Sepsis treatment: heroes and villains

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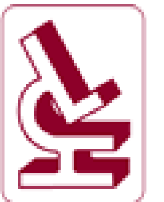
9th Periferal Conference of the Hellenic Haemapheresis Association
Athens - September 30th 2023



Hôpitaux de Lyon

Conflicts of Interest

Scientific partnership with the following companies:

- Baxter
- BBraun
- Biomérieux
- Estor/Toray
- Exthera
- Fresenius Medical Care
- Infomed
- Jafron
- Medtronic
- Nikkiso

Outline

1) Introduction

2)

HEROES	VILLAINS
A	D
B	E
C	F

3) Conclusion

Outline

1) **Introduction**

2)

HEROES	VILLAINS
A	D
B	E
C	F

3) Conclusion

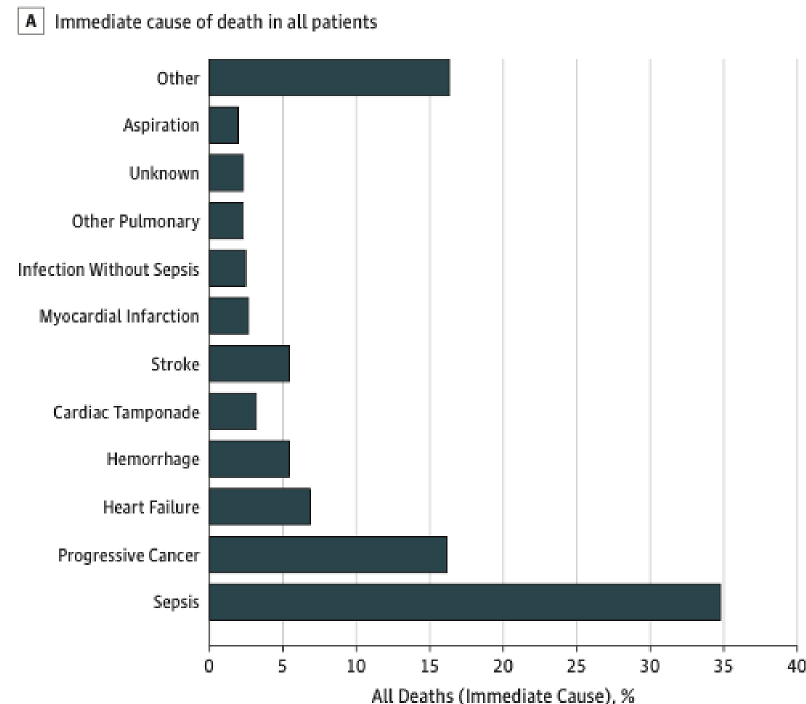
Epidemio: Sepsis = primary cause of death in our ICUs/hospitals

Original Investigation | Critical Care Medicine

Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals

Chanu Rhee, MD, MPH; Travis M. Jones, PharmD; Yasir Hamad, MD; Anupam Pande, MD, MPH; Jack Varon, MD; Cara O'Brien, MD; Deverick J. Anderson, MD, MPH; David K. Warren, MD, MPH; Raymund B. Dantes, MD, MPH; Lauren Epstein, MD, MS; Michael Klompas, MD, MPH; for the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program

Figure 1. Distribution of Causes of Death



Rhee et al. JAMA Netw Open 2019

Epidemio: Sepsis = Twice more deaths as we though…

Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study

Kristina E Rudd, Sarah Charlotte Johnson, Kareha M Agesa, Katya Anne Shackelford, Derrick Tsoi, Daniel Rhodes Kievlan, Danny V Colombara, Kevin S Ikuta, Niranjan Kissoon, Simon Finfer, Carolin Fleischmann-Struzek, Flavia R Machado, Konrad K Reinhart, Kathryn Rowan, Christopher W Seymour, R Scott Watson, T Eoin West, Fatima Marinho, Simon I Hay, Rafael Lozano, Alan D Lopez, Derek C Angus, Christopher J L Murray, Mohsen Naghavi

» Home » News » Sepsis leading cause of death worldwide

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Sepsis leading cause of death worldwide

January 16, 2020

New research published today in *The Lancet* has found that sepsis is responsible for the most deaths worldwide, even more than cancer or coronary disease — previously believed to be the leading causes of death globally.

