# Evolving Evidences for Extracorporeal Therapy in ICUs

## PMX-HP · Therapeutic Plasma Exchange · oXiris · CytoSorb

**REMOVE**
Cytokines & Endotoxins

**MODULATE**
Inflammation & Mediators

**SUPPORT**
Hemodynamics & Organ Function

**IMPROVE**
Outcomes through Evidence


**From Biological Plausibility to Clinical Benefit**
Evidence · Indications · Protocols · Safety · Reimbursement

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2026-08-23

Evidence-Based Synthesis

Phenotype Selection

Protocolized Use

Safety Monitoring

Reimbursement Considerations

# An old hypothesis: sepsis as a blood-borne toxin state

## The premise predates modern sepsis biology:

if the lethal signal is circulating, extracorporeal removal should change physiology.

**1913–14**

### Vividiffusion

Blood could be routed outside the body to remove diffusible substances.

→

**1940s**

### Artificial kidney

Extracorporeal “detoxification” became clinically credible.

→

**1970s–80s**

### Hemoperfusion / TPE

Adsorption and exchange expanded the idea beyond uremic solutes.

→

**1990s→**

### Sepsis mediator era

Endotoxin, cytokines, and plasma homeostasis became therapeutic targets.

**Historical continuity**

**The technology changed from dialysis to exchange to adsorption. The logic barely changed: remove a circulating target early enough to prevent irreversible organ failure.**

Abel JJ et al. Trans Assoc Am Physicians. 1913;28:51–54; reprinted Transfus Sci. 1990 • Kolff WJ, Berk HT. Acta Med Scand. 1944;117:121–134.

The old idea survived by changing its biomarker

# Moving targets: endotoxin → cytokines → plasma homeostasis

## Same therapeutic grammar

1. **Circulating target**
   endotoxin / cytokine / injurious plasma factor
2. **Extracorporeal interaction**
   diffusion, convection, adsorption, or exchange
3. **Systemic response**
   MAP, norepinephrine, lactate, SOFA trajectory
4. **Patient-important outcome**
   survival, organ-support days, recovery

## Three eras of “blood purification for sepsis”

| Era | Target | Therapy |
|---|---|---|
| **Endotoxin era** | LPS / lipid A | PMX hemoperfusion |
| **Cytokine peak era** | IL-6, TNF-α, mediator peaks | HVHF, CRRT, adsorption |
| **Homeostasis era** | protein C, ADAMTS13, vWF, Angpt-2 | TPE / plasma replacement |

Target engagement is plausible; phenotype selection became central.

Physiology may move, but outcome benefit is not automatic.

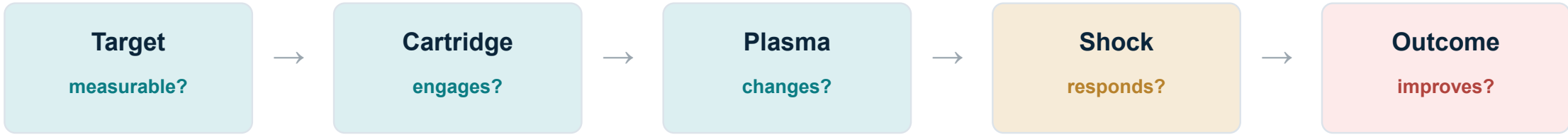
Removal plus replenishment may be the real biologic logic.

**Teaching point: the word “blood purification” is historically continuous, but each generation changed the proposed removable target.**

Marshall JC et al. J Infect Dis. 2004;190:527–534. PMID 15243928 • Stahl K et al. Crit Care. 2022;26:134. PMID 35551628 • Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242.

# Historical lesson: old concept, narrow indication

**The recurring failure mode: biologic plausibility is mistaken for a clinical indication.**



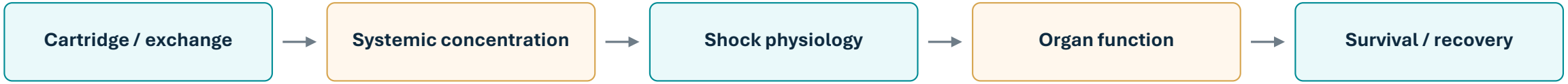

**Most modern devices have evidence for the left side of the chain; fewer have reproducible evidence for the right side.**

| Historical impulse | Modern discipline | How to say it in 2026 |
|---|---|---|
| “Remove inflammatory poison” | **Define the circulating target** | Endotoxin, cytokines, or plasma factors are not interchangeable. |
| “Do it early in shock” | **Define timing and dose** | Late rescue physiology is not the same as disease modification. |
| “The patient improved after the cartridge” | **Demand causal evidence** | Separate target engagement from survival or organ-support benefit. |

Cruz DN et al. JAMA. 2009;301:2445–2452. PMID 19531784 • Dellinger RP et al. JAMA. 2018;320:1455–1463. PMID 30304428 • Becker S et al. Crit Care. 2023;27:215. PMID 37259160.

# Why combine these four therapies?

They share one evidentiary problem: target removal is easier to prove than patient-centered benefit.




| | |
|---|---|
| **Do not collapse mechanism into indication.** | A fall in cytokines, endotoxin, or biomarkers is an intermediate endpoint. |
| **Use phenotype selection.** | The expected treatment effect depends on the amount of removable target and timing. |
| **Prescribe a protocol, not a device.** | Dose, access, anticoagulation, drug exposure, safety monitoring, and stop rules must be explicit. |

**The bedside order should name a target, a clinical objective, and a stopping rule.**

# Before starting: five questions that prevent “device reflex”

Use this as the bridge between evidence and bedside implementation.

1. **What is the removable or replaceable target?**
2. Is this patient in a phenotype where the target matters now?
3. Is the planned dose / timing biologically plausible?
4. What response will be measured in 6–24 hours?
5. **What is the stop rule if response is absent or harms emerge?**

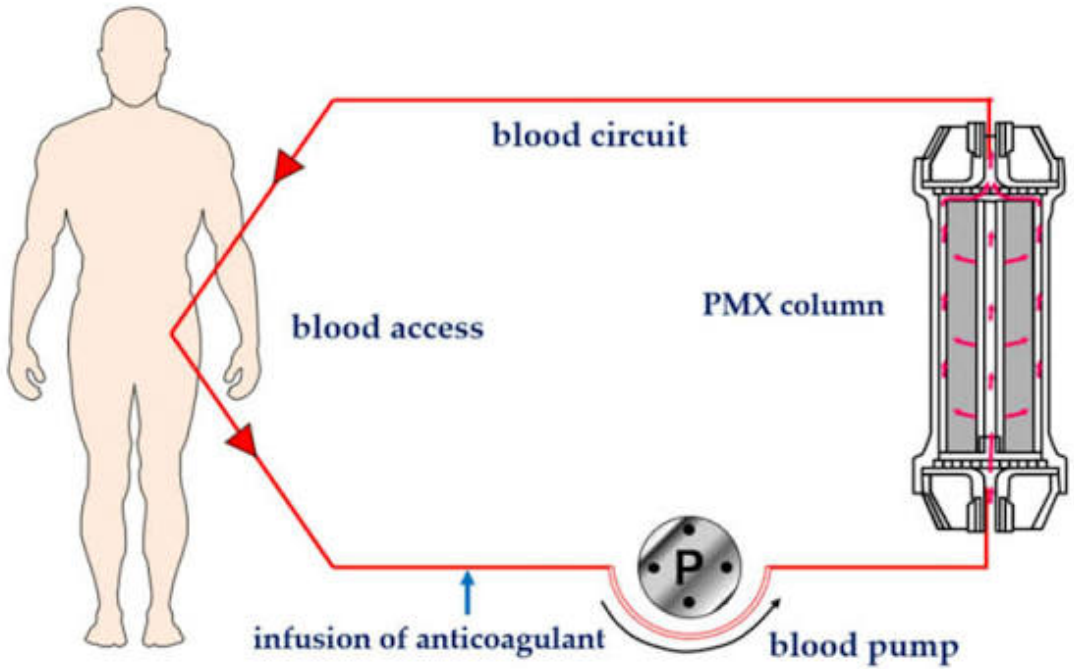
**A serious extracorporeal order states: target + timing + circuit + monitoring + stop rule.**

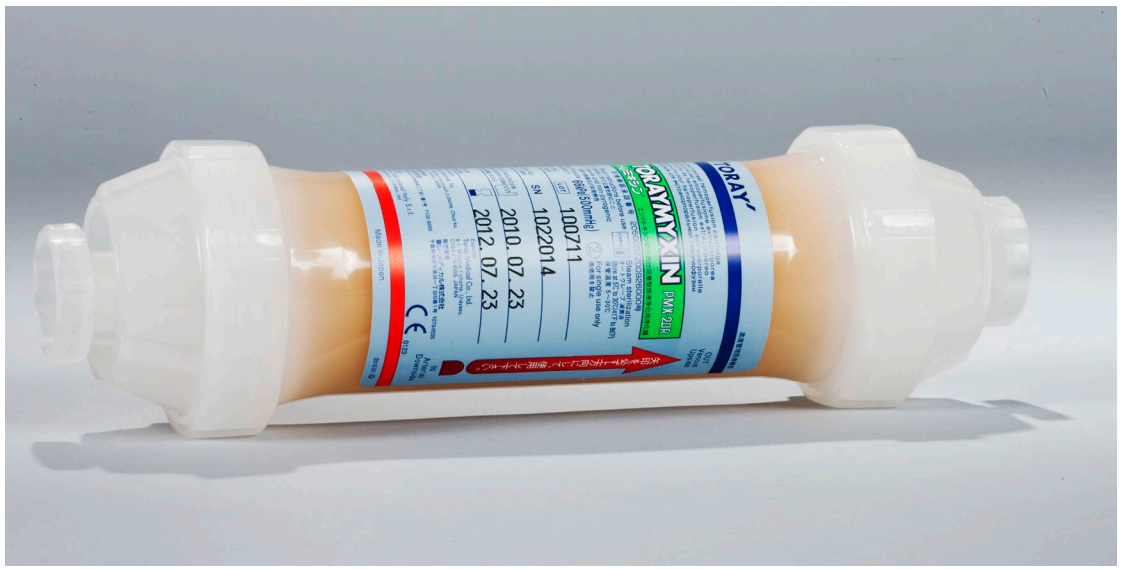
Part 1

# Polymyxin B hemoperfusion

Endotoxin-targeted therapy has moved from broad sepsis labels to narrow EAA-defined endotypes.

