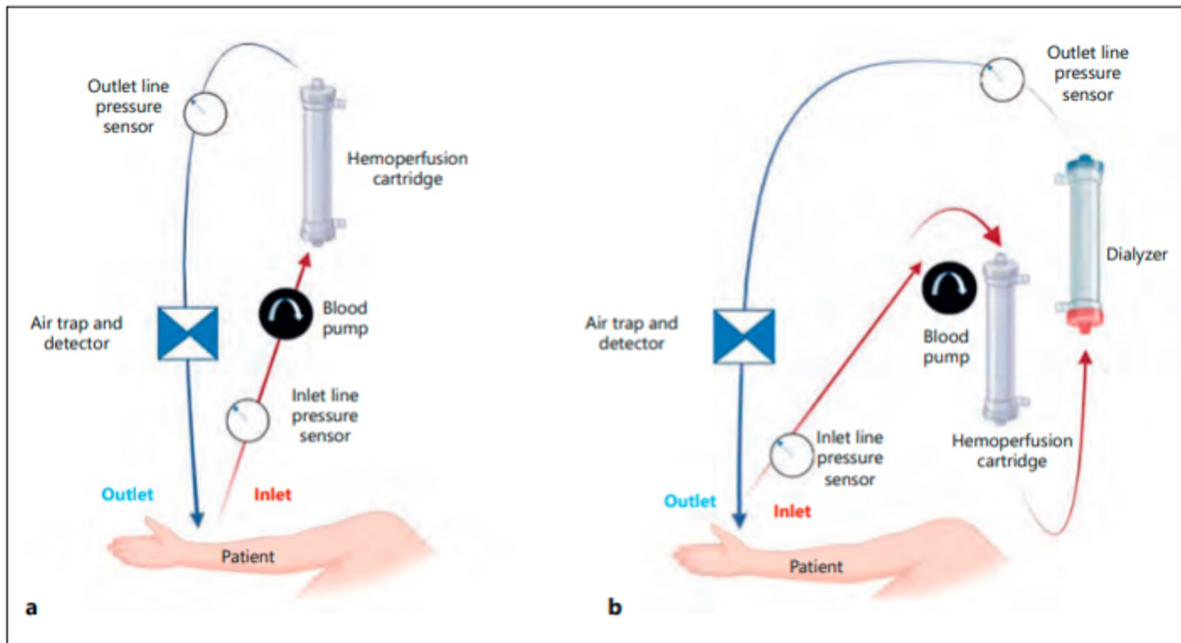


Fig. 1. Various configurations for application of hemoperfusion in clinical practice. **a** Stand-alone hemoperfusion. **b** Hemoperfusion combined with continuous renal replacement therapy in series.