	Male		Female		Both sexes	
	Incident cases (95% UI)	Age-standardised incidence per 100 000 population (95% UI)	Incident cases (95% UI)	Age-standardised incidence per 100 000 population (95% UI)	Incident cases (95% UI)	Age-standardised incidence per 100 000 population (95% UI)
Infections	15 961 632 (11 416 679–22 490 150)	453·5 (323·5–641·6)	17 165 460 (12 324 759–24 539 248)	482·4 (344·1–695·4)	33 127 159 (24 112 267–45 885 664)	466·8 (337·4–654·8)
Injuries	1 202 056 (916 529–1 548 161)	31·7 (24·2–40·8)	663 329 (494 773–850 850)	17·8 (13·2–23·1)	1 865 358 (1 421 131–2 392 774)	24·7 (18·8–31·7)
Non-communicable diseases	5 567 578 (4 499 826–7 157 847)	157·6 (126·8–203·8)	8 349 730 (6 520 440–11 096 832)	216·4 (167·6–290·8)	13 917 451 (11 313 974–17 629 415)	186·0 (150·0–237·0)
All causes	22 731 266 (18 037 098–29 410 723)	642·8 (507·7–834·8)	26 178 518 (20 630 286–33 702 305)	716·5 (560·2–925·1)	48 909 968 (38 929 606–62 859 320)	677·5 (535·7–876·1)

Data are n (95% UI), unless otherwise stated. UI=uncertainty interval.

Table 1: **Incident cases of sepsis and age-standardised incidence of sepsis, for all ages, both sexes, and all locations, according to category of underlying cause, 2017**

YEAR 2017

- **50 million = number of deaths from all causes worldwide = 1.5 death / second**
- **50 million cases of sepsis diagnosed worldwide. 11 million died of this condition.**
- **Sepsis represents one in five deaths worldwide, twice as many as previously estimated**

Rudd et al. Lancet 2020

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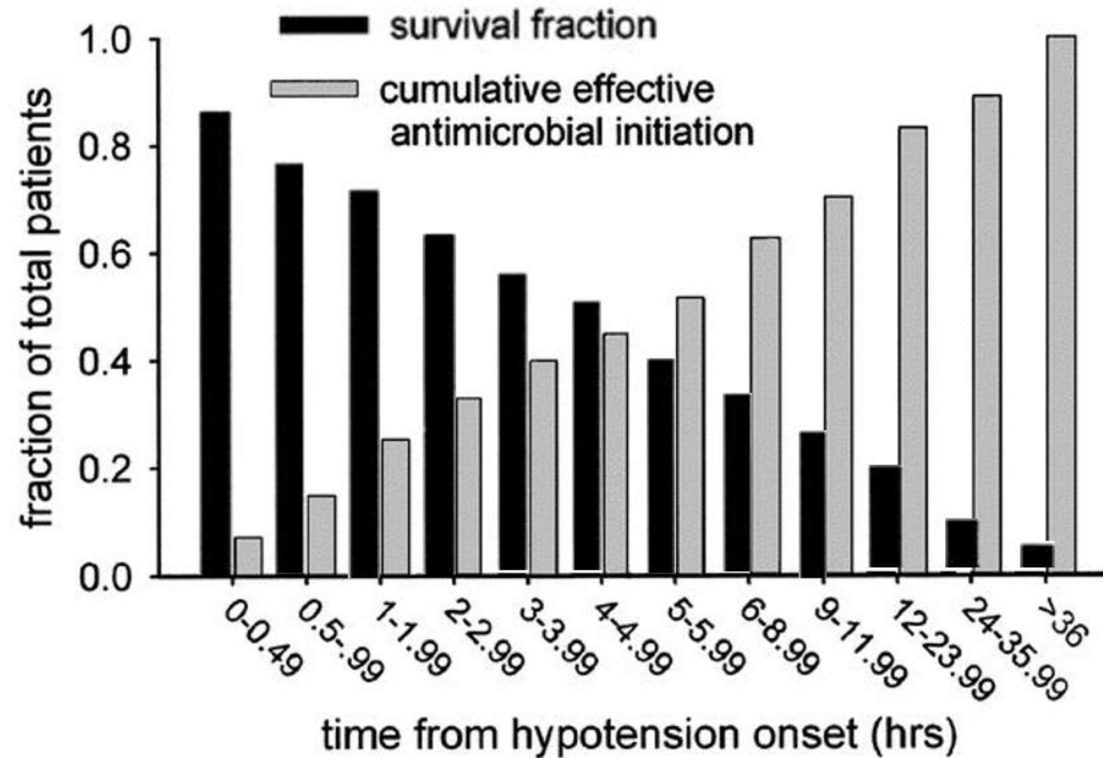
A = The speed of antibiotics administration