**Recurring question: target engagement → physiologic response → patient-important outcome**


blood circuit
blood access
PMX column
P
infusion of anticoagulant
blood pump


TORAY
CRYMYXIN
PMX-20R
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2010. 07. 23
2012. 07. 23
100711

# Why this talk matters in 2026

Guideline position

## 2026 Surviving Sepsis Campaign

**Suggests against polymyxin B hemoperfusion**

**Certainty of evidence: LOW**

*TIGRIS was not incorporated into the guideline evidence synthesis.*

New phase 3 evidence

## TIGRIS 2026

**95.3%**

**Posterior P(benefit) at 28 d**

OR 0.67 [CrI 0.39–1.08]

**99.4%**

**Posterior P(benefit) at 90 d**

OR 0.54 [0.32–0.87]

**The clinical task is to reconcile a new Bayesian signal with still-low-certainty guideline evidence.**

Prescott HC et al. Crit Care Med. 2026. DOI 10.1097/CCM.0000000000007075 • Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242

# Endotoxin Activity Assay: the biomarker that changed PMX trial design

EAA units

| < 0.40<br>LOW | 0.40–0.59<br>INTERMEDIATE | 0.60–0.89<br>TIGRIS / “treatable” window | ≥0.90<br>EXTREME |
|---|---|---|---|

| Study | Selection by EAA | What changed |
|---|---|---|
| EUPHAS 2009 | No | Anatomic phenotype: postoperative intra-abdominal sepsis |
| ABDOMIX 2015 | No | Peritonitis after emergency surgery; no target enrichment |
| EUPHRATES 2018 | Yes: EAA ≥0.60 | First large biomarker-enriched sham-controlled trial |
| EUPHRATES post hoc | 0.60–0.89 | Hypothesis-generating “non-extreme” signal |
| TIGRIS 2026 | 0.60–0.89 | Prospectively tested the narrowed endotype |

**The 0.60–0.89 window is a trial-enrichment strategy — not a universal biological law.**

Marshall JC et al. J Infect Dis. 2004;190:527–534. PMID 15243928 • Klein DJ et al. Intensive Care Med. 2018;44:2205–2212. PMID 30470853 • Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242

# Evidence evolution: the target became progressively narrower

**EUPHAS**
n=64

2009

Intra-abdominal septic shock
28-d mortality 32% vs 53%

**ABDOMIX**
n=243 randomized

2015

Peritonitis after surgery
28-d mortality 27.7% vs 19.5%

**EUPHRATES**
n=450

2018

EAA ≥0.60 + septic shock
RR 1.09 [0.85–1.39]

**Post hoc**
n=194

2018

EAA 0.60–0.89
adj OR 0.52 [0.27–0.99]

**TIGRIS**
n=157

2026

EAA 0.60–0.89 + MOF
Pbenefit 95.3% at 28 d

**The story is not "positive → negative → positive." It is "broad phenotype → biomarker enrichment → precision endotype."**

Cruz DN et al. JAMA. 2009;301:2445–2452. PMID 19531784 • Payen DM et al. Intensive Care Med. 2015;41:975–984. PMID 25862039 • Dellinger RP et al. JAMA. 2018;320:1455–1463. PMID 30304428 • Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242

# Four landmark randomized trials: same cartridge, different experiments

| Trial | N / design | Population enrichment | Primary mortality signal | Critical limitation |
|---|---|---|---|---|
| EUPHAS 2009 | 64 open RCT | Post-op intra-abdominal No EAA | 28 d 32% vs 53% HR 0.43 [0.20–0.94] | Stopped at first interim; small N |
| ABDOMIX 2015 | 243 randomized open RCT | Peritonitis after surgery No EAA | 28 d 27.7% vs 19.5% OR 1.59 [0.86–2.94] | Only 69.8% completed 2 sessions |
| EUPHRATES 2018 | 450 sham RCT | Septic shock + EAA ≥0.60 | 28 d RR 1.09 [0.85–1.39] | EAA threshold may be too broad |
| TIGRIS 2026 | 157 Bayesian RCT | EAA 0.60–0.89 + MOF | 28 d OR 0.67 [CrI 0.39–1.08] Pbenefit 95.3% | Small, open-label, prior-informed, narrow phenotype |

**The trial question changed over time. Pooling these RCTs without phenotype context can obscure treatment-effect heterogeneity.**

Cruz DN et al. JAMA. 2009;301:2445–2452. PMID 19531784 • Payen DM et al. Intensive Care Med. 2015;41:975–984. PMID 25862039 • Dellinger RP et al. JAMA. 2018;320:1455–1463. PMID 30304428 • Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242

# EUPHAS: early shock physiology moved in the expected direction

| Endpoint | PMX baseline | PMX 72 h | Control baseline | Control 72 h | Between-group message |
|---|---|---|---|---|---|
| MAP, mmHg | 76 [72–80] | 84 [80–88]<br>P=.001 | 74 [70–78] | 77 [72–82]<br>P=.37 | Only PMX showed a significant within-group rise |
| Inotropic score | 29.9 [20.4–39.4] | 6.8 [2.9–10.7]<br>P<.001 | 28.6 [16.6–40.7] | 22.4 [9.3–35.5]<br>P=.14 | Large vasopressor reduction in PMX arm |
| $PaO_2/FiO_2$ | 235 [206–265] | 264 [236–292]<br>P=.049 | 217 [188–247] | 228 [199–258]<br>P=.79 | Small oxygenation signal |


Cruz DN et al. JAMA. 2009;301:2445–2452. PMID 19531784.

# ABDOMIX: the first major contradiction

18 French ICUs | 243 randomized | Peritonitis + septic shock | 2 PMX sessions | No EAA enrichment

| Outcome | PMX | Control | Effect size / P | Interpretation |
|---|---|---|---|---|
| 28-day mortality | 27.7% (33/119) | 19.5% (22/113) | OR 1.59 [0.86–2.94]; P=.14 | No survival benefit; point estimate favored control |
| 90-day mortality | 33.6% | 24.0% | OR 1.61 [0.91–2.87]; P=.10 | Still no benefit |
| ΔSOFA day 0→7 | −5 (−11 to 6) | −5 (−11 to 9) | P=.78 | No organ-failure separation |

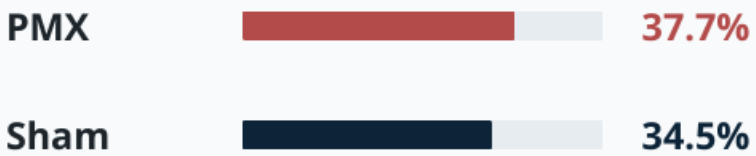
**The same “abdominal septic shock” concept did not reproduce the EUPHAS benefit.**

Payen DM et al. Intensive Care Med. 2015;41:975–984. PMID 25862039.

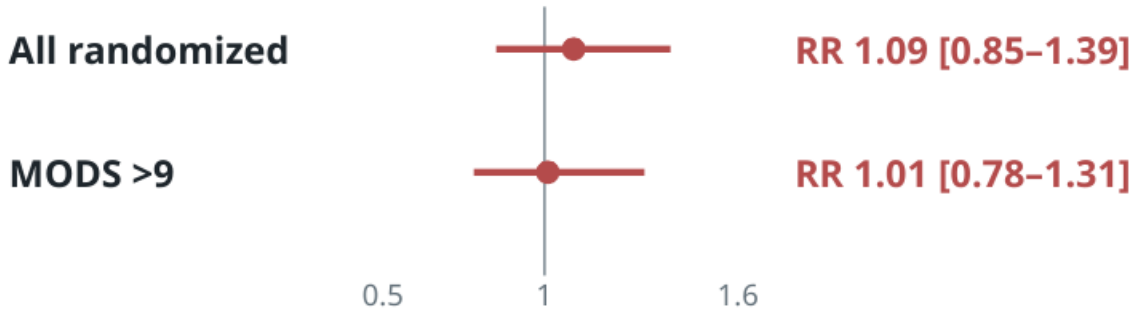
# EUPHRATES primary endpoint: no mortality benefit

**84/223**
PMX deaths by day 28
37.7%

**78/226**
Sham deaths by day 28
34.5%




**Point estimate did not favor PMX.**




| Population | Risk difference | P |
|---|---|---|
| All patients | +3.2 pp [−5.7 to +12.0] | .49 |
| MODS >9 | +0.6 pp [−10.8 to +11.9] | .92 |

Dellinger RP et al. JAMA. 2018;320:1455–1463. PMID 30304428.

# EUPHRATES post hoc: a hypothesis emerges at EAA 0.60–0.89

POST HOC | Per-protocol | MODS >9 | EAA 0.60–0.89

| Outcome | PMX | Sham | Effect / P | Read it as |
|---|---|---|---|---|
| 28-day mortality | 23/88<br>26.1% | 39/106<br>36.8% | Adjusted OR 0.52 [0.27–0.99]<br>P=.047 | Hypothesis-generating; unadjusted P=.11 |
| 28-day survival time | — | — | HR 0.56 [0.33–0.95]<br>P=.03 | Consistent time-to-event signal |
| ΔMAP | +8 mmHg<br>[−0.5 to 19.5] | +4 mmHg<br>[−4 to 11] | P=.04 | Modest hemodynamic separation |
| Ventilator-free days | 20<br>[0.5–23.5] | 6<br>[0–20] | P=.004 | Large secondary signal |

**Adjusted significance emerged after restricting the parent negative trial. This is the hypothesis TIGRIS prospectively tested.**

Klein DJ et al. Intensive Care Med. 2018;44:2205–2212. PMID 30470853.

# TIGRIS: precision-enriched — and extremely selective

**14,890**
patients screened

→

**157**
randomized
1.05% of screened

→

**106 : 51**
PMX : control
2:1 randomization

→

**2 ×**
PMX sessions
90–120 min; 22 h apart

| Prospective enrichment criterion | Specification | Clinical consequence |
|---|---|---|
| Shock | Vasopressor-dependent septic shock | Not sepsis without shock |
| Endotoxin | EAA 0.60–0.89 | Requires rapid EAA access |
| Severity | Multiple organ dysfunction | High-risk endotype |
| Treatment delivery | Qb 80–120 mL/min; 90–120 min/session; 22 h apart | Standardized extracorporeal protocol |

**External validity is the price of enrichment: ≈1 in 95 screened patients was randomized.**

Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242.