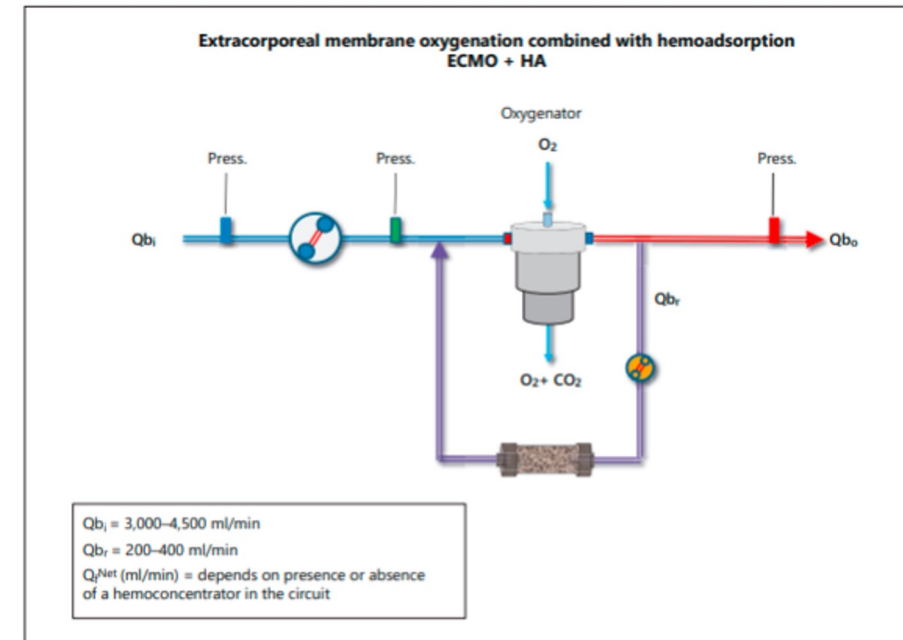


Fig. 7. ECMO + HA: Extracorporeal membrane oxygenation combined with hemoadsorption. Q_{b_i} , inlet blood flow rate; Q_{b_o} , outlet blood flow rate; Q_{ur}^{Net} , net ultrafiltration flow rate, i.e., the net volume of fluid removed from the patient by the machine per unit of time depends on the presence or absence of a hemoconcentrator. Press., pressure sensor. Explanation in the text. Modified with permission from Ronco C.: *Nefrologia Critica* [19].

Technique

Stand alone

Combined with RRT

Combined with ECMO

Extracorporeal blood purification therapy in septic shock patients

Despite widespread use, there is currently **no consensus on how** extracorporeal blood purification therapies **should be applied** or **studied** in patients with sepsis.



Recommendations

67. In adults with sepsis or septic shock and AKI who require renal replacement therapy, we **suggest** using either continuous or intermittent renal replacement therapy.
Weak recommendation, low quality of evidence.

68. In adults with sepsis or septic shock and AKI, with no definitive indications for renal replacement therapy, we **suggest against** using renal replacement therapy.
Weak recommendation, moderate quality of evidence.



Implications of recommendations

	Strong Recommendation	Weak Recommendation
For Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not
For Clinicians	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Different choices are likely to be appropriate for different patients Therapy should be tailored to the individual patient's circumstances, such as patients' or family's values and preferences

Box 5

Extracorporeal and novel therapies for SA-AKI

Consensus statement 5a

Extracorporeal blood purification (EBP) techniques can be used to remove pathogens, microbial toxins, inflammatory mediators and toxic metabolites from the blood as well as replenish solutes (grade 1A).

biological criteria, such as high concentrations of damage-associated molecular patterns and pathogen-associated molecular patterns, as well as other targets of systemic inflammation (not graded).

Consensus statement 5b

Kidney replacement therapy provides organ support through solute control, blood detoxification, and fluid balance via diffusion, convection and adsorption. Peritoneal dialysis can be used for kidney support when extracorporeal techniques are unavailable (grade 1A).

Consensus statement 5e

Optimal delivery of extracorporeal therapies is determined by factors such as timely and safe initiation, treatment duration, appropriate vascular access placement and maintenance, individualized patient dose, safe and effective anticoagulation protocols, appropriate adjustments of medications (for example, antimicrobials or vasopressors) and nutrients, and a dynamic prescription of fluid removal (not graded).

Consensus statement 5c

Emergent indications for initiating kidney replacement therapy do not differ between SA-AKI and other types of acute kidney injury (grade 1A).

Consensus statement 5f

Safe and effective therapy requires objective indicators of treatment response, which must be evaluated throughout the therapy course with a focus on patient-centred care goals (grade 1B).

Consensus statement 5d

Initiation of EBP in sepsis might be considered for immunomodulatory support in patients who meet explicit and timely clinical and/or

Optimization of blood purification therapy for patients with sepsis



1. The **modality** of extracorporeal adsorption:

- - Stand alone/combined with RRT (CVVH/CVVD or CVVHD)

2. **Type** of hemadsorption (membrane adsorption/hemadsorption with sorbets)

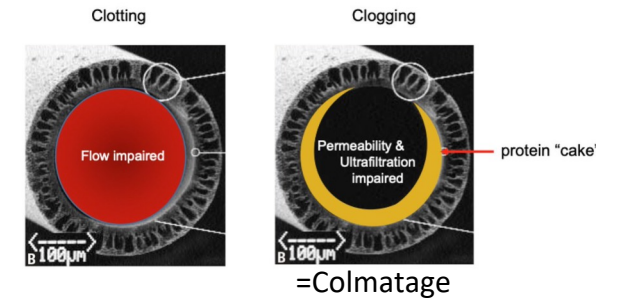
3. **Timing** of therapy:

- a) Treatment initiation time
- b) Time to scheduled adsorber change (*saturation phenomenon/membrane clotting and clogging*)
- c) Scheduled downtime between adsorbers (the duration of each procedure)
- d) Total planned duration of therapy

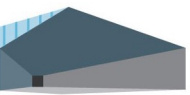
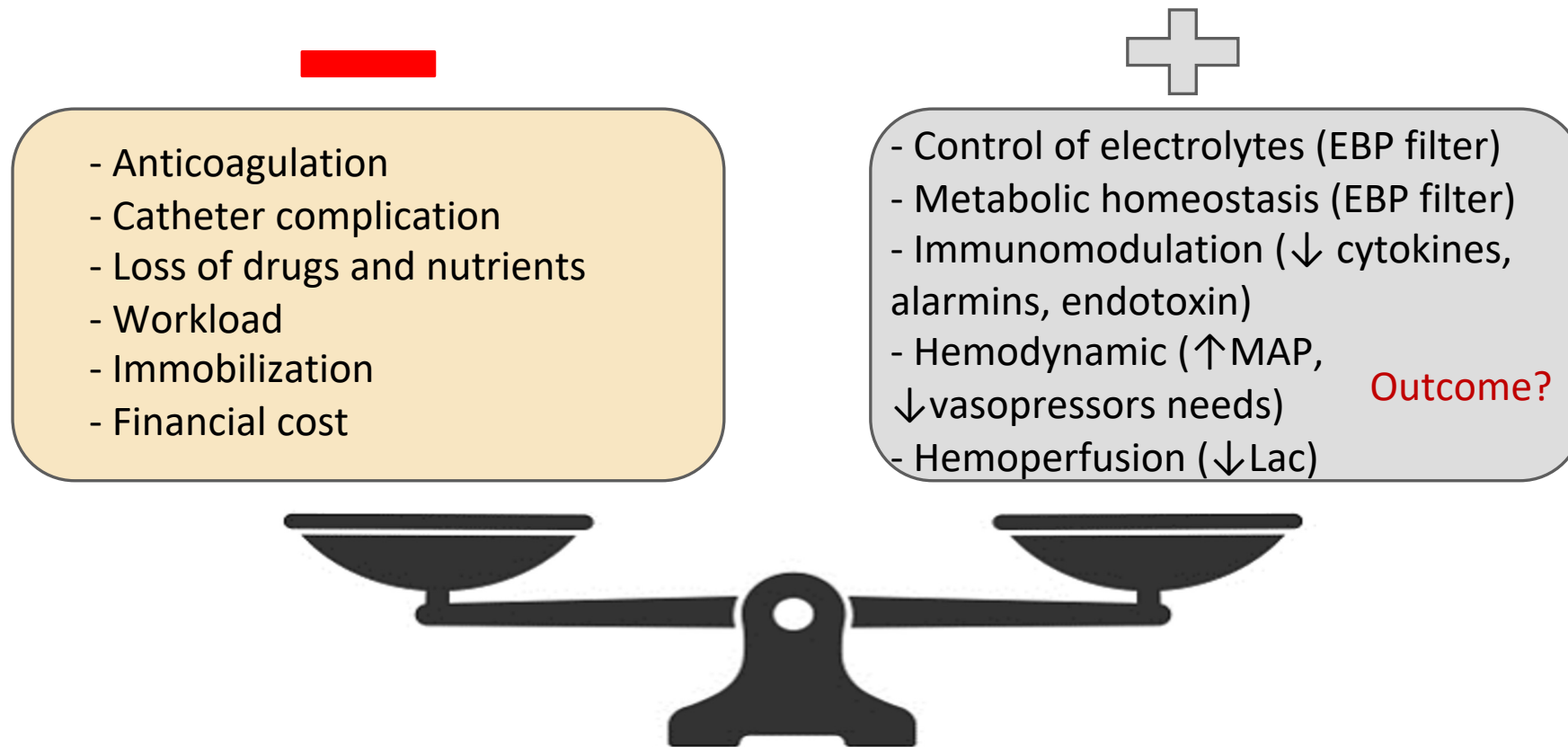
4. Choice of **anticoagulation** (citrate/UFH/LMWH)