Kumar et al. Crit Care Med 2006

B = The rapid and exhaustive organ support management

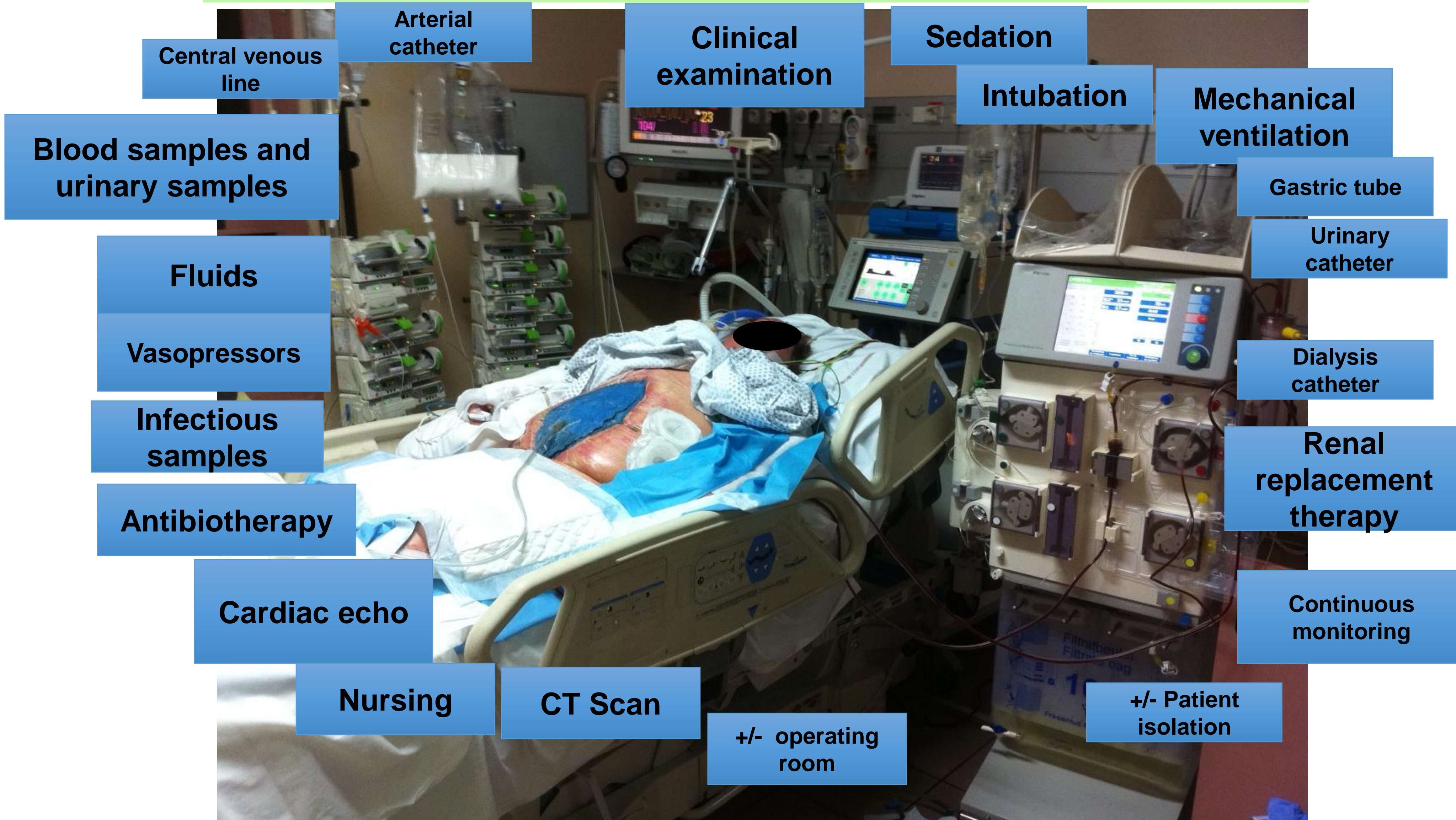
The three cornerstones of sepsis treatment

1) Antibiotherapy
2) Source control
3) Support of organ failures

- Hemodynamic
- Respiratory
- Renal
- Liver
- Coagulopathy
- Neurologic

.....

A patient with septic shock in the ICU…



C = Extracorporeal blood purification techniques ?

HEMOPERFUSION (Sorbents)

PMX-B (Toray/Estor)
Cytosorb (Cytosorbents)
LPS adsorber (Alteco)
HA330, HA380 (Jafron)
MG350 (Biosun)

CRRT filters

high adsorptive hemofiltration (oXiris, Baxter – PMMA, Toray)

high cut-off membranes (Emic2, Fresenius Medical Care)

NEW BLOOD PURIFICATION THERAPIES

(capable of leukocyte or bacteria or virus removal)

Seraph® (Exthera Medical)
FcMBL protein (Opsonix)
Hemopurifier® (Aethlon Medical)
other selective cytapheresis technology…

MISCELLANEOUS, OTHER TECHNIQUES

High-volume hemofiltration/Cascade hemofiltration

Plasma exchanges

Coupled Plasma Filtration Adsorption

C = Extracorporeal blood purification techniques ?

