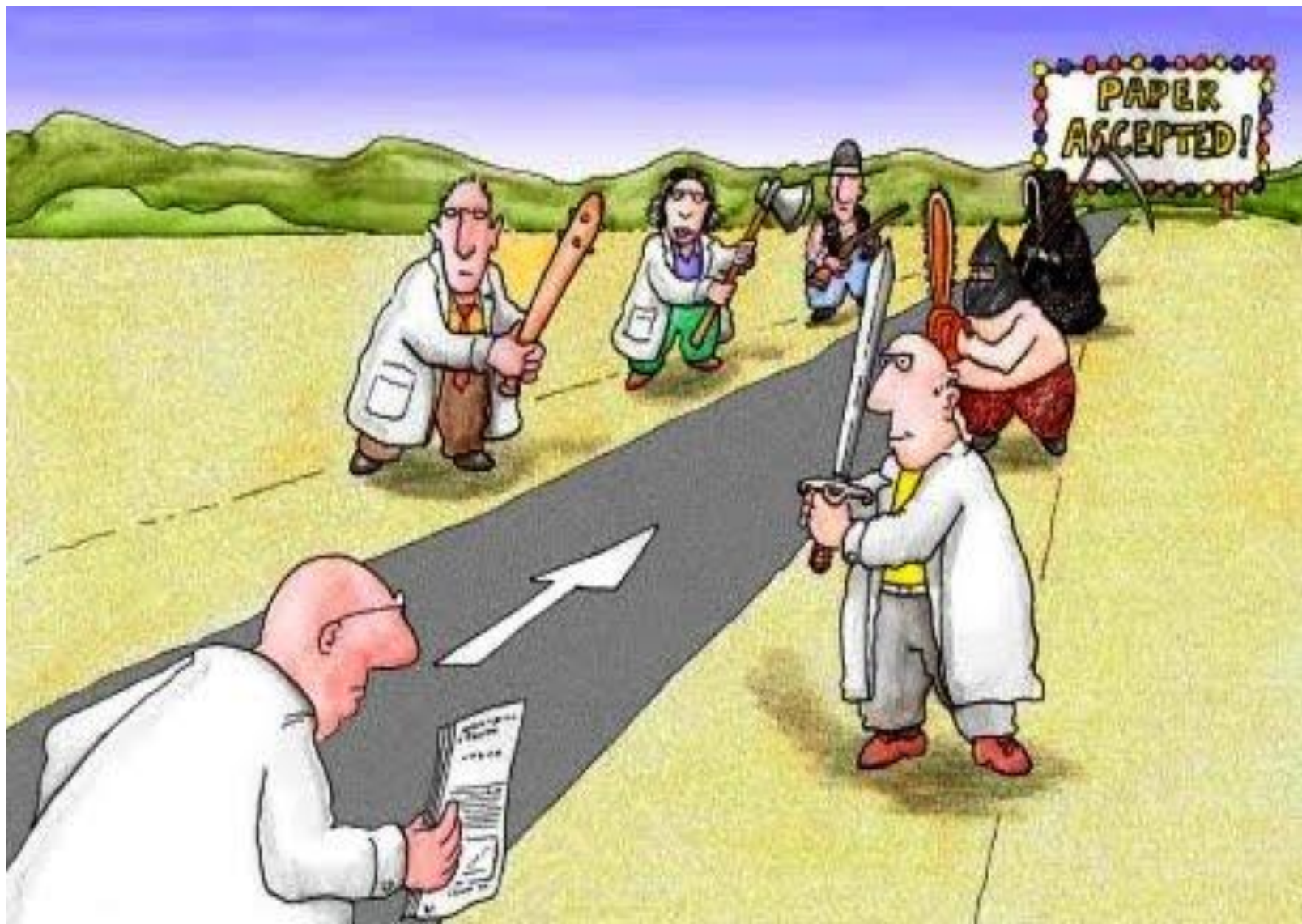


# The guidance for scientific failure-just prescribe EBP

**Vedran Premuzic, MD, PhD**  
**UHC Zagreb, Croatia**





- the groups are extremely heterogenous
- disease severity was extremely heterogenous
- the inclusion criterias were not clear
- these treatments still lack a proof of efficacy and some researchers have even found potential harm
- this is neither a RCT nor a prospective cohort study
- no single RCT shows any survival benefit for BP



Critical Care



[Crit Care](#). 2003; 7(2): 139–145. Published online 2003 Feb 21. doi: [10.1186/cc1889](https://doi.org/10.1186/cc1889)

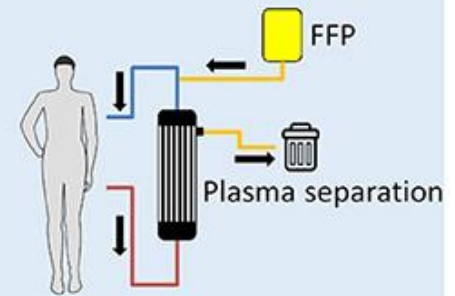
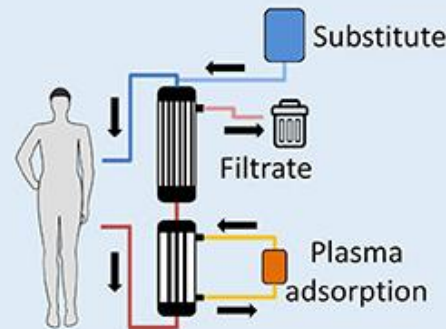
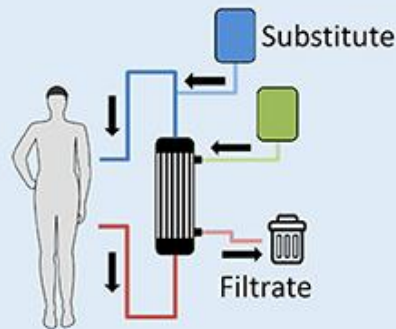
PMCID: PMC270630 | PMID: [12720560](https://pubmed.ncbi.nlm.nih.gov/12720560/)

## Clinical review: Extracorporeal blood purification in severe sepsis

[Ramesh Venkataraman](#),<sup>1</sup> [Sanjay Subramanian](#),<sup>2</sup> and [John A Kellum](#)<sup>3</sup>



# Extracorporeal Blood Purification



Convection  
Therapies

Adsorption  
Therapies

Combination  
Therapies

Other Therapies

Continuous Renal  
Replacement  
Therapy (CRRT)

Immobilized  
Polymyxin B  
(PMX)

Coupled Plasma  
Filtration Adsorption  
(CPFA)

Plasma  
Exchange

High Volume  
Hemofiltration  
(HVHF)

Hemoadsorption  
(e.g. CytoSorb)

Combined filtration  
and Adsorption  
(e.g. oXiris)

Renal Assist Device  
(RAD)