5. Objective **indicators of treatment response** (Lactate/hemodynamic/systemic inflammatory response markers/DAMPs and PAMPs)

6. **Adverse events** (removal of antimicrobial/micro and macronutrients)



Pro and cons to extracorporeal blood purification



ANESTHESIOLOGY

Blood Purification and Mortality in Sepsis and Septic Shock

A Systematic Review and Meta-analysis of Randomized Trials

Alessandro Putzu, M.D., Raoul Schorer, M.D.,
Juan Carlos Lopez-Delgado, M.D., Ph.D.,
Tiziano Cassina, M.D., Giovanni Landoni, M.D.

ANESTHESIOLOGY 2019; 131:580–93



Toraymyxin®

- 2,499 adults with sepsis and septic shock
- Blood purification therapies (hemadsorption with Toraymyxin®, Alteco®, CytoSorb®; hemofiltration and plasmapheresis) vs. conventional septic shock therapy

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

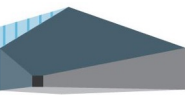
The EUPHRATES Randomized Clinical Trial

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

Post hoc analysis of the EUPHRATES trial → in the subgroup of patients with septic shock and endotoxin activity between **(EAA) 0.6 and 0.89 (endotoxic shock)** Toraymyxin® had positive effect on (Toraymyxin vs. sham hemoperfusion):

- hemodynamics (change in MAP [median (IQR) 8 mmHg (−0.5, 19.5) vs. 4 mmHg (−4.0, 11) P=0.04)
- ventilator-free days [median (IQR) 20 days (0.5, 23.5) vs. 6 days (0, 20), P=0.004]
- 28-day mortality [HR 0.56 (95% CI 0.33, 0.95) P=0.03]

Results: Thirty-seven trials with 2,499 patients were included in the meta-analysis. Hemoperfusion was associated with lower mortality compared to conventional therapy (relative risk = 0.88 [95% CI, 0.78 to 0.98], P = 0.02, very low certainty evidence). Low risk of bias trials on polymyxin B immobilized



REVIEW

Open Access



Continuous renal replacement therapy with the adsorptive oXiris filter may be associated with the lower 28-day mortality in sepsis: a systematic review and meta-analysis

Guizhong Wang^{1†}, Yuxuan He^{1†}, Qingling Guo^{1†}, Ying Zhao^{1†}, Jie He¹, Yue Chen¹, Weijia Chen¹, Yi Zhou¹, Zichong Peng¹, Ke Deng¹, Jianbin Guan¹, Wenting Xie¹, Ping Chang^{1*} and Zhanguo Liu^{1*}