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PMX-B (Toray/Estor)
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MISCELLANEOUS, OTHER TECHNIQUES

High-volume hemofiltration/Cascade hemofiltration

Plasma exchanges

Coupled Plasma Filtration Adsorption

Intensive Care Med (2002) 28:1434–1439
DOI 10.1007/s00134-002-1410-7

ORIGINAL

Rolf Busund
Vladimir Koukline
Uri Utrobin
Edvard Nedashkovsky

Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial

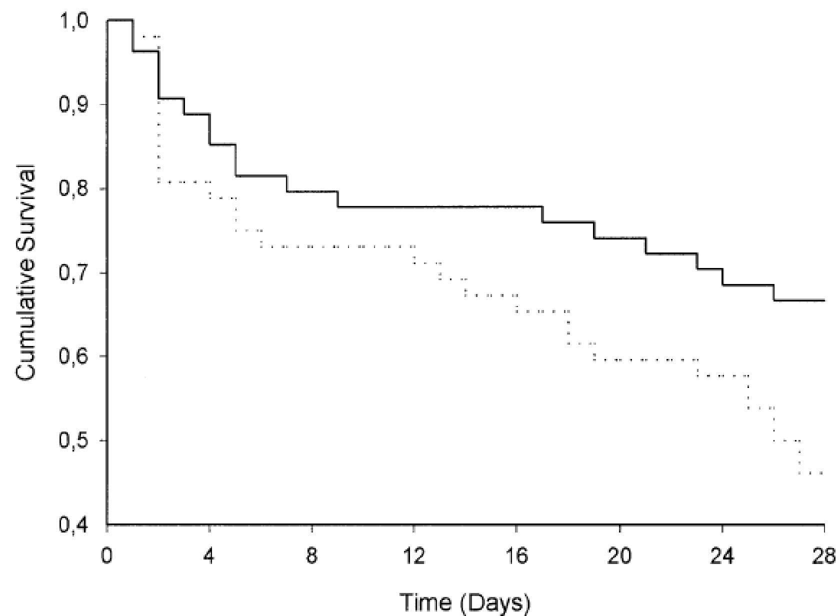


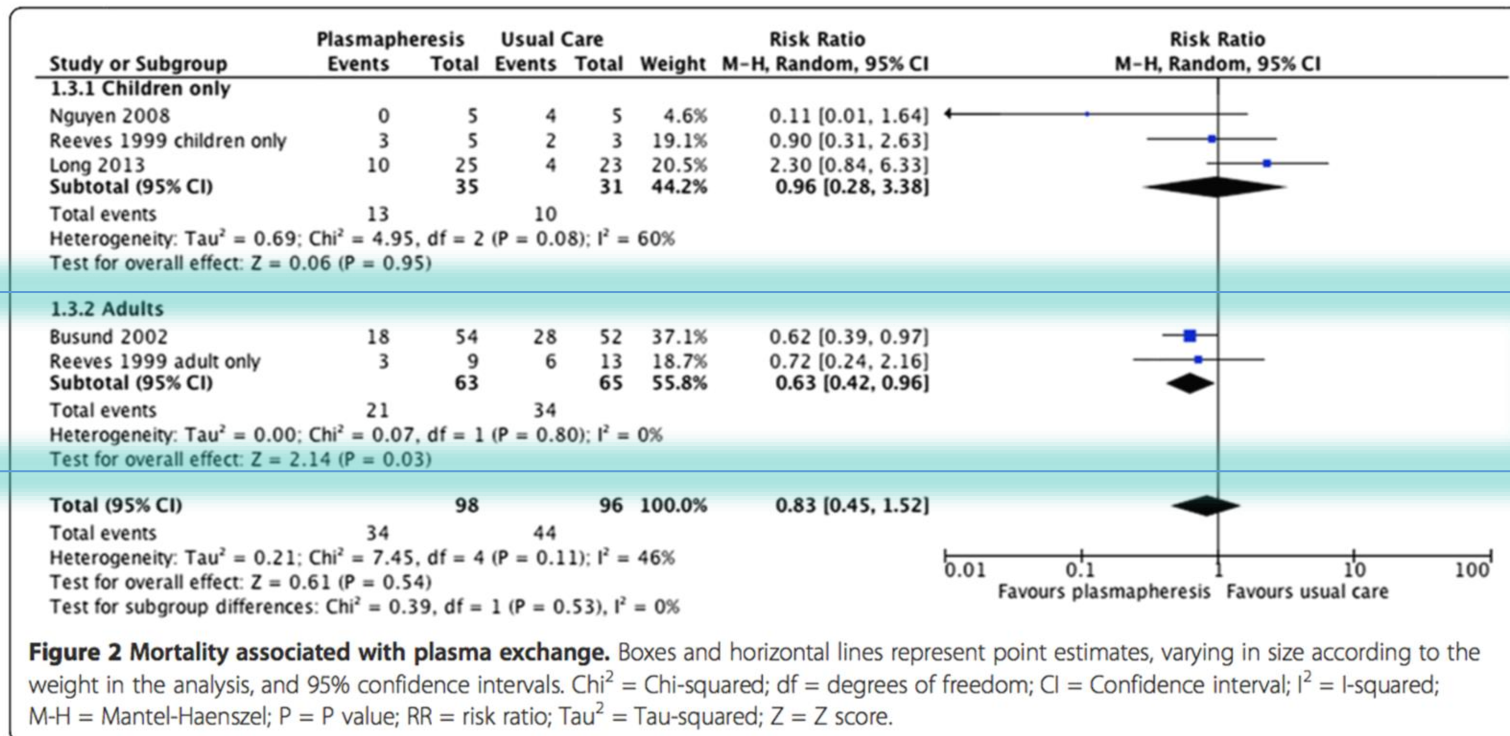
Fig. 1 Cumulative survival in 106 patients with severe sepsis or septic shock randomly assigned to plasmapheresis (*solid line*) or not (*dotted line*) in addition to standard sepsis treatment