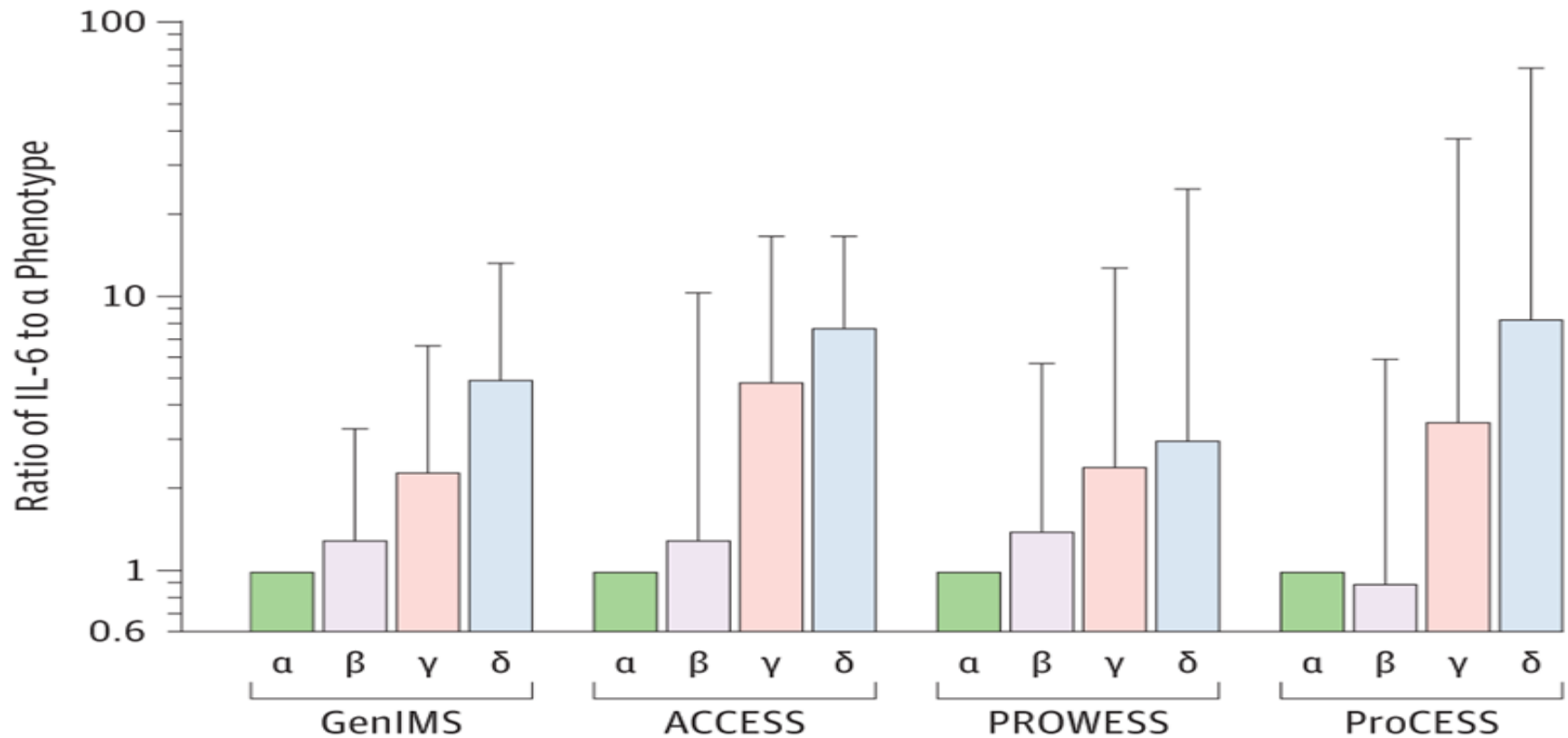
High Cut-Off  
Membranes  
(HCO)

Selective  
Cytapheretic  
Device (SCD)

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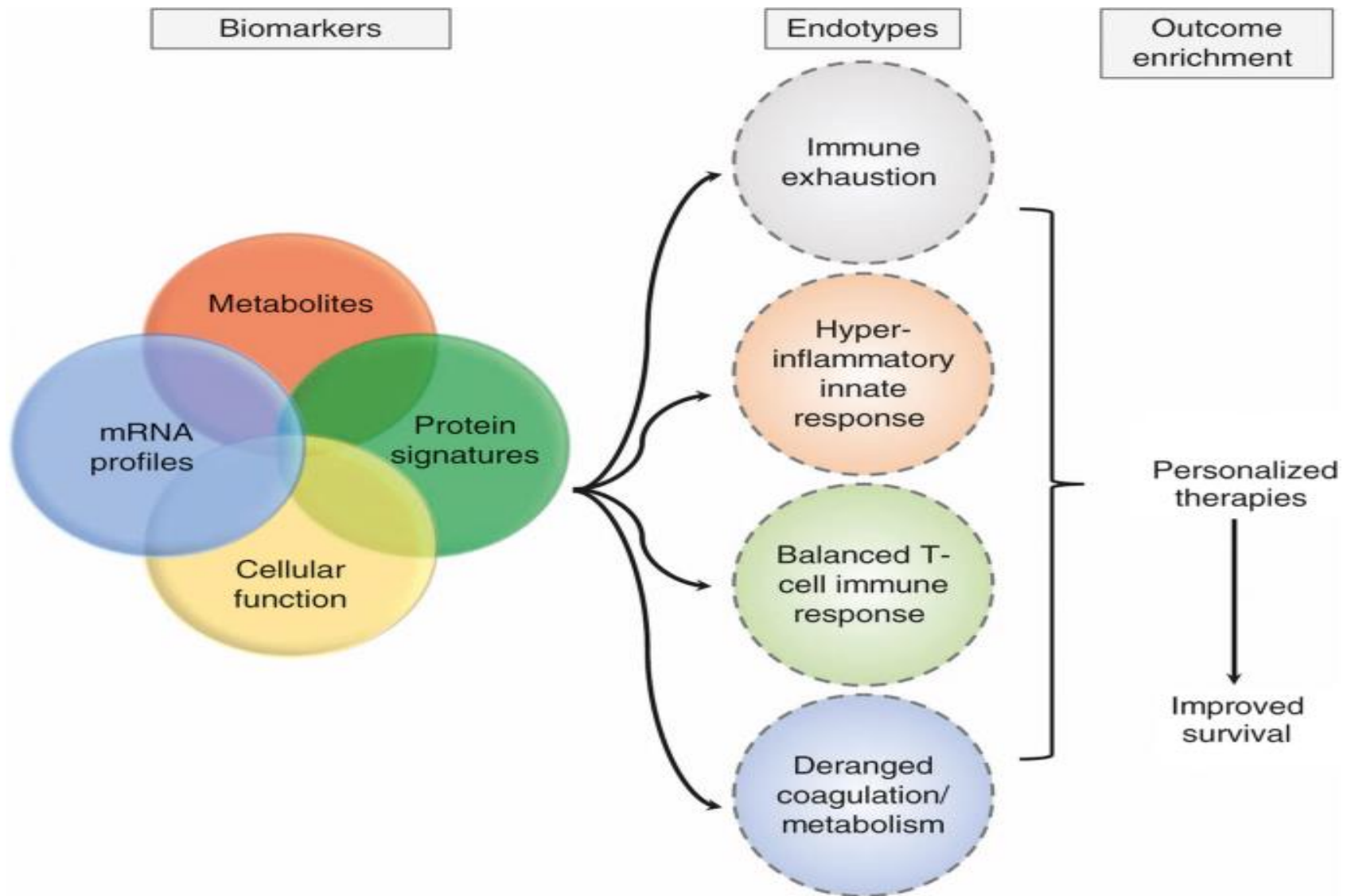
# Different sepsis phenotypes