# TIGRIS 28-day mortality: the prespecified Bayesian primary endpoint was met

**41/106**
PMX deaths
39%

**23/51**
Control deaths
45%


Observed absolute difference ≈ −6.4 pp

**95.3%**
Posterior probability of benefit
prespecified threshold >95%

**0.67**
APACHE-II adjusted OR
95% CrI 0.39–1.08

## Why can the CrI cross 1 while P(benefit) >95%?

- The posterior distribution is asymmetric on the odds-ratio scale.
- The trial used an informative prior derived from the EUPHRATES 0.60–0.89 subgroup.

**Bayesian "positive" does not mean conventional 95% CrI excludes the null.**

Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242.

# TIGRIS 90-day mortality and safety: a stronger-looking secondary signal

**99.4%**

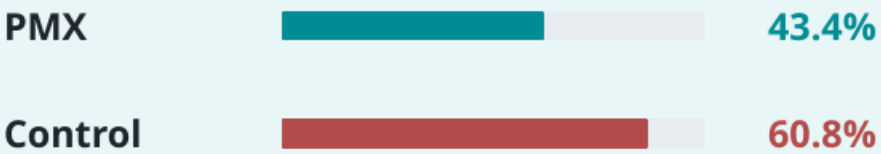
Posterior P(benefit) at 90 d

**0.54**

Adjusted OR

95% CrI 0.32–0.87

Observed mortality




**90-day mortality was the key secondary endpoint.**

## Safety cohort

| Outcome | PMX | Control |
|---|---|---|
| Serious adverse event | 30/100<br>30% | 11/51<br>22% |
| Treatment-related serious AE | 2/100<br>2% | — |

- Treatment-related SAEs: severe hypotension attributed to PMX; catheter-related bleeding.

*Reported SAE difference: −8 pp [95% CI −22 to +6] as presented by the trial.*

Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242.

# Guidelines today: still against routine PMX

SSC 2026

## “Suggest against” PMX hemoperfusion

**Certainty: LOW**

Also suggests against blood purification techniques overall.

**Panel commentary: TIGRIS was not included and should be interpreted prudently.**

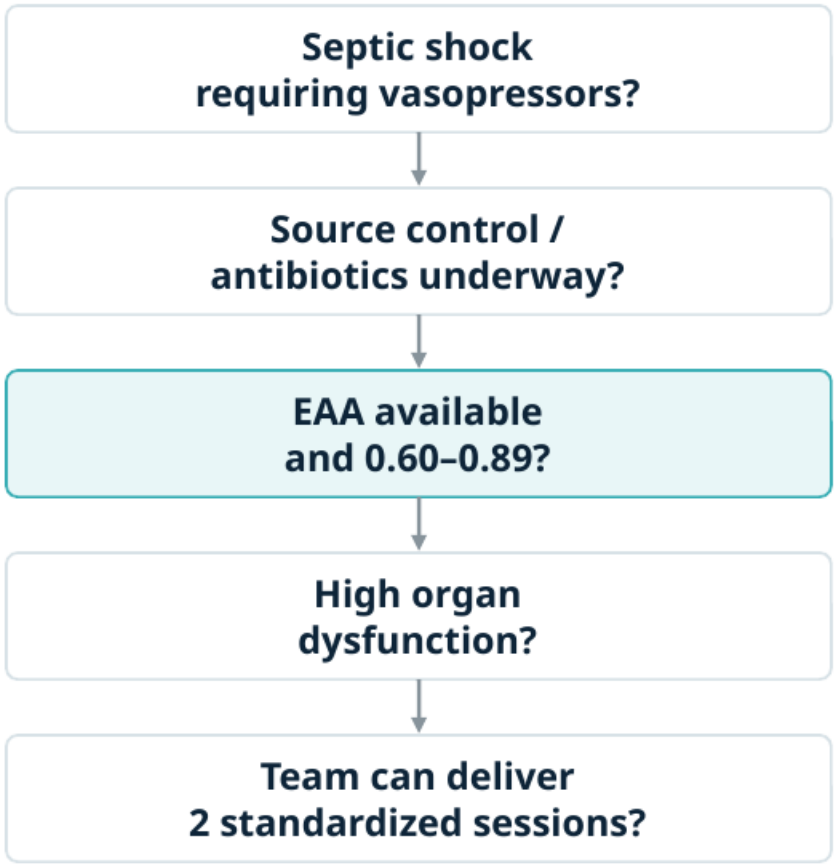
J-SSCG 2024

## PMX-DHP in septic shock: GRADE 2D

| Outcome | Pooled RCT estimate |
|---|---|
| Mortality | 37 fewer /1000 [134 fewer to 110 more] |
| Organ dysfunction | SMD −0.49 [−1.20 to +0.21] |
| Complications | 216 more /1000 [91 fewer to 1000 more] |
| Vasopressor-free days | MD −1.8 d [−4.1 to +0.5] |

Prescott HC et al. Crit Care Med. 2026. DOI 10.1097/CCM.0000000000007075 • Shime N et al. J Intensive Care. 2025;13:15. PMID 40087807

# A bedside decision flow for evidence-concordant PMX use




## If ALL are yes

- Most evidence-concordant candidate resembles TIGRIS rather than broad septic shock.
- Define a measurable target and response trajectory before starting.
- Run PMX as an adjunct to source control, antibiotics, and shock resuscitation — never as a substitute.

**If EAA is unavailable, the current randomized precision evidence cannot be reproduced at the bedside.**

Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242 • Yessayan L et al. Crit Care. 2026. DOI 10.1186/s13054-026-06182-8 • Prescott HC et al. Crit Care Med. 2026. DOI 10.1097/CCM.0000000000007075

# Final clinical position: selective, biomarker-guided, protocolized

| Question | Answer in 2026 |
|---|---|
| Does PMX adsorb endotoxin? | Yes — biologically plausible and clinically measurable target engagement. |
| Does broad septic shock benefit? | Not established; ABDOMIX and EUPHRATES were neutral. |
| Is there now a positive randomized signal? | Yes — TIGRIS met its prespecified Bayesian endpoint in EAA 0.60–0.89 + multiple organ dysfunction. |
| Does that make PMX standard care? | No — current SSC 2026 and J-SSCG 2024 still suggest against routine use. |
| Most defensible candidate? | Early vasopressor-dependent septic shock + source control underway + EAA 0.60–0.89 + high organ dysfunction + ability to complete a standardized 2-session protocol. |

**Endotoxin-positive ≠ PMX indication. The decision is phenotype + target + timing + treatment fidelity + measurable response.**

**Selective • protocolized • measurable • evidence-calibrated**

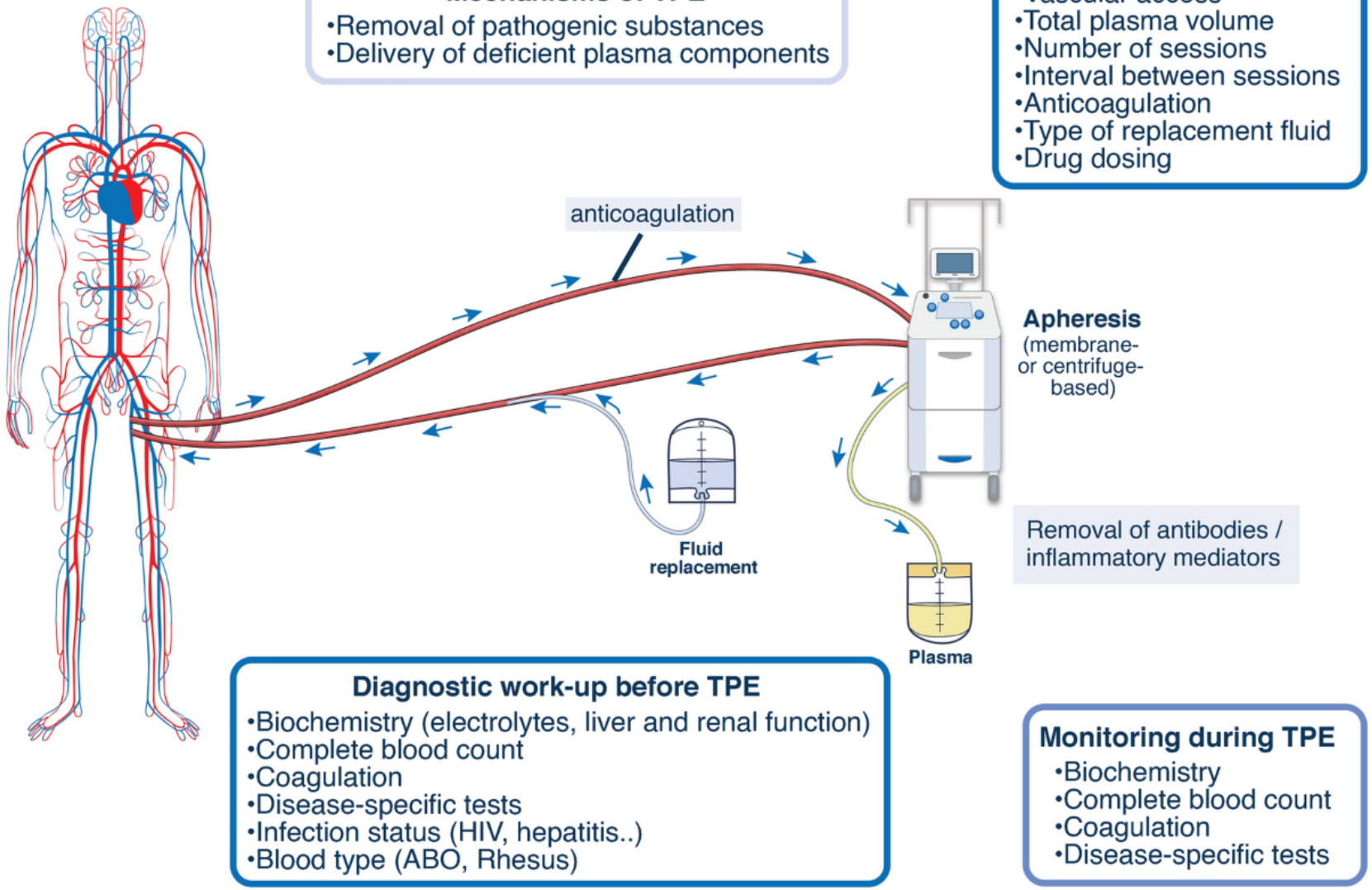
Prescott HC et al. Crit Care Med. 2026. DOI 10.1097/CCM.0000000000007075 • Neyra JA et al. Lancet Respir Med. 2026;14:443–452. PMID 41887242 • Dellinger RP et al. JAMA. 2018;320:1455–1463. PMID 30304428 • Payen DM et al. Intensive Care Med. 2015;41:975–984. PMID 25862039

Part 2

# Therapeutic plasma exchange

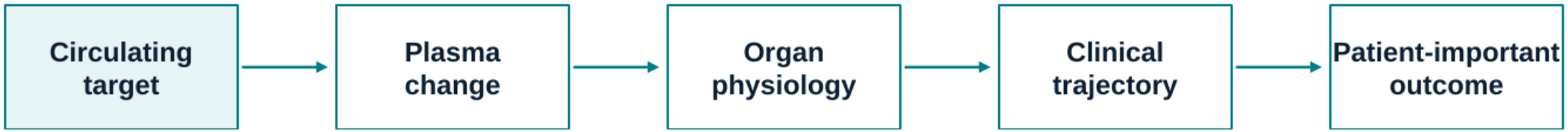
TPE is strongest when the pathogenic compartment is plasma-accessible, time-sensitive, and paired with a disease-specific prescription.