Variable[a]	Plasmapheresis (*n*=54)	Control (*n*=52)	*p*
Gender: M/F	34/20	26/26	0.24
Mean age (years)	41±15	48±16	0.03
Septic shock	31 (57%)	28 (54%)	0.84
Mean APACHE III score	56.4±18.8	53.5±15.8	0.40
Mean APACHE III score for respiratory functions			
Respiratory rate	5.2±2.6	4.8±2.8	0.42
PaO_2	3.5±3.5	2.7±3.1	0.24
Site of infection			0.04
Abdominal	33	16	
Lung	3	9	
Urological	2	8	
Skin/soft tissue	5	5	
Female genital	2	7	
Brain	3	4	
Other sites[b]	6	3	

Busund et al. intensive Care Med 2002

The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis

Emily Rimmer[1,2], Brett L Houston[3], Anand Kumar[1], Ahmed M Abou-Setta[4], Carol Friesen[5], John C Marshall[6], Gail Rock[7], Alexis F Turgeon[8], Deborah J Cook[9,10], Donald S Houston[1,2] and Ryan Zarychanski[1,2,4*]



Study or Subgroup	Plasmapheresis Events	Plasmapheresis Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Children only						
Nguyen 2008	0	5	4	5	4.6%	0.11 [0.01, 1.64]
Reeves 1999 children only	3	5	2	3	19.1%	0.90 [0.31, 2.63]
Long 2013	10	25	4	23	20.5%	2.30 [0.84, 6.33]
Subtotal (95% CI)		**35**		**31**	**44.2%**	**0.96 [0.28, 3.38]**
Total events	13		10			
Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 4.95$, df = 2 (P = 0.08); $I^2 = 60\%$						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.3.2 Adults						
Busund 2002	18	54	28	52	37.1%	0.62 [0.39, 0.97]
Reeves 1999 adult only	3	9	6	13	18.7%	0.72 [0.24, 2.16]
Subtotal (95% CI)		**63**		**65**	**55.8%**	**0.63 [0.42, 0.96]**
Total events	21		34			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.07$, df = 1 (P = 0.80); $I^2 = 0\%$						
Test for overall effect: Z = 2.14 (P = 0.03)						
Total (95% CI)		**98**		**96**	**100.0%**	**0.83 [0.45, 1.52]**
Total events	34		44			
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 7.45$, df = 4 (P = 0.11); $I^2 = 46\%$						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: $Chi^2 = 0.39$, df = 1 (P = 0.53), $I^2 = 0\%$						

Figure 2 Mortality associated with plasma exchange. Boxes and horizontal lines represent point estimates, varying in size according to the weight in the analysis, and 95% confidence intervals. Chi^2 = Chi-squared; df = degrees of freedom; CI = Confidence interval; I^2 = I-squared; M-H = Mantel-Haenszel; P = P value; RR = risk ratio; Tau^2 = Tau-squared; Z = Z score.