**A** Ratio of IL-6 to a phenotype



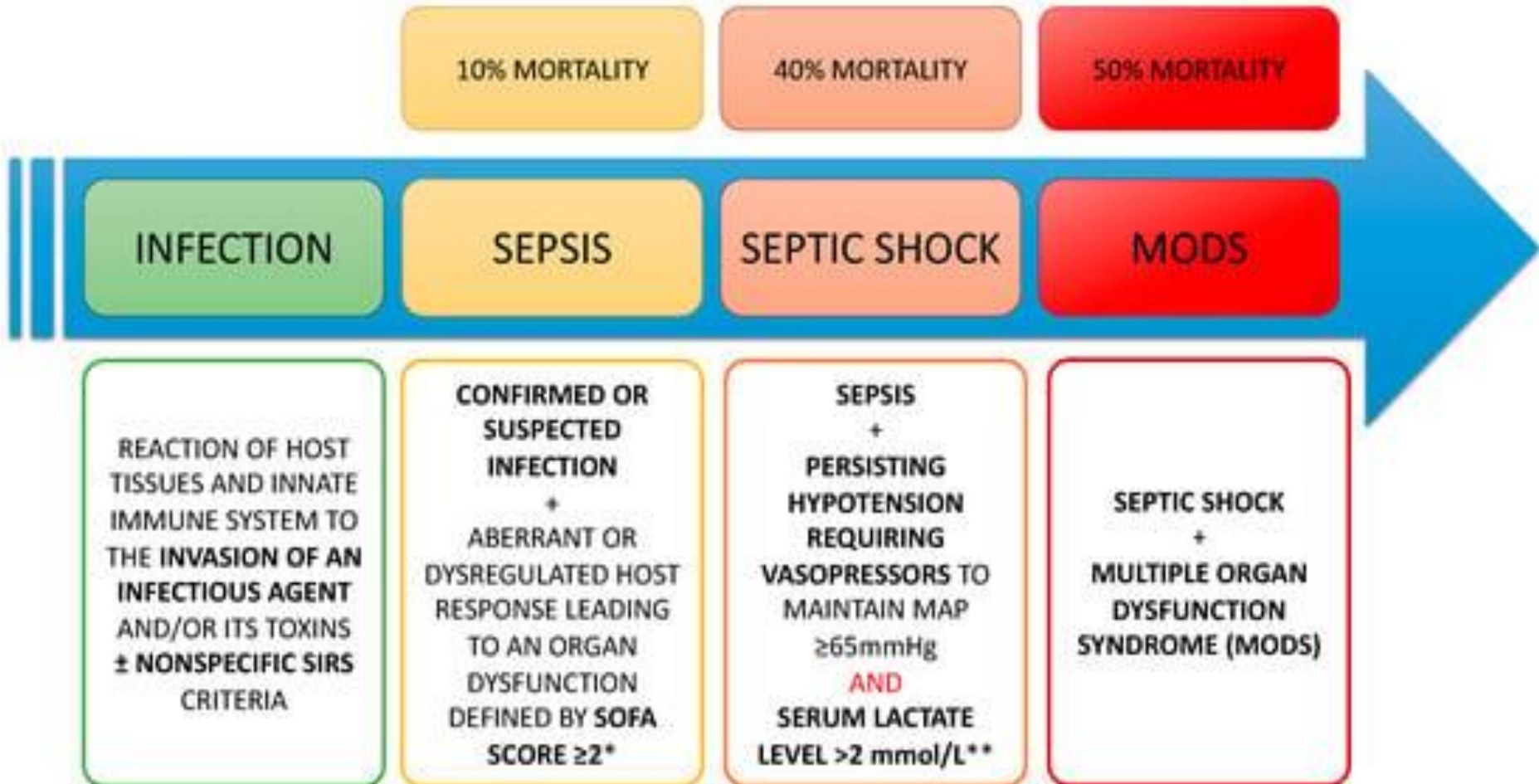
**B** Ratio of IL-10 to a phenotype

# Sepsis endotypes



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# Severity of Sepsis

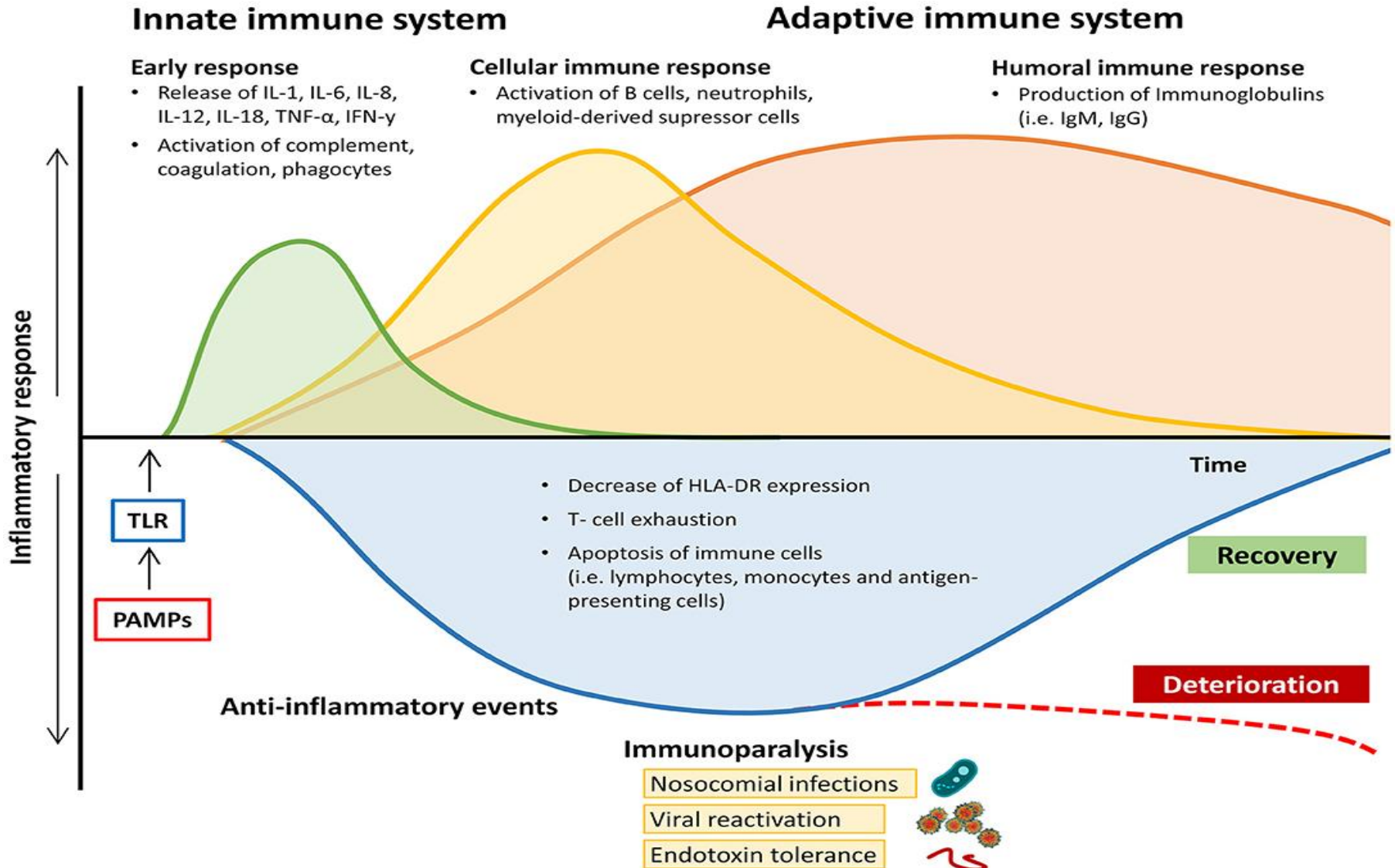


\* or an increase of 2 points compared to the initial value of the SOFA

\*\* Despite adequate volume/fluid resuscitation

- the groups are extremely heterogenous
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- **the inclusion criterias were not clear**
- these treatments still lack a proof of efficacy and some researchers have even found potential harm
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# When to start EBP?