**Recurring question: target engagement → physiologic response → patient-important outcome**




Philippe R Bauer et al. Intensive Care Med . 2022 Oct;48(10):1382-1396.

# The ICU question is not “Can plasma be exchanged?”




### Three failure modes that matter at the bedside

- The target is not predominantly intravascular or rebounds faster than it is removed.
- The plasma signal changes, but organ injury is already irreversible.
- Benefit is offset by replacement-fluid toxicity, drug removal, bleeding, or procedural delay.

**TPE should be ordered for a target + clinical objective — not for “inflammation” alone.**

Connelly-Smith L et al. J Clin Apher. 2023;38:77–278. PMID 37017433. | Reeves HM, Winters JL. Br J Haematol. 2014;164:342–351. PMID 24172059.

# Evidence map: TPE is disease-modifying in some syndromes, optional in others

| Clinical bucket | Examples | How to speak about the evidence |
|---|---|---|
| Established / time-critical | Immune TTP · GBS · severe MG · anti-GBM | Treatment delay can worsen irreversible injury. |
| Evidence-based but context-dependent | Acute liver failure · severe AAV / DAH | Use disease-specific criteria; do not generalize. |
| Selective / investigational | Septic shock · TAMOF · HTG pancreatitis | Biologic or pooled signals exist; hard-outcome certainty is limited. |
| Procedure-only rationale is insufficient | “Cytokine storm” without a defined target | Do not treat a biomarker label. |

**The same extracorporeal procedure can be standard of care, selective rescue, or research therapy — depending on the disease.**

Connelly-Smith L et al. J Clin Apher. 2023;38:77–278. PMID 37017433. | KDIGO ANCA Vasculitis Work Group. Kidney Int. 2024;105:S71–S116. PMID 38388102.

# Prescription is disease-specific: “TPE” is not one uniform dose

| Indication / trial | Published prescription | Target / stop rule |
|---|---|---|
| Moderate–severe MG (Barth) | 1.0 PV × 5 exchanges | Clinical improvement |
| AAV severe kidney disease (KDIGO 2024) | 60 mL/kg; 7 treatments ≤14 d | Kidney / pulmonary phenotype |
| Anti-GBM (KDIGO 2021) | 40–50 mL/kg daily | Anti-GBM Ab undetectable; usually ~14 d |
| Acute liver failure (Larsen) | High-volume FFP exchange × 3 d | Bridge to recovery / transplant |
| Early refractory septic shock (EXCHANGE-2) | 1.2 × individual PV; single exchange ≤6 h after randomization | 28-d mortality trial endpoint |

**Dose, fluid, frequency, and stopping rule belong in the order — not only the word “plasmapheresis.”**

Connelly-Smith L et al. J Clin Apher. 2023;38:77–278. PMID 37017433. | Barth D et al. Neurology. 2011;76:2017–2023. PMID 21562253. | KDIGO ANCA Vasculitis Work Group. Kidney Int. 2024;105:S71–S116. PMID 38388102.

# Replacement fluid is part of the treatment — and part of the toxicity

| Replacement | Advantages | Numerical safety signal |
|---|---|---|
| 5% albumin | Lower allergic burden; simple volume replacement | Post-exchange fibrinogen −54% [48–66] in ICU cohort |
| Plasma / FFP | Replaces coagulation + protective plasma factors | Post-exchange fibrinogen −4% [−5 to 17] |
| Clinical consequence | Choose fluid for disease + bleeding risk | TTP / DAH often require plasma; routine albumin may be inappropriate |

**26.9%**
Any adverse reaction
70/260 ICU procedures

**8%**
Hypotension
21/260 procedures

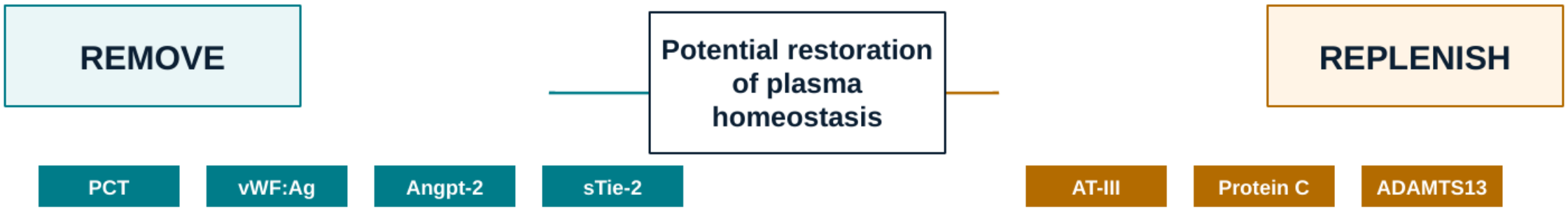
**22.8%**
Filter clotting
23/101 filtration sessions

**rare**
Severe TPE events
trained-team setting

**Fluid choice should follow the disease biology and the bleeding phenotype — not habit.**

Lemaire A et al. J Clin Apher. 2017;32:405–412. PMID 28146331. | Shemin D et al. J Clin Apher. 2007;22:270–276. PMID 17722046.

# Septic shock rationale: TPE may remove injurious mediators and replete depleted protective factors

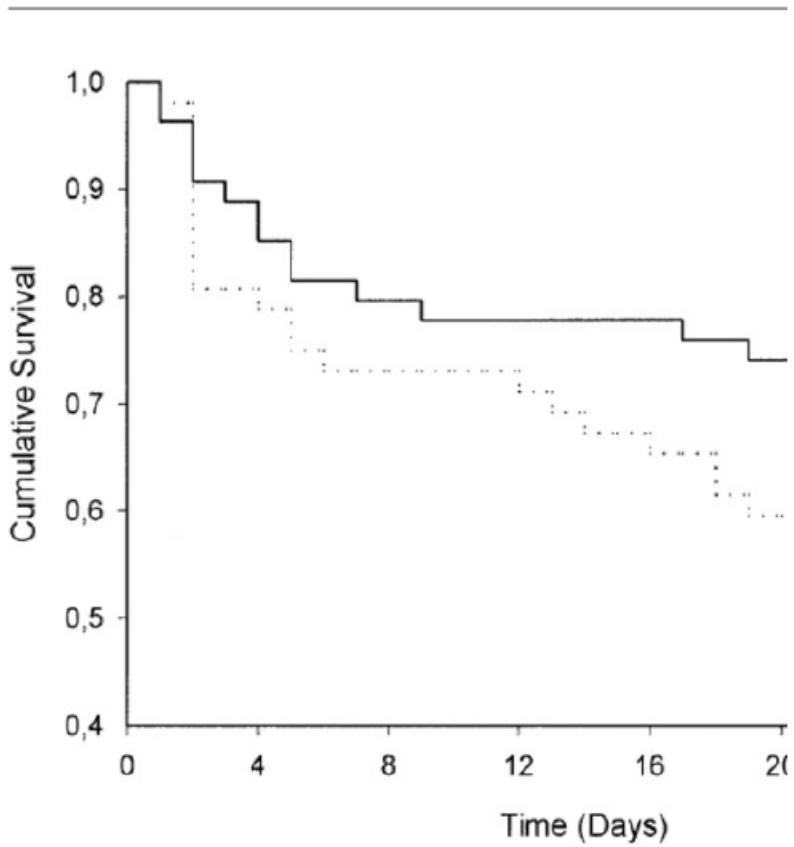



| EXCHANGE-1 biomarker | Between-group signal |
|---|---|
| PCT | P=0.037 |
| vWF:Ag | P<0.001 |
| Angpt-2 | P=0.009 |
| sTie-2 | P=0.005 |
| AT-III | P=0.026 |
| Protein C | P=0.012 |
| ADAMTS13 | P=0.008 |

**This is a coherent mechanistic package — but mechanism remains a surrogate until mortality or organ-failure benefit is proven.**

Stahl K et al. Crit Care. 2022;26:134. PMID 35551628. | Reeves HM, Winters JL. Br J Haematol. 2014;164:342–351. PMID 24172059.

# Severe sepsis / septic shock: a large RCT signal — with an important statistical caveat




**Unadjusted benefit was statistically significant; adjusted treatment effect was not (P=0.07).**

| Outcome | TPE | Control | Effect / uncertainty |
|---|---|---|---|
| 28-d mortality | 18/54 (33.3%) | 28/52 (53.8%) | RR 0.61 [0.39–0.97]; P=0.050 |
| Absolute effect | ARR 20.5 pp [2–39] | — | NNT 4.9 [2.5–50] |
| Adjusted mortality model | — | — | OR 0.41 [0.15–1.09]; P=0.07 |

| Protocol feature | Published detail |
|---|---|
| Timing | Initiated ≤6 h after sepsis/septic-shock diagnosis |
| Exchange | 30–40 mL/kg |
| Replacement | Equal-volume FFP diluted 1:1 with 5% albumin |
| Repeat | 27 patients received a second session within 24 h |

Busund R et al. Intensive Care Med. 2002;28:1434–1439. PMID 12373468.