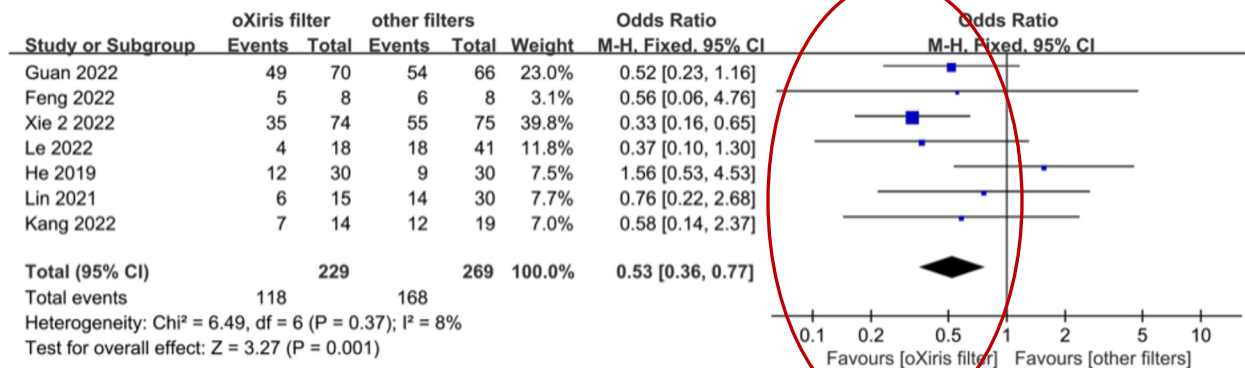


Fig. 3. 28-day mortality (adopting Xie et al's data after IPTW)

oXiris® vs ST150 or M150 filters

SA-AKI adults diagnosed with sepsis undergoing CRRT

The oXiris filter was associated with significant reduction of:

28-day mortality in sepsis patients [OR 0.53; 95% CI 0.36–0.77, p=0.001]

the length of ICU stay [WMD–1.91; 95% CI–2.56 to–1.26, p<0.001]

SOFA scores [WMD–1.41; 95% CI–1.92 to–0.91, p<0.001]

dosage of Norepinephrine [WMD -0.11; (95% CI–0.17, to–0.06; p<0.001]

lactate level [WMD= –0.49; 95% CI= –0.78, to–0.19, p=0.001]

IL-6 levels [SMD–0.75; 95% CI –1.02 to – 0.48, p<0.001]

The 90-day mortality, ICU and hospital mortality, and length of hospital stay were comparable to control group



RESEARCH

Open Access

Efficacy of CytoSorb®: a systematic review and meta-analysis

Sören Becker^{1†}, Hannah Lang^{1†}, Clara Vollmer Barbosa¹, Zhejia Tian¹, Anette Melk² and Bernhard M. W. Schmidt^{1*}



BUT..

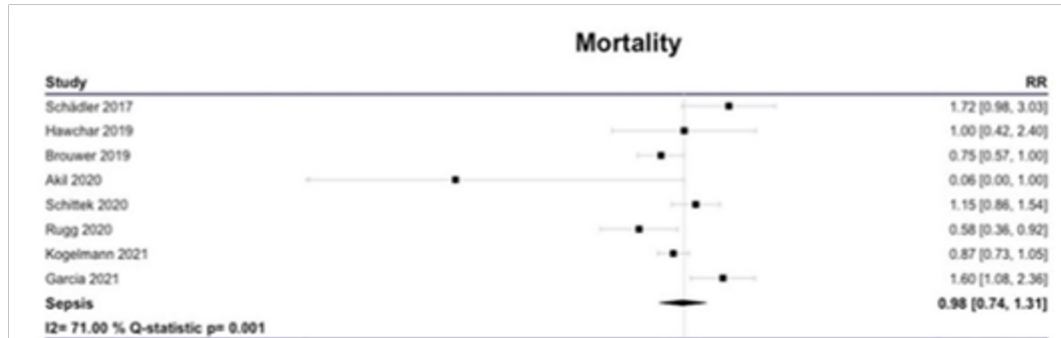


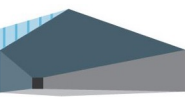
Table 1 Study characteristics

First author	Year	Study design	Patient characteristics	Treatment scheme	N (CytoSorb®/ Control)	Age (CytoSorb®/ Control) M or Md	Sex (% male) (CytoSorb®/ Control)
Schädler	2017	RCT, open-label, multi-centre	Severe sepsis or septic shock and ARDS	6 h per day for up to 7 consecutive days	47/50	66/65	74/70
Hawchar	2019	RCT, open-label, single-centre	Early (< 24 h) onset of septic shock, mechanical ventilation, norepinephrine > 10 µg/min	1 treatment for 24 h	10/10	60/71	70/60
Brouwer	2019	Retrospective PS weighted register study, single-centre	Septic shock with CRRT treated on ICU	Treatment until improvement	47/49	61/69	55/61
Akil	2020	Retrospective control group, prospective intervention group, single-centre	Pneumogenic sepsis and ECMO therapy	≥ 2 treatments; device changed every 24 h	3/7	61/61	38/29
Schittek	2020	Retrospective control group, prospective intervention group, single-centre	Septic shock with acute kidney injury and noradrenaline dose (> 20 µg/min)	≥ 1 treatment	43/33	63/62	88/72
Rugg	2020	Retrospective PS matched study, single-centre	Septic shock patients with RRT	≥ 1 treatment	42/42	64/68	64/60
Kogelmann	2021	Retrospective register study, multi-centre	Septic shock patients treated on ICU	≥ 1 treatment	198/69	62/66	61/NA
Garcia	2021	Retrospective control group, prospective intervention group, PS matched study, single-centre	severe, refractory septic shock	3 treatments for 24 h	48/48	57/58	65/65