- the groups are extremely heterogenous
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Nature Public Health Emergency Collection

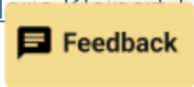
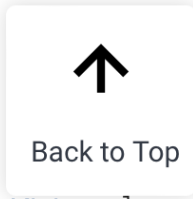
Public Health Emergency COVID-19 Initiative

Intensive Care Med. 2021; 47(11): 1334–1336. Published online 2021 Sep 1.  
doi: 10.1007/s00134-021-06512-0

PMCID: PMC8409473 | PMID: 34471938

Cytokine adsorption in severe, refractory septic shock

Pedro David Wendel Garcia,<sup>1</sup> Matthias Peter Hilty,<sup>1</sup> Ulrike Held,<sup>2</sup> Eva-Maria ...  
and Marco Maggiorini<sup>✉1</sup>



THE LANCET  
Respiratory Medicine

Log in Q ≡

ARTICLES | VOLUME 9, ISSUE 7, P755-762, JULY 2021

Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single centre, open-label, randomised, controlled trial

Alexander Supady, MD • Enya Weber, PhD • Marina Rieder, MD • Achim Lothar, MD • Tim Niklaus, BA • Timm Zahn • et al. Show all authors

Published: May 14, 2021 • DOI: https://doi.org/10.1016/S2213-2600(21)00177-6



Check for updates



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**THINKING OUTSIDE THE BOX: PROCEEDINGS OF A ROUND TABLE CONFERENCE IN BRUSSELS, BELGIUM, MARCH 2010**

## **We should abandon randomized controlled trials in the intensive care unit**

Vincent, Jean-Louis MD, PhD, FCCM



Cite



Share

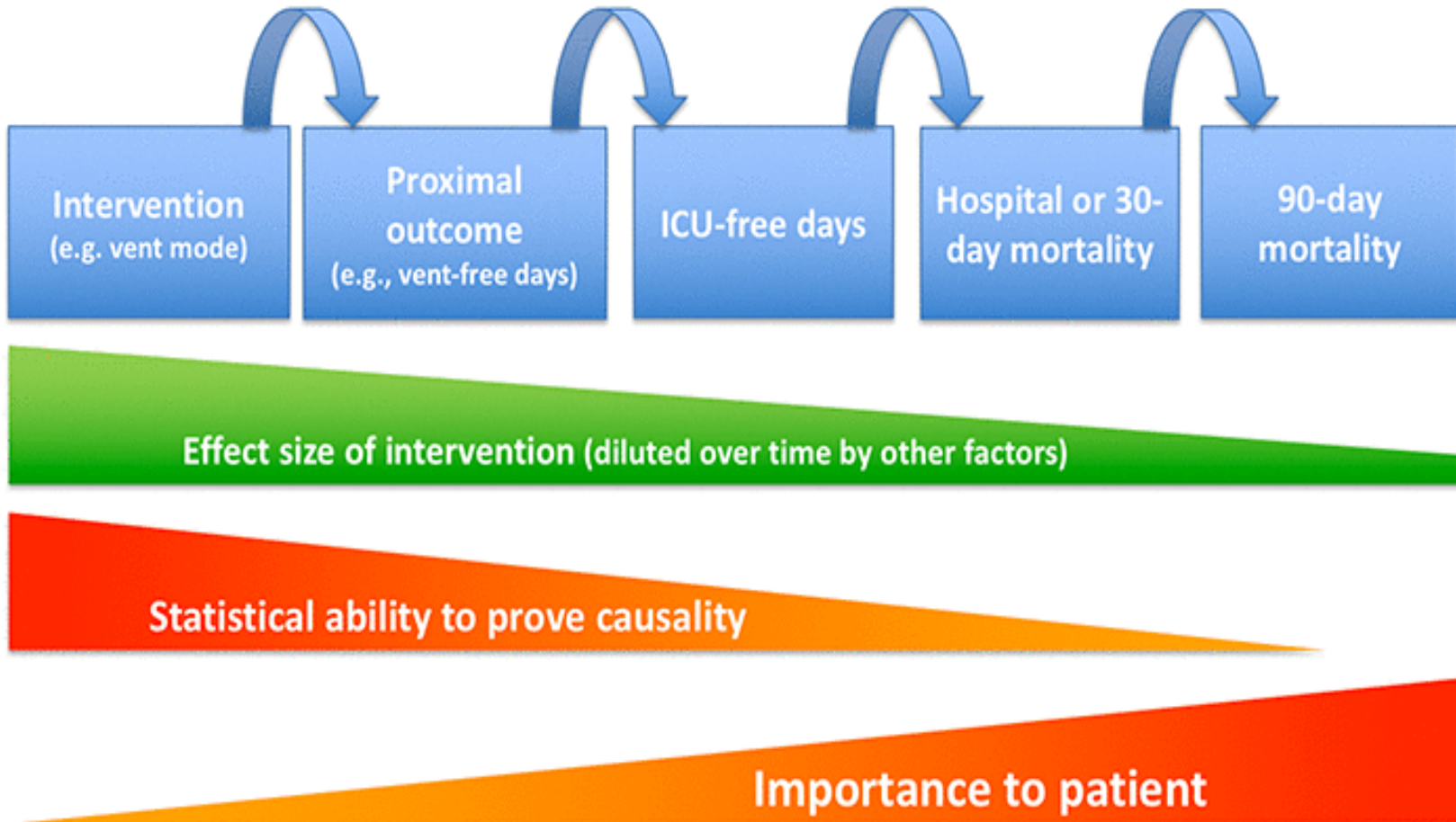


Favorites



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## Mortality endpoint vs. proximal endpoint



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- this is neither a RCT nor a prospective cohort study
- **no single RCT shows any survival benefit for BP**



JAMA Network

# JAMA

View Article ▶

[JAMA](#). 2018 Oct 9; 320(14): 1455–1463.