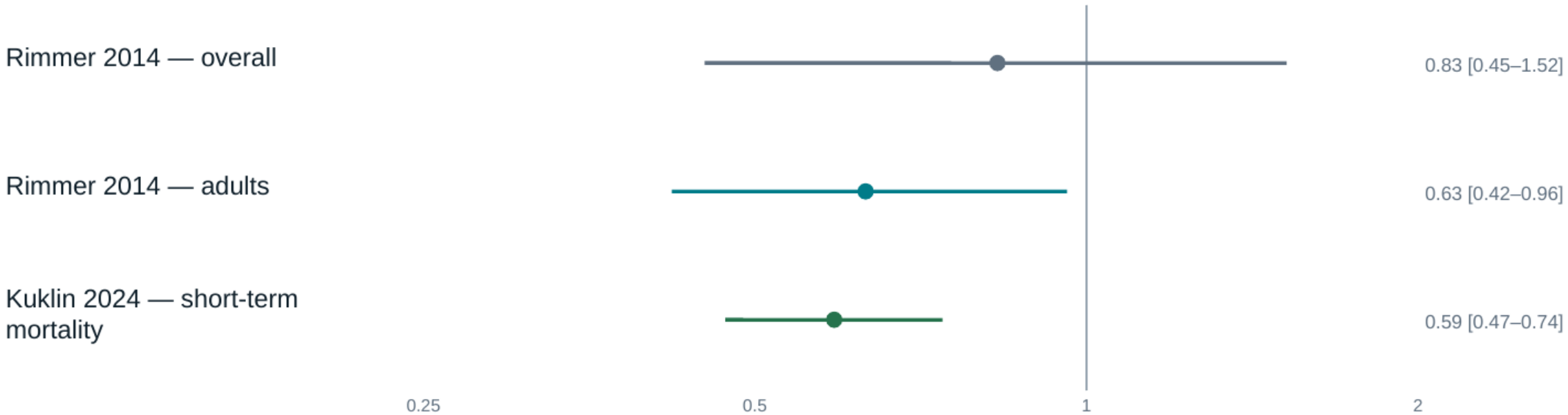
# EXCHANGE-1: early TPE accelerated norepinephrine de-escalation

| Endpoint | TPE | SOC | P |
|---|---|---|---|
| NE dose reduction / hour | 0.018 µg/kg/min | 0.005 µg/kg/min | 0.004 |
| Lactate trajectory | Continuous fall over 24 h | Increased over 24 h | 0.001 |
| Response interaction | Greater NE effect at higher baseline lactate | Less NE reduction as lactate increased | 0.004 |


**This trial defines a plausible time window and response phenotype — not a proven survival indication.**

Stahl K et al. Crit Care. 2022;26:134. PMID 35551628.

# Sepsis meta-analyses: pooled estimates are favorable, but the design mix matters




| Review | Evidence base | Important limitation |
|---|---|---|
| Rimmer 2014 | 4 unique trials; n=194 | Unclear / high risk of bias; I² 60% overall |
| Kuklin 2024 | 20 studies screened; meta-analysis n=627 | RCTs + matched cohorts; residual confounding remains |

**Pooled effect size answers “what do the included studies average?” — not “is the intervention proven?”**

Rimmer E et al. Crit Care. 2014;18:699. PMID 25527094. | Kuklin V et al. Crit Care. 2024;28:12. PMID 38178170.

# ICU decision algorithm: decide by target, evidence, urgency, and reversibility


| Decision | Examples | Action |
|---|---|---|
| Start now | iTTP · anti-GBM · severe GBS / MG with appropriate phenotype | Do not delay for perfect diagnostic certainty |
| Select high risk | AAV with advanced kidney injury / hypoxemic DAH · ALF HVP context | Use disease-specific criteria and protocol |
| Protocol / trial | Refractory septic shock · TAMOF | Define timing, target, and hard outcome |
| Usually avoid routine use | HTG-AP solely for rapid TG reduction · undefined “cytokine storm” | Use conventional disease-directed therapy |

**The question is not “Is TPE available?” — it is “Is the biology, evidence, and timing aligned for this patient?”**

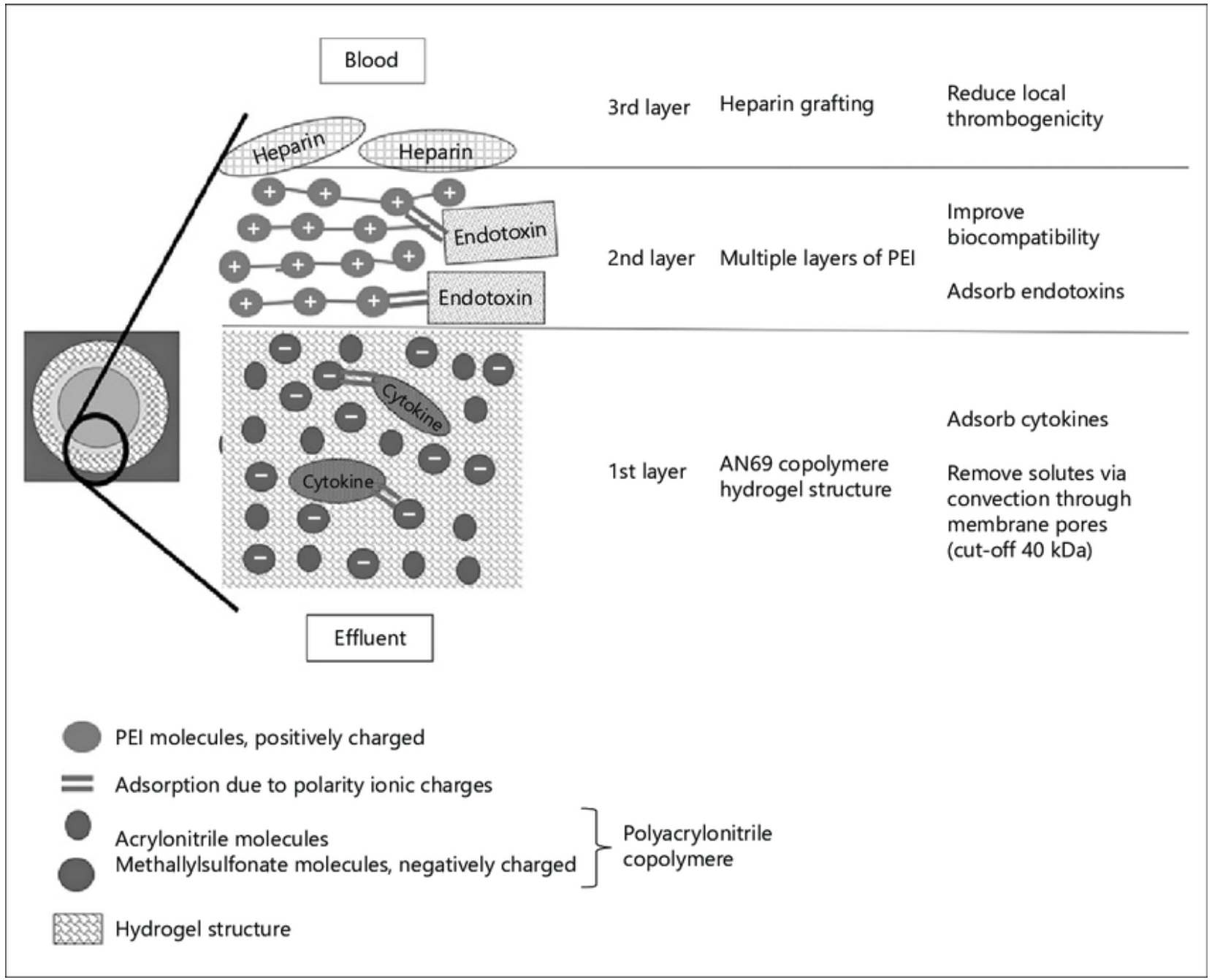
Connelly-Smith L et al. J Clin Apher. 2023;38:77–278. PMID 37017433. | KDIGO ANCA Vasculitis Work Group. Kidney Int. 2024;105:S71–S116. PMID 38388102. | Kuklin V et al. Crit Care. 2024;28:12. PMID 38178170.

Part 3

# oXiris

The defensible niche is not “cytokine removal alone,” but CKRT-required septic shock with plausible endotoxin/cytokine burden.

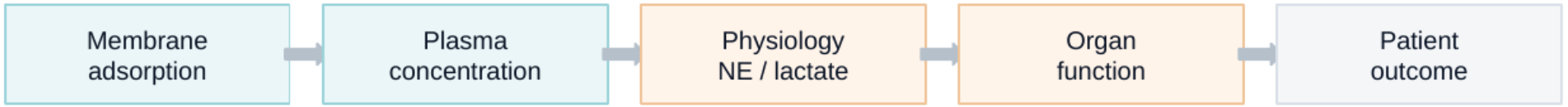
**Recurring question: target engagement → physiologic response → patient-important outcome**




Céline Monard et al. Blood Purif . 2019:47 Suppl 3:1-14.

# The clinical question is narrower than “Can it adsorb?”

- Does endotoxin / cytokine extraction translate into a systemic effect?
- Does the systemic effect improve shock, organ dysfunction, or survival?
- If used, what prescription and monitoring prevent unintended harm?




**For practice, do not collapse a mechanistic endpoint into a clinical indication.**

Siew LY et al. J Crit Care. 2024;83:154844. PMID 38901069; Broman ME et al. PLoS One. 2019;14:e0220444. PMID 31369593.

# Where the evidence is clinically plausible

| Use case | Evidence signal | Current stance |
|---|---|---|
| **Septic shock + AKI needing CKRT** | Best biologic fit; early hemodynamic and biomarker signals | Reasonable to consider by protocol in selected patients |
| **Septic shock without CKRT indication** | Sparse and confounded | Not a routine stand-alone hemoadsorption indication |
| **Cardiac surgery / prolonged CPB** | OXICARD neutral for microcirculation and outcomes | Do not use routinely |
| **VA-ECMO cardiogenic shock** | CLEAN-ECMO and ECMORIX neutral on endotoxin/outcomes | Routine nonrenal use not supported |
| **Anticoagulation-free CKRT** | Filter life not prolonged | Use a real anticoagulation strategy when possible |

**Best-supported phenotype: septic shock with a real CKRT indication, early enough to plausibly modify mediator burden.**

Integrated synthesis from Broman 2019, Feng 2022, Siew 2024, Ko 2025, Abou-Arab 2025, Wong 2021, Naorungroj 2023.