Rimmer et al. Crit Care 2014

Knaup *et al. Critical Care*
https://doi.org/10.1186/s13054-018-2220-9

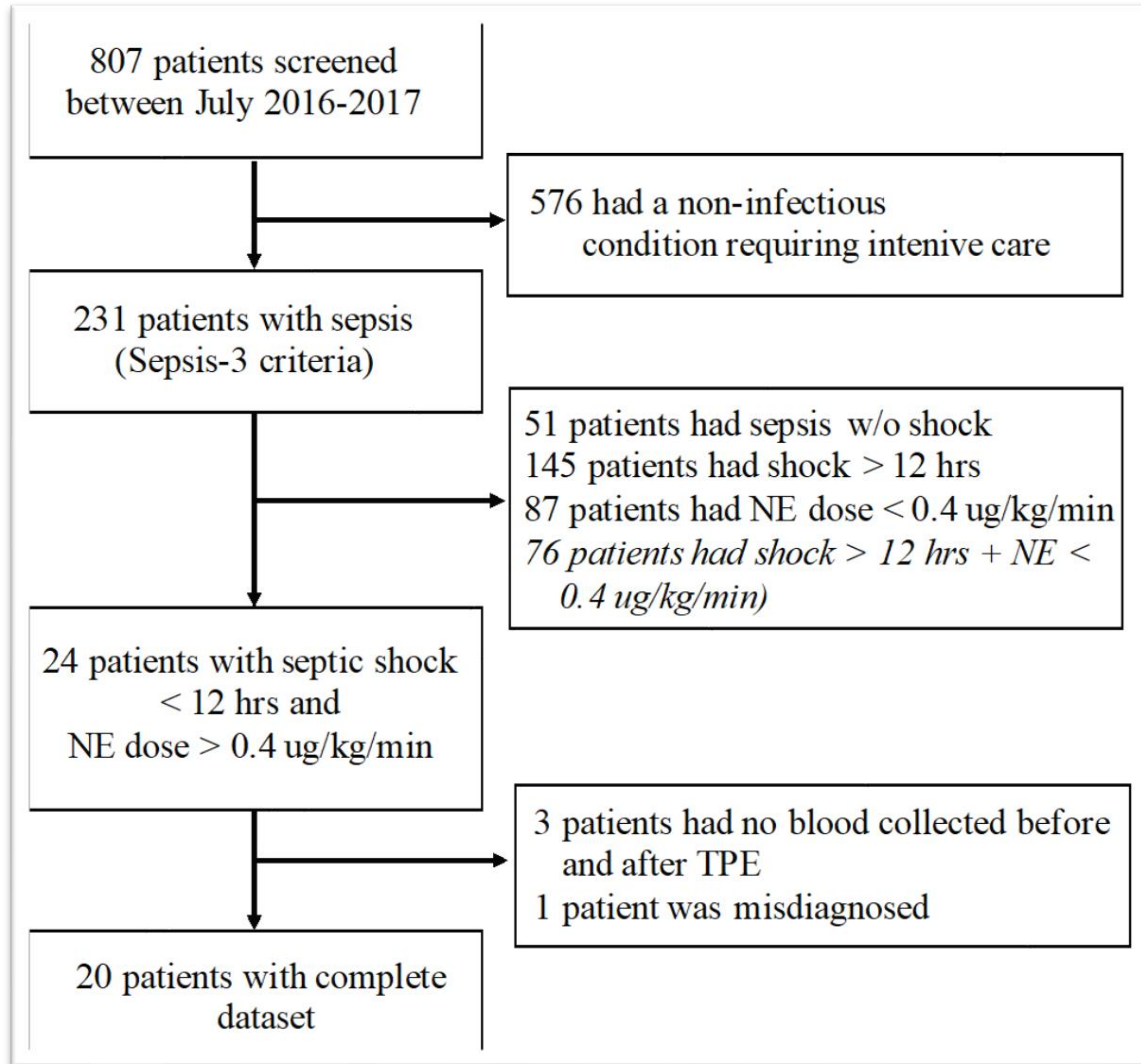
Critical Care

RESEARCH **Open Access**

Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers

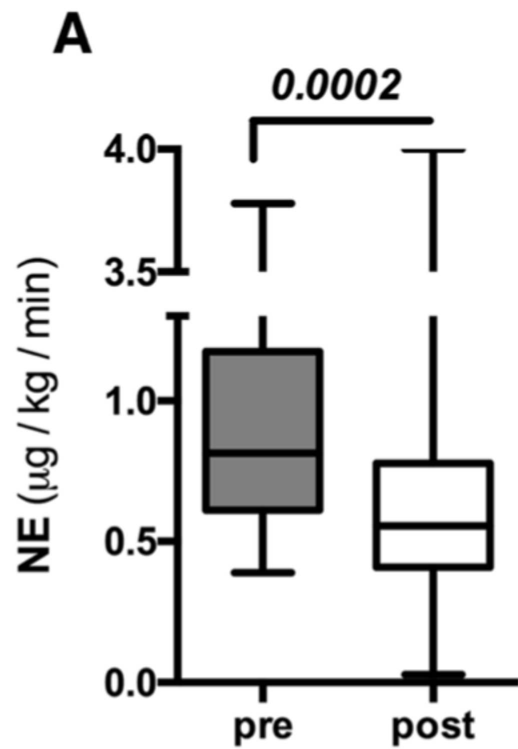
Hannah Knaup[1†], Klaus Stahl[2†], Bernhard M. W. Schmidt[1], Temitayo O. Idowu[1], Markus Busch[2], Olaf Wiesner[3], Tobias Welte[3], Hermann Haller[1], Jan T. Kielstein[4], Marius M. Hoeper[3] and Sascha David[1*]