Published online 2018 Oct 9.

doi: [10.1001/jama.2018.14618](https://doi.org/10.1001/jama.2018.14618)

PMCID: PMC6233793 | PMID: [30304428](https://pubmed.ncbi.nlm.nih.gov/30304428/)

## 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, <sup>1</sup>

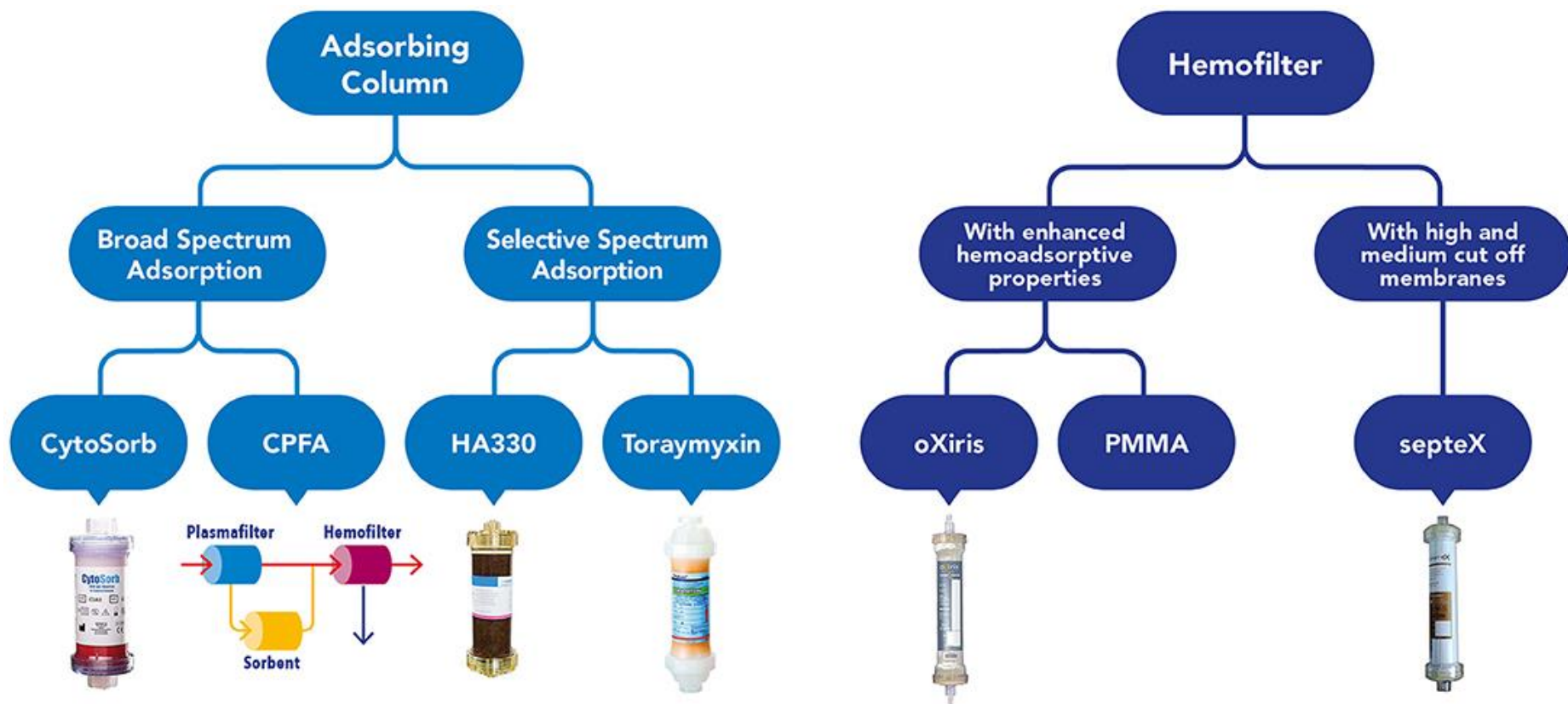
[Sean M. Bagshaw](#), MD, MSc,<sup>2</sup>

[Massimo Antonelli](#), MD,<sup>3</sup> [Debra M.](#)