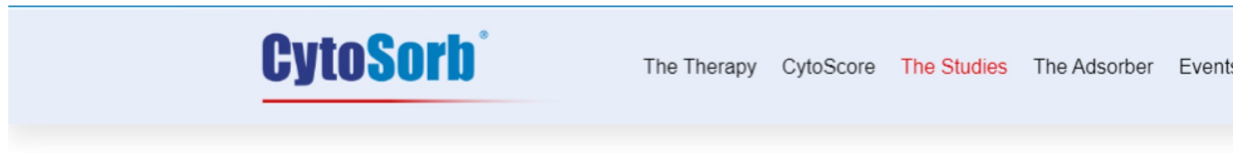
Intervention group: at least one CytoSorb® treatment

Control group: no CytoSorb® treatment

No significant differences in mortality, ICU length of stay, lactate levels or IL-6 levels after treatment.



Clinical registries



The CytoSorb-Registry



ICH GCP > Registro de ensayos clínicos de EE. UU. > Publications > 1 de abril de 2023 4:20

oXirisNet Registry: A Prospective, National Registry on the oXiris Membrane



Home > Clinical research > EUPHAS 2 WEB REGISTRY

EUPHAS 2 is a patient registry for the collection of clinical data from patients undergoing polymyxin B hemoperfusion therapy (Toraymyxin®).



Proposed indications, dose, and prescription of blood purification devices

EBP device	Indications	Dose	Prescription
CytoSorb®	Adjuvant therapy for sepsis, inflammatory states, liver failure, rhabdomyolysis, drug intoxication <i>Pediatric and adult population</i>	Patients weight >45kg Stand-alone approach: 150-700mL/min Combined with RRT: 150-300mL/min Anticoagulation: RCT or UFH	Early start (within 12 h) of septic shock onset Session: 24h (consider to change every 12 h) ¹ Up to 7 consecutive sessions
HA330/380	Adjuvant therapy for sepsis, inflammatory states, acute lung injury, intoxications	Stand-alone approach: 100-200mL/min Combined with RRT: 150-300mL/min Anticoagulation: so far RCT, UFH or LMWH are acceptable	Session 2-3 h (can be extended up to 12 h) 3 consecutive sessions
Toraymyxin®	Adjuvant therapy for gram negative septic shock: with endotoxin activity between 0,6-0,89 and SOFA score 7-12 points. <i>Pediatric and adult population</i>	Adult patients: 100 mL/min Pediatric patients: 5-10mL/min Anticoagulation for adults: heparin 3000 U bolus and 20 U/kg/h; RCA based on case reports is possible	Session: 2 h, can be extended to 24 h 1 session per day for 2 days
Seraph® 100	Adjuvant therapy for bacteremia, viremia, toxemia, and fungemia	Blood flow 400mL/min Anticoagulation: bolus heparin and monitored continuous administration	Session: 4 hours Criteria for treatment repetition not yet established
oXiris®	Adjuvant therapy for SA-AKI caused by gram-negative bacteria <i>Pediatric and adult population</i>	Patients weight >30kg; Blood flow: 100-450mL/min Anticoagulation: RCA or UFH (RCA better for filter lifespan) Without systemic anticoagulation 18.6% of patients develop premature clotting ²	Session: 72 h (recommended to change every 24 h)