# Mechanistic RCT: endotoxin removal is demonstrable

| Endpoint | oXiris | Standard filter | Interpretation |
|---|---|---|---|
| **Endotoxin fell during first period** | 7/9 (77.8%) | 1/6 (16.7%) | P=0.02 |
| **Cytokines** | TNF-α, IL-6, IL-8, IFN-γ fell more | Smaller / less consistent | Biologic signal |
| **Lactate** | Median change −1.3 mmol/L | No significant fall | P=0.02 |
| **Mortality** | Not powered | Not powered | Mechanistic trial, not outcome trial |

**This is target engagement: useful, necessary, but insufficient for an ICU indication.**

Broman ME et al. PLoS One. 2019;14:e0220444. PMID 31369593.

# Pilot RCT in surgical septic shock + AKI: early hemodynamic signal

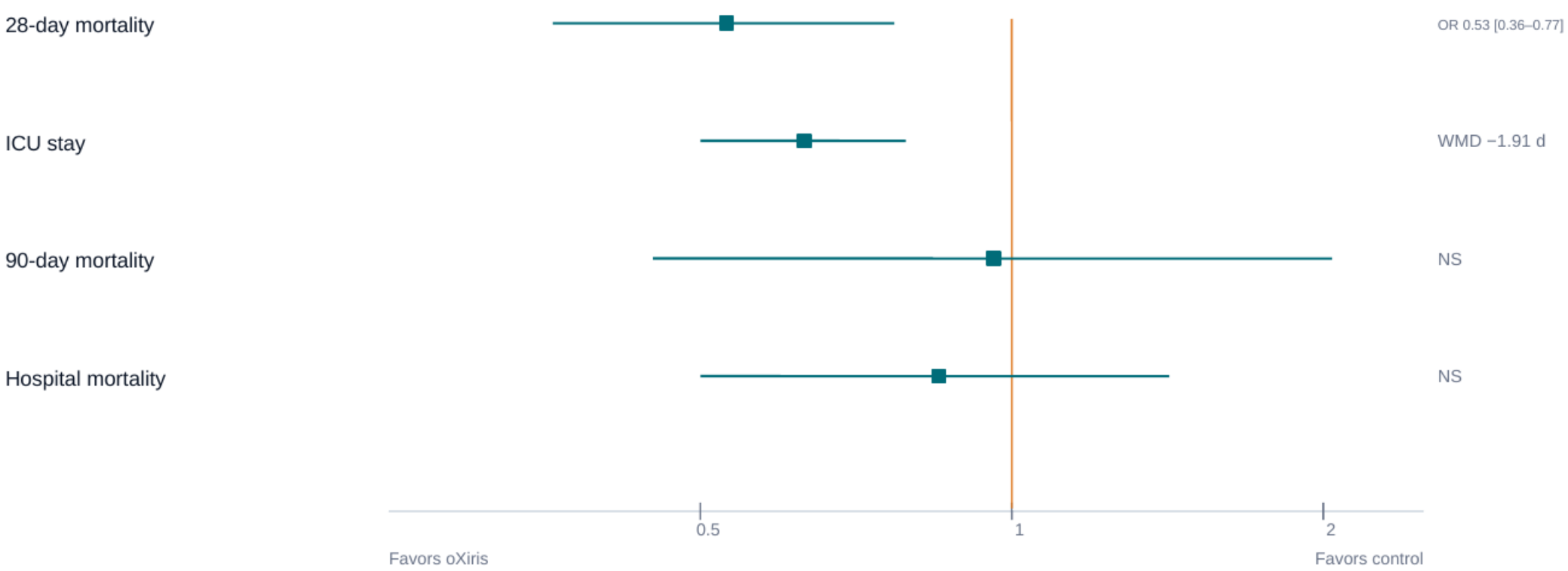
| Design | Population | Comparator | Main results |
|---|---|---|---|
| **Single-center pilot RCT** | Surgical septic shock + KDIGO stage 3 AKI; n=16 | oXiris n=8 vs AN69-ST n=8 | PCT and IL-6 fell after first treatment; NE lower at 4, 6, 8 h |
| **Prescription** | CVVH; blood 150–200 mL/min; dose 30–35 mL/kg/h | Median first CRRT 23.5 h | 28-d mortality 62.5% vs 75%; P=0.519 |

- NE decrease versus AN69-ST: −0.06, −0.05, −0.11 μg/kg/min at 4, 6, 8 h.
- Small N and severe surgical sepsis: do not infer mortality benefit.

**Best use in the lecture: evidence for early shock physiology, not patient-centered efficacy.**

Feng J et al. Int J Artif Organs. 2022;45:801-808. PMID 35864718.

# Sepsis meta-analysis: favorable pooled estimates, low certainty

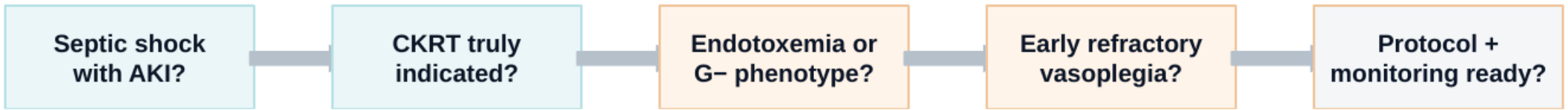



- 14 studies, 695 patients; primary outcome was 28-day mortality.
- Evidence certainty was low or very low; RCTs were small and had unclear risk of bias.

**Do not quote the pooled OR without also quoting the certainty problem.**

Wang G et al. Crit Care. 2023;27:275. PMID 37424026.

# Bedside decision flow: when oXiris is most defensible




| If yes to all | Most evidence-concordant use: septic shock + CKRT + plausible endotoxin/cytokine burden + explicit target |
|---|---|
| **If CKRT not indicated** | Evidence becomes weaker; routine stand-alone hemoadsorption is not supported by RCTs |
| **If no target / no stop rule** | Do not start; create protocol first |

**A clinically serious oXiris order should state: target, timing, circuit, exchange plan, antibiotic plan, stop rule.**

Synthesis from Broman 2019; Feng 2022; Siew 2024; Wong 2021; Naorungroj 2023.

# Final clinical position

**Use oXiris when the patient phenotype, CKRT indication, measurable target, monitoring plan, and stopping rule are explicit — not because inflammation is high.**

| Question | Answer today |
|---|---|
| **Does it adsorb?** | Yes — endotoxin and cytokine target engagement is demonstrable. |
| **Does it improve shock?** | Possibly in selected septic shock + CKRT phenotypes; RCT evidence remains small. |
| **Does it improve survival?** | Not proven; pooled survival signals are low-certainty and observationally driven. |
| **Can it harm?** | Possible through drug underexposure, circuit failure, or unmeasured nonselective effects. |
| **Current ICU standard** | Selective protocolized use, not routine broad cytokine-removal therapy. |

**Discussion**

Evidence summary: oXiris in critical illness, selected RCTs, observational cohorts, meta-analyses, and PK/safety studies.

Part 4

# CytoSorb

The key clinical distinction is evidence versus indication versus reimbursement; a reimbursed use is not automatically an outcome-proven ICU therapy.

**Recurring question: target engagement → physiologic response → patient-important outcome**

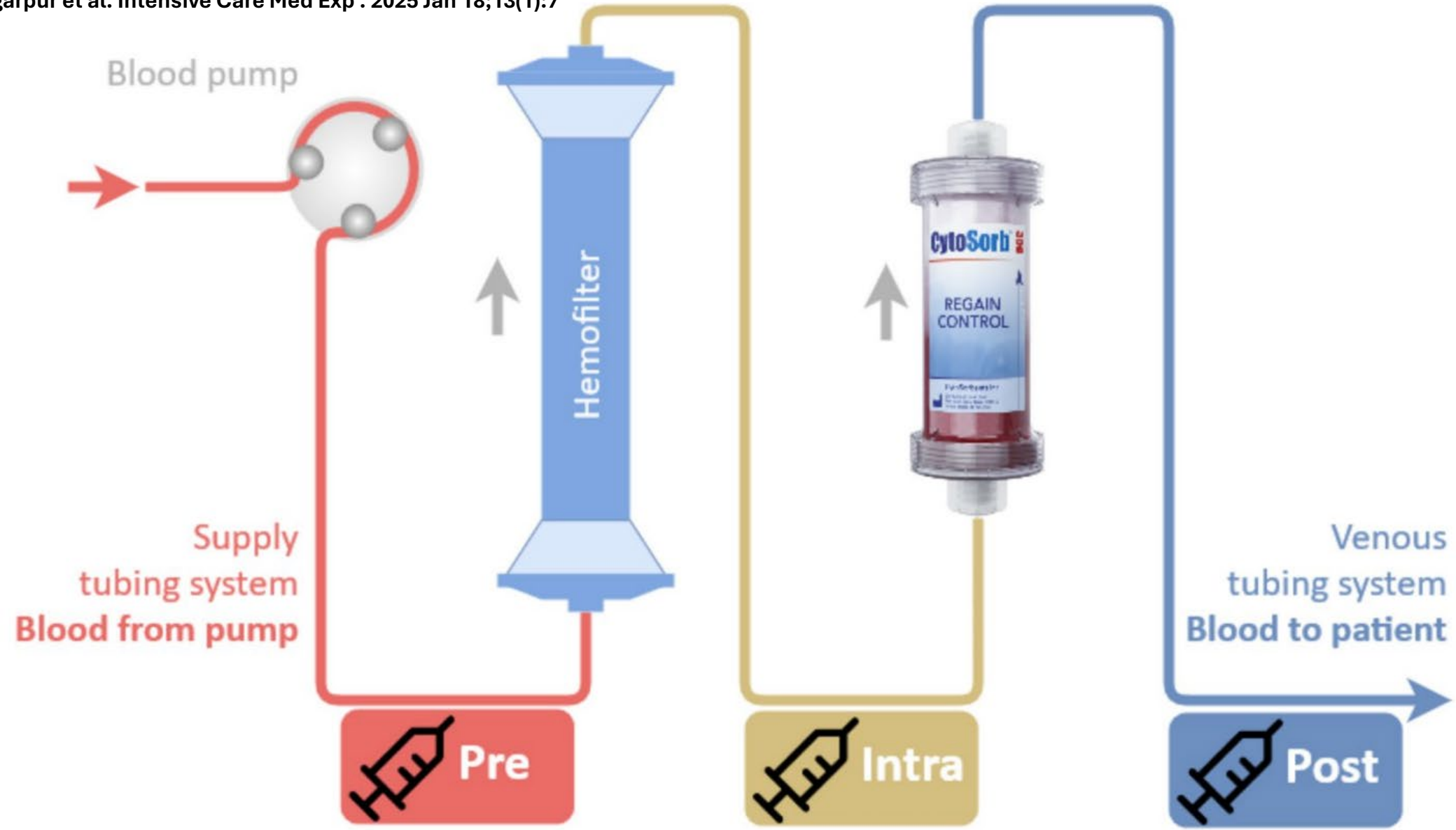



**Fig. 1** Schematic representation of the CKRT-CS set-up and the corresponding blood sampling sites Pre, Intra, and Post for meropenem and piperacillin quantification. *CKRT* renal replacement therapy, *CKRT-CS* continuous renal replacement therapy followed by CS, *Pre* before CKRT-CS setup, *Intra* between CKRT and CS, *Post* after CKRT-CS setup. Image adapted with courtesy of CytoSorb® Europe, Berlin, Germany

# The clinical question is not “Can it adsorb?”

The bedside question is narrower and harder.