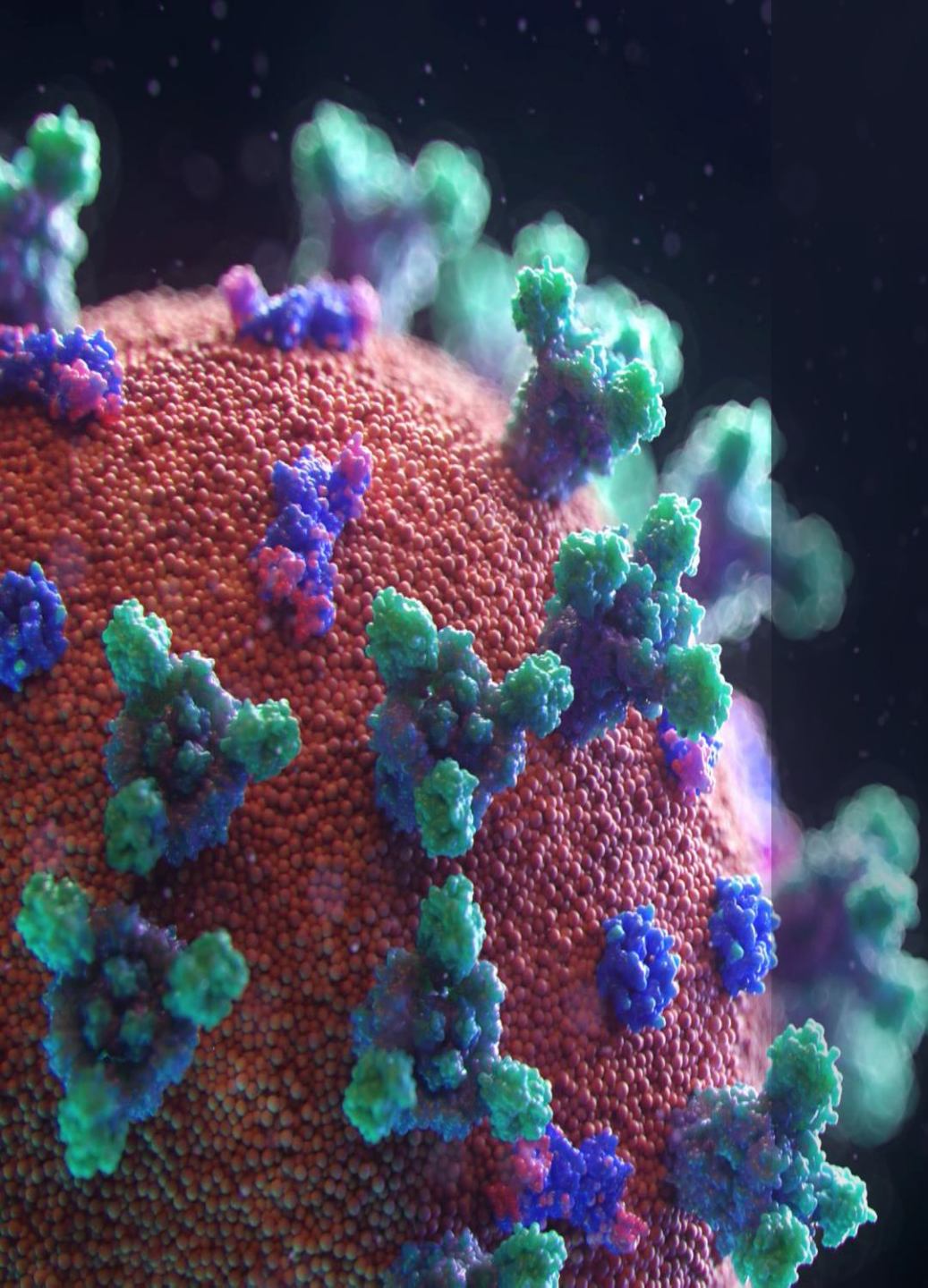
Feedback

# All the possibilities.....









**SOUTH-EASTERN EUROPE  
REGISTRY FOR  
HEMOPERFUSION IN  
COVID-19 ICU PATIENTS  
HERICC**

# HERICC-Outcome Measures

**Main goal:** to investigate the short- and long-term EBP effects on:

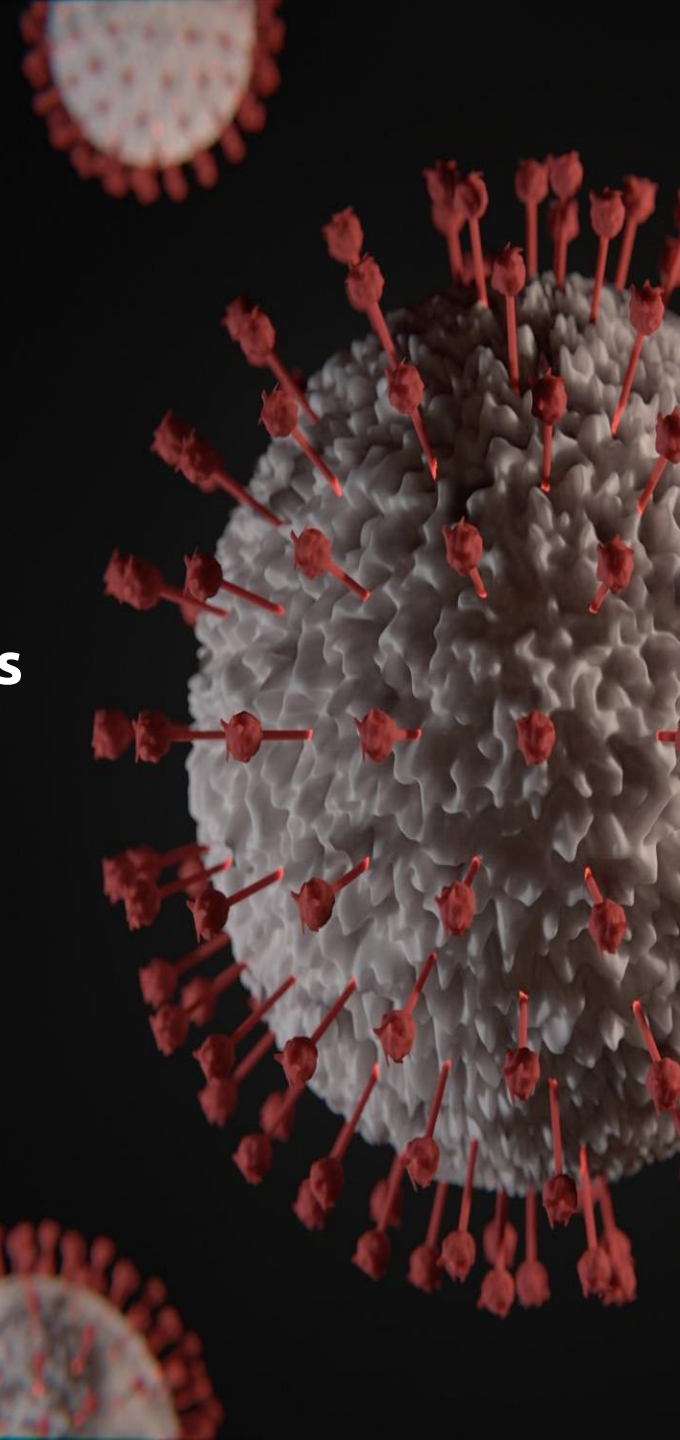
inflammatory (cytokine) removal

clinical recovery (i.e. an improvement in hemodynamic stability, inflammatory status and respiratory status)

**Secondary outcome:**

Define the inclusion criteria for EBP (hemoperfusion) with different filters/hemadsorbers in ICU COVID-19 patients

- overall (ICU) survival



# HERICC REGISTRY

Patients were divided in two groups

A) treated with EBP hemadsorbers

---

B) control group, treated with CRRT or other organ support methods without hemadsorbers (i.e. ECMO, mechanical ventilation, vasopressors...)

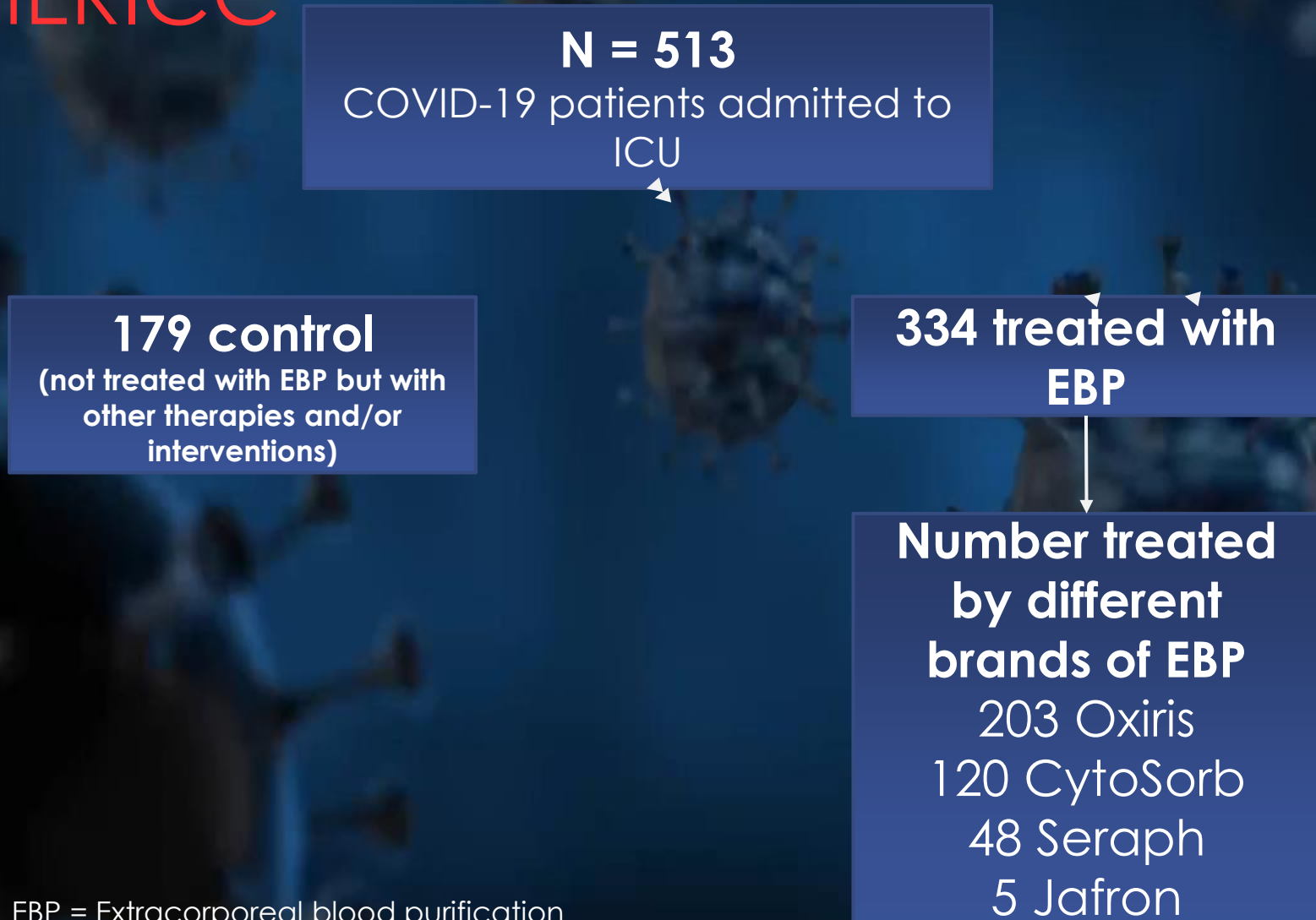
# HERICC REGISTRY



**Preliminary data  
from 10  
Centers:**

**Croatia: 3 (2)**  
**Serbia: 1 (2)**  
**Bosnia: 2**  
**Slovenia: 1 (1)**  
**Montenegro: 1**  
**Greece: 1**  
**Italy: 1**