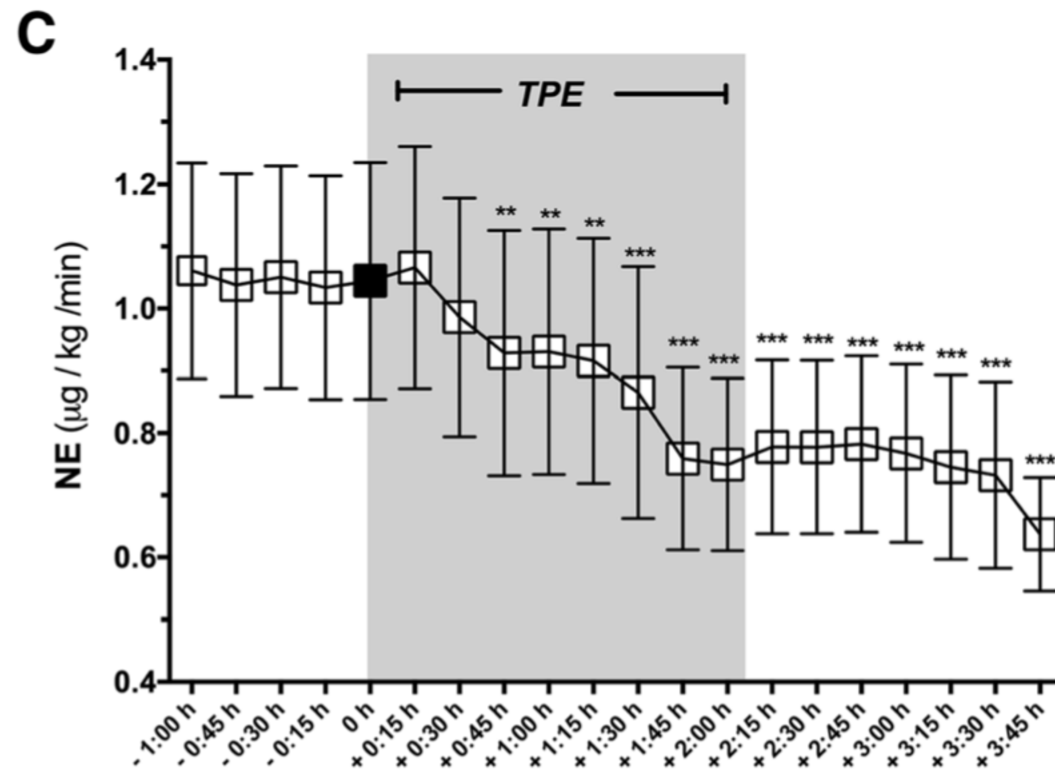
Knaup et al. Crit Care 2018



PARAMETER	VALUE
Age (years)	47.9 +/- 16
BMI	29.2 +/- 11
Side of infection	
pulmonary	55 %
abdominal	20 %
blood stream	5 %
soft tissue	20 %
Organ Failure (n)	3 +/- 1
Mechanical ventilation (%)	100%
pAO2 / FiO2	161 +/- 89
Renal Replacement Therapy	90%
APACHE II	38.2 +/- 4.8
SOFA	17.2 +/- 3.5
Biochemical abnormalities	
CRP (mg/L)	236 +/- 93
PCT	68 +/- 92
Hemodynamics	
Cardiac index (L/m2 bodysurface)	3.1 +/- 1.1
MAD (mmHg)	63 +/- 11
NE (ug/kg/min)	0.81 +/- 0.4
fluid balance -6hrs (L)	3.45 +/- 1.8
Acid Base Status	
pH	7.28 +/- 0.13
pCO2	45 +/- 11
HCO3-	20.3 +/- 4.4

Knaup et al. Crit Care 2018





Knaup et al. Crit Care 2018

Table 2 Changes in clinical and biochemical parameters after TPE

Variable	Therapeutic plasma exchange (TPE)		p value
	Before	After	
Clinical parameters			
MAP (mmHg)	65.5 (54.5–75.3)	69 (64–79.3)	0.07
NE dose (μg/kg/min)	0.82 (0.61–1.17)	0.56 (0.41–0.78)	0.0002*
MAP/NE (mmHg/μg/kg/min)	74.9 (48.5–116.8)	114.3 (75.3–166.7)	< 0.0001*
HR (bpm)	110.5 (91.3–125.5)	103.5 (86.8–119)	0.11
SVV (%)	20 (12.5–29)	11 (6–14.5)	0.008*
SVRI (dyne/s/cm^5/m^2)	1450 (980–1873)	1520 (1060-2126)	0.67
SVRI/NE (dyne/s/cm^5/m^2)/(μg/kg/min)	1743 (1008-2921)	2547 (1213-3923)	0.06
EVLWI (mL/kg)	14 (8–17)	11.5 (8–16.5)	0.93
GEDI (mL/m^2)	670 (483–909)	755 (622–998)	0.12
Cardiac index (L/min/m^2)	2.85 (2.39–4.32)	3.42 (2.71–5.19)	0.39
Fluid balance/6 h (mL)	3411 (2295-4933)	2190 (1431-4060)	0.007*
Gas exchange			
Oxygenation index (PaO_2/FiO_2)	132 (96–229)	115 (102–212)	0.94
$AaDO_2$ (mmHg)	360 (251–541)	329 (247–489)	0.28
Inflammatory biomarkers			
CRP (mg/L)	236 (147–302)	174 (86–288)	0.07
PCT (ng/mL)	24.1 (16.9–83.7)	31 (14.8–87.3)	0.86
WBC (1/nL)	11.2 (0.93–34.8)	8.4 (1.2–25.6)	0.73
PLT (1/nL)	43.0 (16.8–112)	34.0 (20–66)	0.11
INR	1.76 (1.44–2.1)	1.43 (1.26–2.1)	0.16
Acid base balance			
pH	7.28 (7.19–7.34)	7.33 (7.23–7.38)	0.01*
pCO_2 (mmol/L)	44.5 (35.3–56.3)	46 (37–55)	0.99
HCO_3^- (mmol/L)	20.0 (17–23.8)	22.0 (20–24.7)	0.001*
Lactate (mmol/L)	6.5 (2.8–11.3)	6.5 (3.2–10.8)	0.84
Cytokines			
IL-8 (ng/mL)	1.35 (0.6–10.81)	1.09 (0.4–7.1)	0.009*
IL-1b (pg/mL)	147.1 (57.1–241.6)	92.2 (42.9–184.8)	0.01*
IL-6 (ng/mL)	10.8 (2.54–27.6)	4.6 (0.9–13.7)	0.005*
IL-10 (pg/mL)	143.3 (65.5–259.2)	98.1 (59.6–180.4)	0.05