- Does extracorporeal adsorption change patient-important outcomes?
- Which use cases are legally indicated or reimbursed locally?
- If used, what must be monitored to avoid unintended harm?

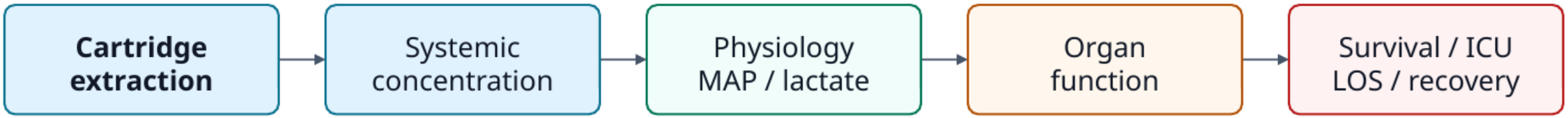
**Evidence** | **Indication** | **Payment** | **Protocol**

**For ICU practice, regulatory authorization and biological plausibility are not enough.**

Synthesis from RCTs, meta-analyses, regulatory documents, and reimbursement notices.

# Five-link evidence chain for hemoadsorption

Every arrow needs evidence; most trials fail after the first link.



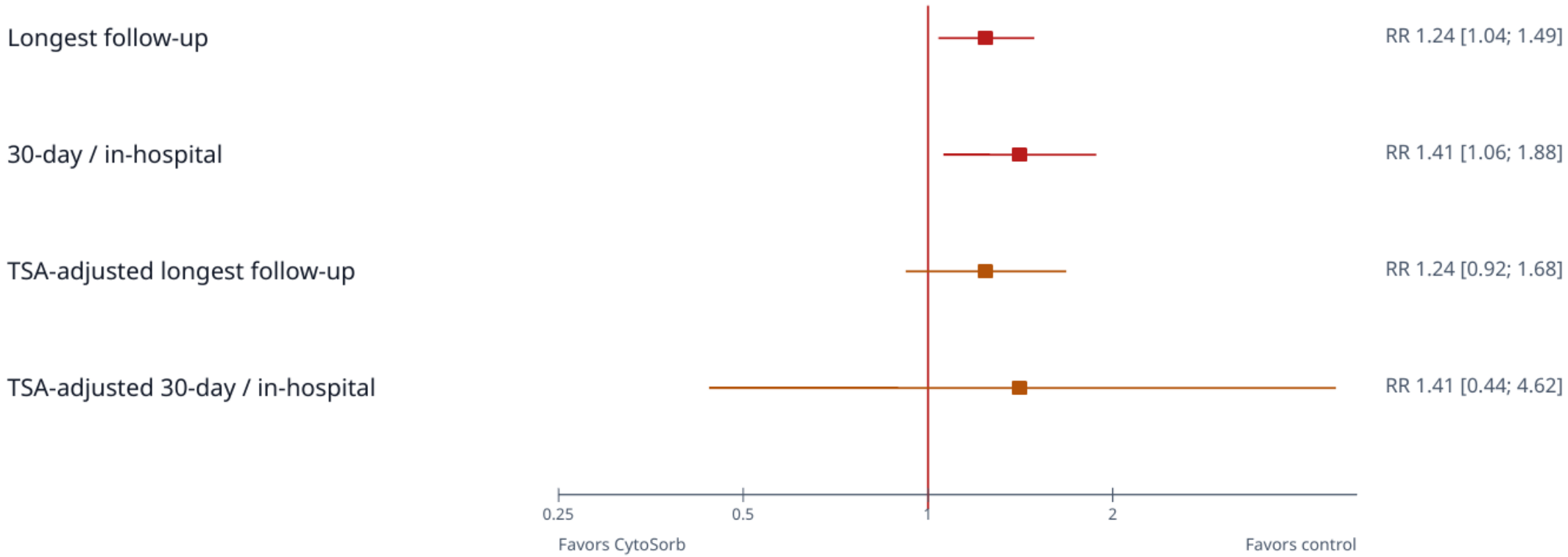

- Cytokine extraction is plausible; systemic cytokine control is inconsistent.
- Outcome benefit has not been reproduced across high-quality randomized trials.

**Do not collapse a mechanistic endpoint into a clinical indication.**

Concept based on Schädler D et al. PLoS One. 2017;12:e0187015; Diab M et al. Circulation. 2022;145:959-968; Becker S et al. Crit Care. 2023;27:215.

# RCT-only safety signal: mortality point estimates lean against routine use

## Mortality in randomized trials

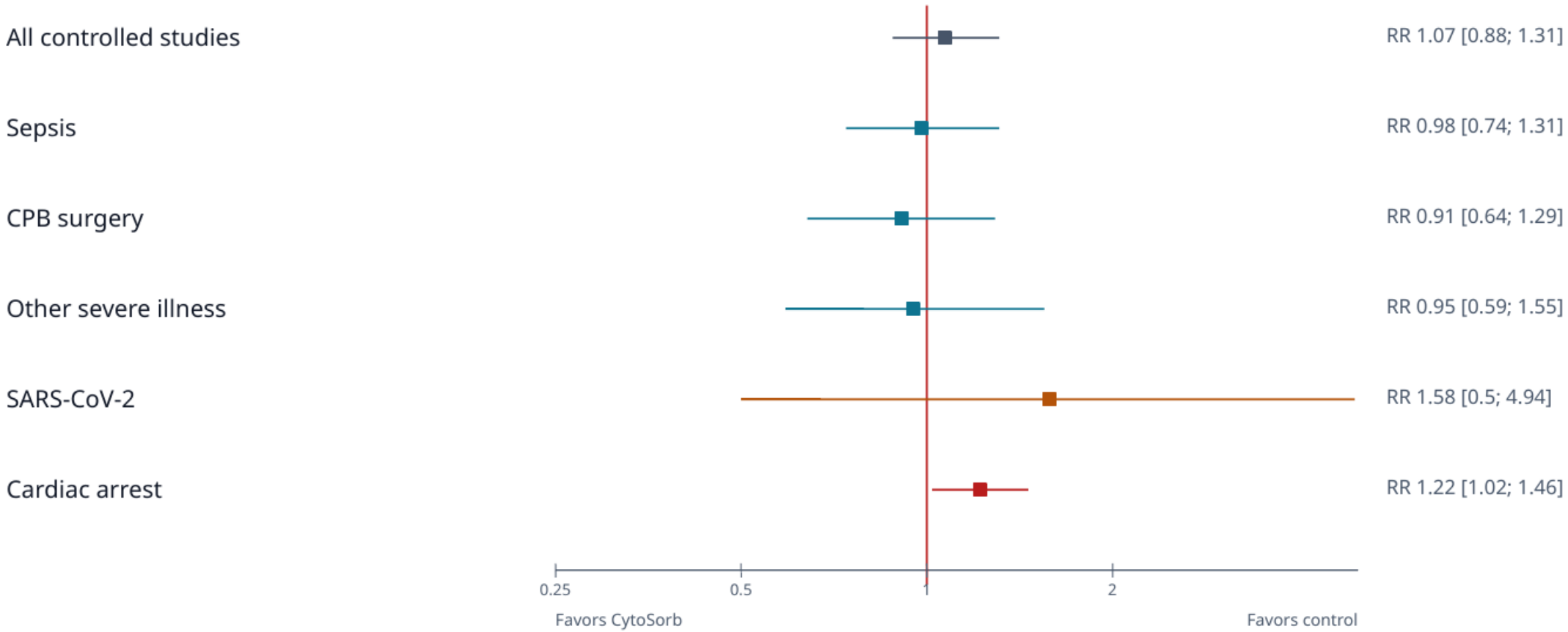



- Low to very-low certainty: not proof of harm, but no basis for routine use.
- Adverse events were frequent but underreported and inconsistently defined.

Heymann M et al. Acta Anaesthesiol Scand. 2022;66:1037-1050. PMID 35788557.

# Controlled-study meta-analysis: no mortality benefit across indications

## Longest reported mortality by indication




**The pooled evidence does not justify widespread ICU use.**

Becker S et al. Crit Care. 2023;27:215. PMID 37259160.

# Septic shock meta-analyses: results depend heavily on design mix

| Analysis | Main result | Interpretation |
|---|---|---|
| Critical Care Science 2023 | 28–30 d mortality: RCT RR 0.98 [0.12–8.25]; cohorts RR 0.74 [0.49–1.13] | Very-low certainty; no recommendation outside trials |
| Orban 2025 | Overall mortality OR 0.95 [0.58–1.56], p=0.85; early initiation OR 2.02 [1.06–3.85] | No overall effect; high risk of bias; correction published |
| Steindl 2025 | 28–30 d mortality OR 0.46 [0.28–0.78], p=0.003; mostly observational | Positive signal, but quality and heterogeneity require caution |

**For septic shock, observational survival signals have not become reproducible RCT evidence.**

Orban C et al. Biomedicines. 2025;13:180. PMID 39857764; Steindl D et al. J Clin Med. 2025;14:2285; Critical Care Science 2023.