# Patient flow diagram - HERICC



EBP = Extracorporeal blood purification

# EBP vs. Other Therapies

Model>> Survival ~ EBP + ECMO + CRRT + Mechanical Ventilation

Variable	Odds Ratio (95% Confidence Interval)	p-value
EBP	1.81 (1.16 - 2.85)	0.009
ECMO	1.34 (0.61 - 2.91)	0.463
CRRT	0.62 (0.35 - 1.12)	0.112
Mechanical Ventilation	0.34 (0.22 - 0.53)	<0.001

EBP: No, ECMO: No, CRRT: No, and Mechanical Ventilation: No were used as reference in model

P-values calculated from Wald test

$P < 0.05$

Use of EBP and Mechanical Ventilation are significantly associated with survival. However, EBP is associated with **increased survival** while mechanical ventilation is associated with **decreased survival**.

# EBP with Mech. Vent. adjusting for clinical factors

Model>> Survival ~ EBP + Mechanical Ventilation + **Clinical Factor**

Clinical factors considered\*:

Age, gender, Glasgow score, use of vasoactive therapy, acute kidney injury, diuretic use, and sepsis phenotype

Approach: clinical factor added to model one a time. Those that are stat. sig. were added to final model

Variable	Odds Ratio (95% CI)	p-value
EBP	1.86 (1.21 - 2.89)	0.005
Mechanical Ventilation	0.39 (0.24 - 0.63)	<0.001
Age**	0.66 (0.53 - 0.80)	<0.001
Vasoactive Therapy	0.37 (0.25 - 0.56)	<0.001
Acute Kidney Injury: Yes	0.57 (0.37 - 0.87)	0.010
Acute Kidney Injury: ESRD	1.32 (0.64 - 2.72)	0.452

Interpretation: EBP and Mechanical Ventilation remain significant when adjusted for clinical factors. Use of vasoactive therapy is associated with **decreased survival**. Presence of AKI is associated with **decreased survival** but not ESRD.

- Only clinical factors where data was complete (N=513) were considered to facilitate comparison between models and to avoid dataset size reduction

\*\* Age is a continuous variable, centered by the population mean (63) and scaled by the standard deviation (12.85)

# EBP use and top 5 clinical variables

Survival ~ EBP use + Urea + Comorbidity Index + LDH + APACHE + ARDS Difficulty

Variable	Odds Ratio (95% Confidence Interval)	P-value for odds ratio
EBP use: Yes	1.75 (1.11 - 2.80)	0.018
Urea	0.72 (0.56 - 0.91)	0.008
Comorbidity index	0.82 (0.65 - 1.04)	0.100
LDH	0.70 (0.39 - 0.99)	0.129
APACHE	0.39 (0.28 - 0.53)	< 0.001
ARDS: severe	1.11 (0.36 - 3.73)	0.861

p < 0.05

Interpretation: EBP use, urea levels, APACHE score remain significantly associated with survival in expanded model. 116 patients (out of 513) were removed from analysis due to missing data in one or more variables.

# EBP use and next 5 clinical variables

Survival ~ EBP use + SOFA + pH + Systolic BP + Diastolic BP + Vasoactive Therapy

Variable	Odds Ratio (95% Confidence Interval)	P-value for odds ratio
EBP use: Yes	2.36 (1.53 - 3.71)	<0.001
SOFA	0.62 (0.48 - 0.80)	<0.001
pH	2.62 (1.77 - 3.94)	<0.001
Systolic BP	1.06 (0.82 - 1.38)	0.646
Diastolic BP	1.34 (1.03 - 1.75)	0.031
Use of vasoactive therapy: Yes	0.55 (0.35 - 0.87)	0.011

0.05

Interpretation: EBP use, SOFA score, pH, diastolic BP, and use of vasoactive therapy all remain significantly associated with survival in expanded model..

# EBP and bacterial superinfection

Model >> Survival ~ EBP + Bact. Superinfection + EBP \*  
Bact. Superinfection

Variable	Odds Ratio (95% Confidence Interval)	P-value for odds ratio
EBP: Yes	0.87 (0.55 - 1.37)	0.541
Superinfect.: Yes	0.13 (0.05 - 0.29)	<0.001
EBP: Yes & Superinfect.: Yes	5.09 (2.06 - 13.72)	<0.001

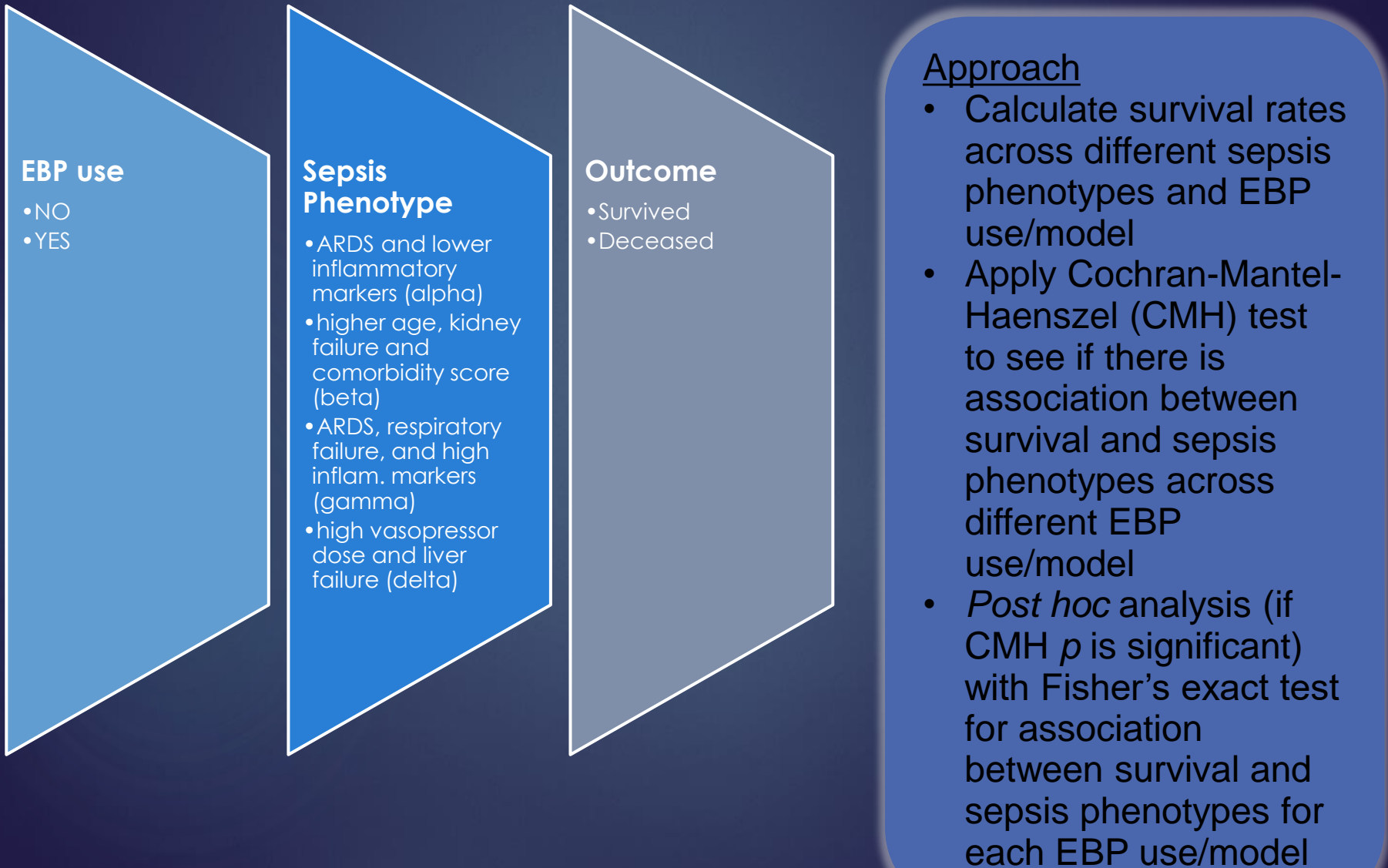
EBP: No and Bact. Superinfection: No were used as reference in model; bact. superfection refers to the subject status one day before EBP initiation (period P2)