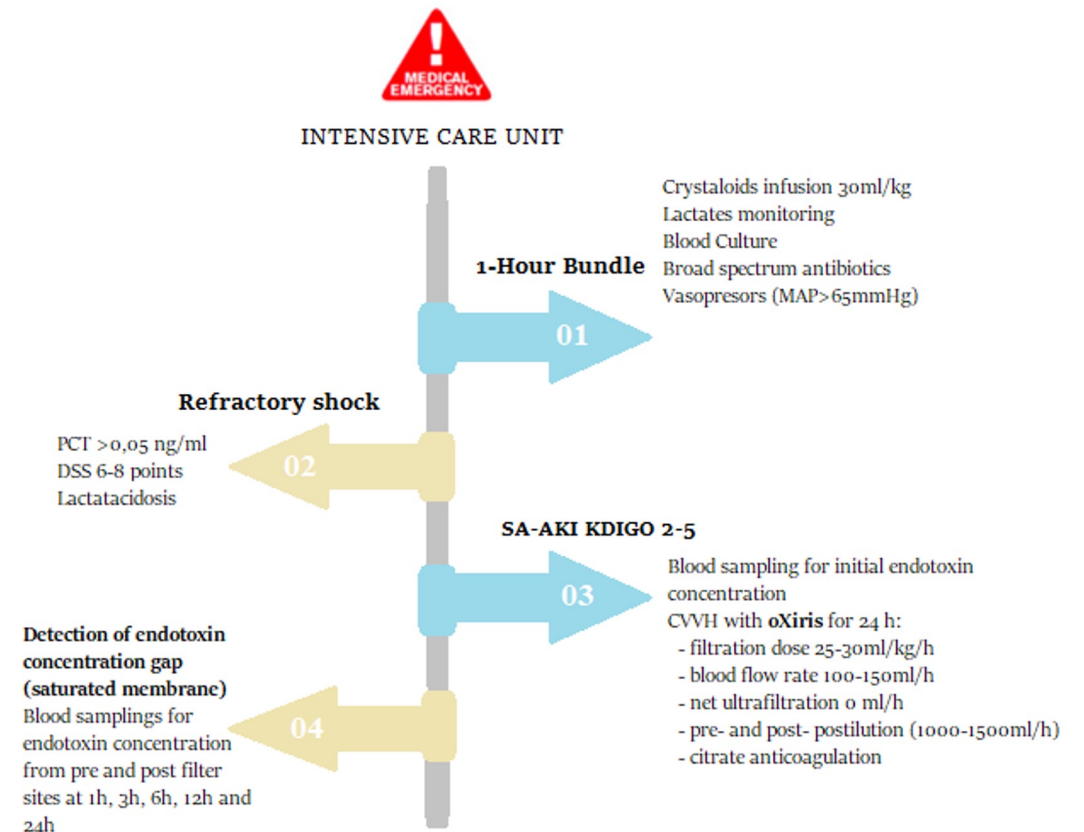
Endotoxin and cytokine adsorption properties of the oXiris[®] membrane in septic shock patients.

Septic shock adults patients + oXiris[®] at least for 24 hours

Baseline endotoxin concentration and subsequent **pre** and **post** filter endotoxin concentration (quantitative LAL tests, EA/mL) during first 24 h

The main goal – oXiris[®] **hemofilter saturation phenomenon *in vivo***

Secondary outcome: premature saturated hemofilter impact on clinical course, 28-day mortality, ICU length of stay, CVVH free days.