# Sepsis / septic shock: RCTs do not support routine cytokine removal

| Trial | Population / trigger | Key numeric result |
|---|---|---|
| Schädler 2017 | Sepsis + acute lung injury/ARDS; n≈97 | Primary IL-6 not improved; unadjusted 60-d mortality higher, adjusted signal not confirmed |
| Hawchar 2019 | Septic shock proof-of-concept; n=20 | NE/PCT/big-endothelin-1 signals; no powered clinical endpoint |
| Lotz 2026 | Septic shock + IL-6 >500 pg/mL; n=31; 93% treated within 24 h | 72-h NE: 78 vs 100.7 mg, p=0.09; survival 48 h: 100% vs 64%, p=0.01 favoring control |

**Even early hyperinflammatory septic shock has not yielded reproducible outcome benefit.**

Schädler D et al. PLoS One. 2017;12:e0187015; Hawchar F et al. J Crit Care. 2019;49:172-178; Lotz C et al. Shock. 2026;65:637-647.

# Practical ICU decision grid

| Use category | Examples | Recommended stance |
|---|---|---|
| Do not use routinely | Unselected septic shock; routine CPB/IE prophylaxis; COVID VV-ECMO; post-ECPR PCAS | No reproducible patient-important benefit; some harm signals |
| May consider only by protocol | Extreme vasoplegia; heart transplantation; burn septic shock; severe rhabdomyolysis | Prospective data collection; predefined targets and stopping rules |
| Locally reimbursed/label-driven | Taiwan emergency CPB + ticagrelor/rivaroxaban within 72 h | Follow coverage rule and surgical drug-removal protocol |
| Research priority | Biomarker-high phenotype + target-specific cartridge exchange | Randomized, blinded endpoint assessment whenever feasible |

**CytoSorb should be a protocolized intervention, not a reflex response to “high inflammation.”**

Synthesis from RCTs, meta-analyses, local reimbursement documents, and drug-removal evidence.

# Final clinical position

**Use CytoSorb when the target, indication, monitoring plan, and stopping rule are explicit—not because inflammation is high.**

| Question | Answer today |
|---|---|
| Does it adsorb? | Yes — but extraction does not guarantee systemic control or outcome benefit. |
| Can it improve shock? | Possibly in selected phenotypes; RCT evidence remains insufficient. |
| Can it harm? | Possible: drug underexposure, cytopenia/coagulation effects, and negative RCT signals. |
| What is the ICU standard? | Protocolized, selective use; routine broad cytokine-removal use is not evidence-based. |

## Discussion

# Sepsis / severe sepsis / septic shock evidence table: PMX-HP

Older trials use “severe sepsis” terminology; current bedside interpretation should focus on shock phenotype and target selection.

| Trial / design | Population | Key numeric result | Interpretation |
|---|---|---|---|
| **EUPHAS 2009 open RCT; n=64** | Post-op intra-abdominal septic shock<br>No EAA enrichment | 28-d mortality 32% vs 53%; HR 0.43 [0.20–0.94] | Large early signal; small and stopped at interim. |
| **ABDOMIX 2015 open RCT; n=243** | Peritonitis after emergency surgery<br>No EAA enrichment | 28-d mortality 27.7% vs 19.5%; OR 1.59 [0.86–2.94] | Neutral / point estimate favored control; delivery and phenotype dilution matter. |
| **EUPHRATES 2018 sham RCT; n=450** | Septic shock + EAA ≥0.60 | 28-d mortality RR 1.09 [0.85–1.39] | Biomarker enrichment alone was not sufficient. |
| **EUPHRATES post hoc per-protocol n=194** | MODS >9 + EAA 0.60–0.89 | 28-d adjusted OR 0.52 [0.27–0.99] | Hypothesis-generating “treatable window.” |
| **TIGRIS 2026 Bayesian RCT; n=157** | EAA 0.60–0.89 + multiple organ dysfunction | 28-d OR 0.67 [CrI 0.39–1.08]; Pbenefit 95.3%<br>90-d OR 0.54 [0.32–0.87]; Pbenefit | New signal in a very narrow endotype; still selective, not routine. |

**PMX-HP: most defensible as selective, EAA-guided, protocolized therapy — not routine septic shock rescue.**

Cruz DN et al. JAMA. 2009;301:2445-2452. PMID 19531784. • Payen DM et al. Intensive Care Med. 2015;41:975-984. PMID 25862039. • Dellinger RP et al. JAMA. 2018;320:1455-1463. PMID 30304428. • Klein DJ et al. Intensive Care Med. 2018;44:2205-2212. PMID 30470853. • Neyra JA et al. Lancet Respir Med. 2026;14:443-452. PMID 41887242.

# Sepsis / severe sepsis / septic shock evidence table: TPE

TPE has coherent remove + replenish biology, but definitive sepsis mortality evidence remains limited.

| Study / design | Population / protocol | Key numeric result | Interpretation |
|---|---|---|---|
| **Busund 2002 RCT; n=106** | Severe sepsis / septic shock TPE ≤6 h; 30–40 mL/kg; FFP + albumin | 28-d mortality 33.3% vs 53.8%; RR 0.61 [0.39–0.97]; adjusted OR 0.41 [0.15–1.09], P=0.07 | Important signal with statistical caveat. |
| **EXCHANGE-1 mechanistic RCT** | Early refractory septic shock single TPE | Accelerated norepinephrine de-escalation and favorable mediator/protective-factor changes | Physiologic response phenotype; not survival proof. |
| **Meta-analyses** | Mixed RCTs and observational studies | Pooled estimates often favorable, but design mix changes conclusions | Do not translate pooled signal into routine use. |
| **EXCHANGE-2** | Adult septic shock trial designed for hard outcomes | Designed to test 28-d mortality after early 1.2-PV TPE | Needed to define modern practice; do not overgeneralize before hard outcomes. |

**TPE in sepsis: promising biology and early physiologic response; routine use remains investigational/selective.**

Busund R et al. Intensive Care Med. 2002;28:1434-1439. PMID 12373468. • Stahl K et al. Crit Care. 2022;26:134. PMID 35551628. • Connelly-Smith L et al. J Clin Apher. 2023;38:77-278. PMID 37017433.

# Sepsis / severe sepsis / septic shock evidence table: oXiris and CytoSorb

CKRT-based adsorption and hemoadsorption show biologic or physiologic signals, but outcome certainty remains low.

| Modality / study | Population / trigger | Key numeric result | Interpretation |
|---|---|---|---|
| **oXiris Broman 2019 RCT** | Septic shock; mechanistic crossover RCT; n=16 | Endotoxin fell in 7/9 (77.8%) vs 1/6 (16.7%); P=0.02; lactate −1.3 mmol/L | Target engagement; not powered for outcomes. |
| **oXiris Feng 2022 pilot RCT** | Surgical septic shock + KDIGO stage 3 AKI; n=16 | NE lower at 4, 6, 8 h; 28-d mortality 62.5% vs 75%; P=0.519 | Early hemodynamic signal, no mortality inference. |
| **oXiris Wang 2023 meta-analysis** | 14 studies; 695 patients | 28-d mortality OR 0.53 [0.36–0.77]; 90-d and hospital mortality not significant; certainty low/very low | Quote effect size with certainty limitation. |
| **CytoSorb controlled evidence** | Sepsis / septic shock mixed trials | Sepsis longest mortality RR 0.98 [0.74–1.31]; RCT-only mortality signals do not support routine use | Routine septic shock cytokine removal not supported. |
| **CytoSorb Lotz 2026 RCT** | Septic shock + IL-6 >500 pg/mL; n=31 | 72-h NE 78 vs 100.7 mg, P=0.09; 48-h survival 100% vs 64%, P=0.01 favoring control | Even hyperinflammatory phenotype remains uncertain. |

**Adsorption in sepsis: physiologic signal can justify protocols or trials, not broad claims of survival efficacy.**

Broman ME et al. PLoS One. 2019;14:e0220444. PMID 31369593. • Feng J et al. Int J Artif Organs. 2022;45:801-808. PMID 35864718. • Wang G et al. Crit Care. 2023;27:275. PMID 37424026. • Becker S et al. Crit Care. 2023;27:215. PMID 37259160. • Lotz C et al. Shock. 2026;65:637-647.

# Evidence-concordant bedside selection in septic shock

A practical table for rounds, ICU governance, and protocol writing.

| Question | PMX-HP | TPE | oXiris | CytoSorb |
|---|---|---|---|---|
| **Best phenotype** | EAA 0.60–0.89 + septic shock + MOF | Early refractory septic shock; ideally protocol/trial | Septic shock + true CKRT indication + plausible endotoxin/cytokine burden | Defined molecule/drug-removal indication; not broad sepsis |
| **Main endpoint to monitor** | EAA if available; NE, MAP, lactate, SOFA | NE/VIS, lactate, organ trajectory, coagulation/fibrinogen | NE/VIS, lactate, TMP, filter life, antibiotic exposure | Target molecule/drug, NE/VIS, cytopenia, antibiotics/TDM |
| **Strongest caution** | No rapid EAA = weak match to TIGRIS phenotype | Replacement-fluid toxicity and drug removal | Heparin grafting is not anticoagulation; antibiotic underexposure | RCTs do not support routine septic shock cytokine removal |
| **Current stance** | Selective use may be defensible | Selective / investigational in sepsis | Protocolized filter choice when CKRT is needed | Protocolized only for clear target/approved use |

**The safest clinical language: selective, monitored, protocolized, and evidence-humble.**

Neyra JA et al. Lancet Respir Med. 2026;14:443-452. PMID 41887242. • Busund R et al. Intensive Care Med. 2002;28:1434-1439. PMID 12373468. • Siew LY et al. J Crit Care. 2024;83:154844. PMID 38901069. • Becker S et al. Crit Care. 2023;27:215. PMID 37259160.

# Final take-home messages

What to say in a scientific ICU lecture.

| | | |
|---|---|---|
| 01 | **Mechanism is necessary, not sufficient.** | Target engagement must be connected to physiology and patient-important outcomes. |
| 02 | **Phenotype selection is the main story.** | PMX-HP illustrates how trial questions changed as EAA-defined endotypes narrowed. |
| 03 | **TPE is disease-specific, not procedure-specific.** | Dose, fluid, frequency, and stop rule belong in the order. |
| 04 | **Adsorptive CKRT filters are not magic.** | oXiris is most defensible when CKRT is truly indicated; antibiotic exposure and circuit strategy matter. |
| 05 | **CytoSorb requires governance language.** | Separate evidence, indication, reimbursement, protocol, and safety monitoring. |

**Target + phenotype + protocol + monitoring + stop rule = the minimum standard for bedside use.**