P-values for odds ratio calculated from Wald test

P < 0.05

Interpretation: significant interaction between EBP use and bacterial superinfection. Multiple pairwise comparison showed that for patients with bacterial superinfection, those who received EBP treatment had ~1.5 times better odds (p=0.002) of survival compared to those who did not receive EBP treatment.

# Rate of survival by sepsis phenotypes and EBP – description of approach



# Rate of survival by sepsis phenotypes and EBP

Number of survivors / Total number in group (% survived)

EBP Use Yes/No	Sepsis Phenotype			
	Alpha	Beta	Gamma	Delta
No	24/43 (56%)	16/48 (33%)	19/56 (34%)	5/32 (16%)
Yes	41/84 (49%)	30/73 (41%)	46/109 (42%)	27/68 (39%)
<b>Total</b>	<b>65/127 (51%)</b>	<b>46/121 (38%)</b>	<b>65/165 (39%)</b>	<b>32/100 (32%)</b>

p-value calculated by Cochran-Mantel-Haenszel test is 0.033.

**Interpretation:** Cochran-Mantel-Haenszel test shows significant association between sepsis phenotype and survival across the EBP use/model. *Post hoc* Fisher's exact test for EBP use/model indicates that the survival rate is different by sepsis phenotype for only those who did not receive EBP treatment.

1

513 patients analyzed  
(63% of all patients)

2

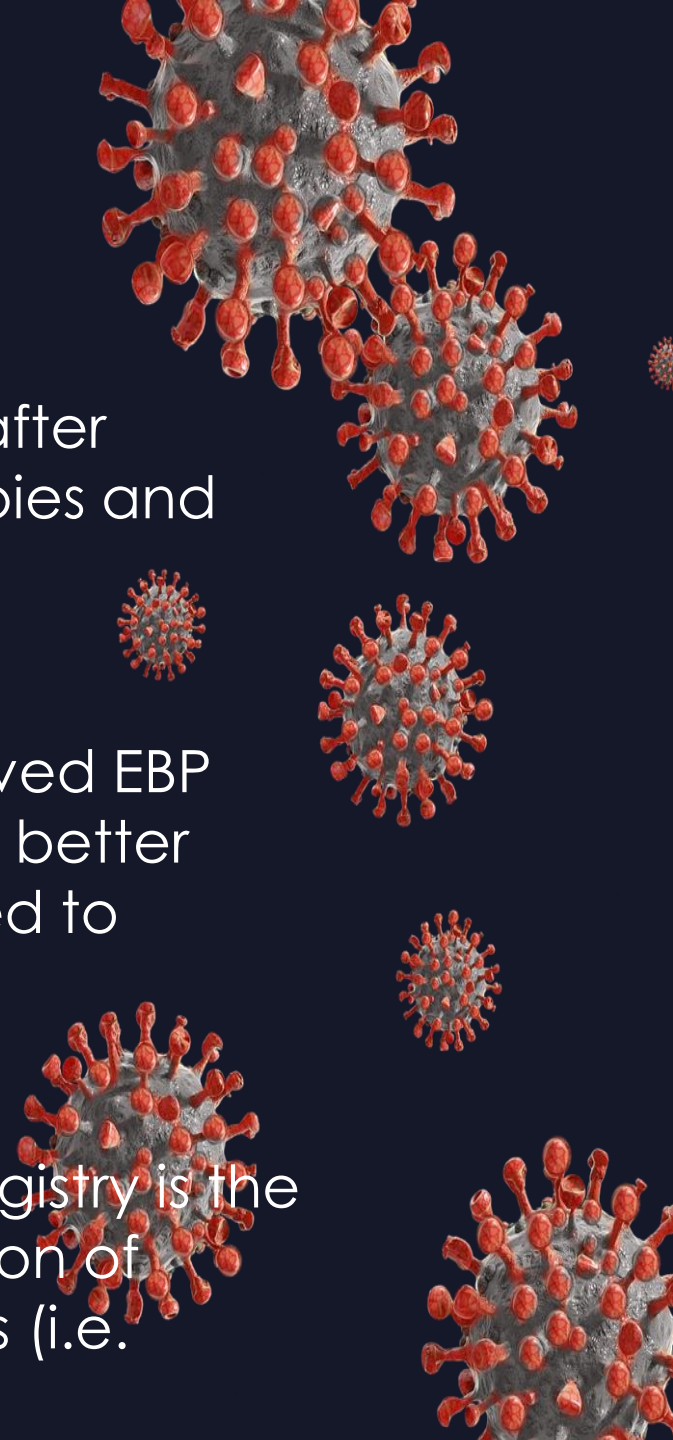
EBP use was significantly  
associated with survival after  
adjusting for other therapies and  
clinical factors

3

Patients with bacterial  
superinfection who received EBP  
treatment had ~1.5 times better  
odds of survival compared to  
those  
without EBP treatment

4

Limitation of the study/registry is the  
missing data on elimination of  
specific target molecules (i.e.  
endotoxins)



# HERICC Registry – 2.nd phase

Data from 35 Centers / 21 Countries:

## Europe:

Croatia: 6      Spain: 1  
Serbia: 3      Portugal: 1  
Bosnia: 2      Germany: 2  
Slovenia: 2      Switzerland: 1  
Montenegro:1      Austria: 1  
Greece: 1      Romania: 1  
Italy: 2      Belgium: 1  
Sweden: 1      France: 1

## World:

USA: 4      Brazil: 1  
Bolivia: 1      Argentina: 1  
Japan: 1

Clin.gov: NCT05470907

Contact:  
vpremuzic@gmail.com