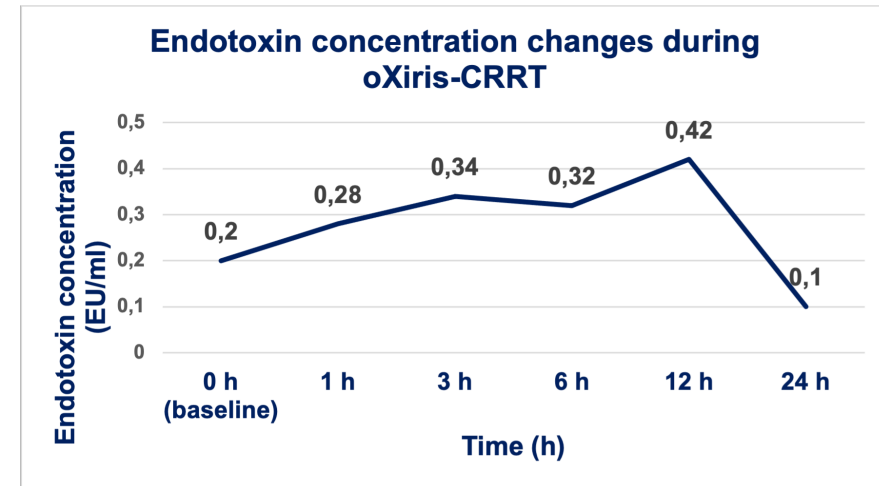
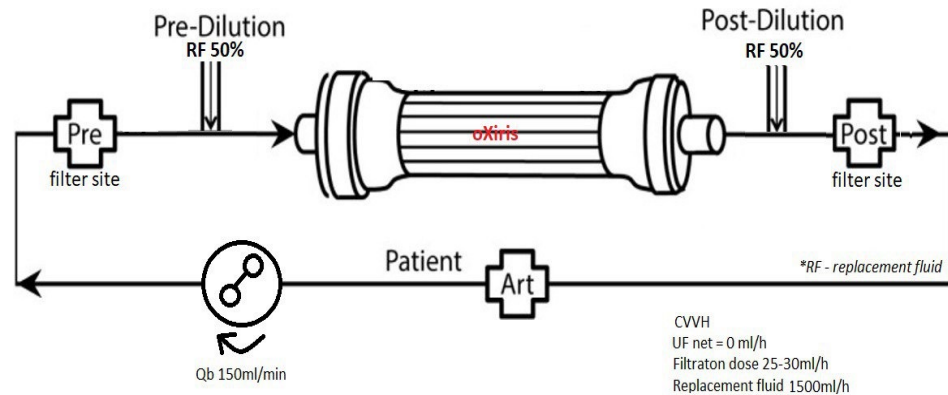


Endotoxin and cytokine adsorption properties of the oXiris[®] membrane in septic shock patients.

Dynamics of endotoxin, inflammatory markers and organ dysfunction in patients with septic shock undergoing hemadsorption with oXiris[®]

D. Smirnova ^{a,c,d}, E. Stasane ^{a,e}, V. Liguts ^{a,b}, P. Zviedre ^{a,c}, G. Freijs ^a, O. Sabelnikovs ^{a,c}

^a Pauls Stradins Clinical University Hospital, Department of Anesthesiology and Intensive Care, Riga, Latvia; ^b Riga Stradins Clinical University Hospital, Department of Acute Renal and Liver Replacement Therapy, Riga, Latvia; ^c Riga Stradins University, Department of Clinical Skills and Medical Technology, Riga, Latvia; ^d Riga Stradins University, Department of Doctoral Studies, Riga, Latvia; ^e Riga Stradins University, Faculty of Residency, Riga, Latvia.



7 Gram negative septic shock patients undergoing CVVH with the oXiris[®] hemofilter.

Median treatment initiation time: 3 h [IQR 3; 17] upon admission to the ICU.

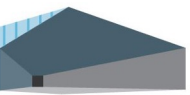
Median SOFA score: 11 [IQR 9-12]

Median Noradrenaline dosage: 0.33 μ g/kg/min [0.12–0.53]

Median baseline endotoxin concentration 0.2 EU/ml [0.19-1.5] vs 0.1 EU/ml [0.07-0.57] after 24 h of treatment (p=0.047).

Take-home messages

- There is a biological rationale for blood purification in sepsis
- Adsorption is an interesting option for blood purification (indicated to remove large medium molecules)
- EBP with the oXiris[®] showed promising results in case of SA-AKI
- Toraymyxin[®] showed promising results in case of endotoxic shock
- Inconclusive data on EBP therapy in sepsis for CytoSorb[®]
- Limited data from qualitative RCT in all hemadsorption devices



Thank you for your attention!



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