Knaup et al. Crit Care 2018

David and Stahl *Critical Care* (2019) 23:14
https://doi.org/10.1186/s13054-018-2289-1

Critical Care

LETTER **Open Access**

To *remove* and *replace*—a role for plasma *exchange* in counterbalancing the host response in sepsis

S. David[1*] and K. Stahl[2]

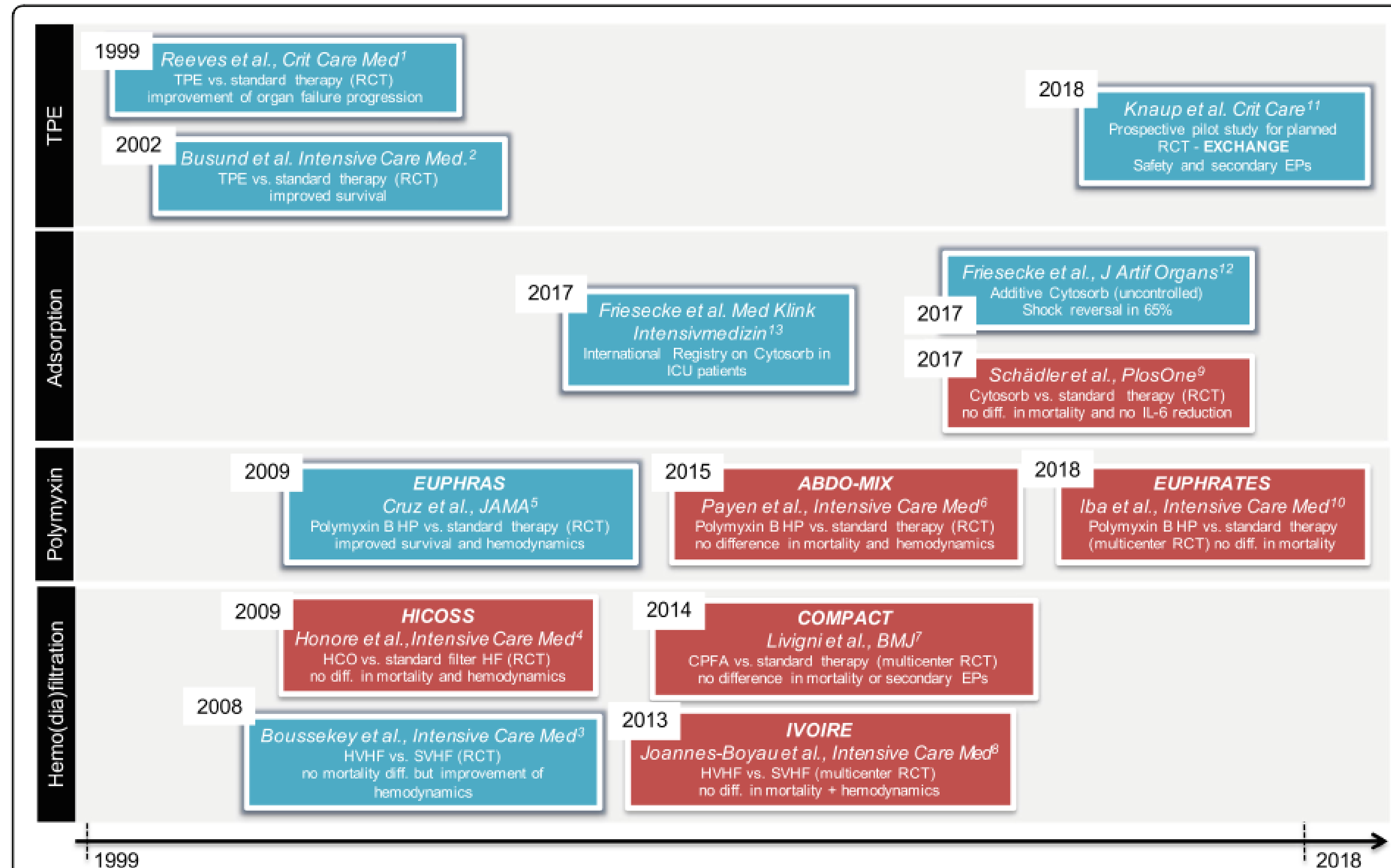


Fig. 1 Timeline of important prospective trials of various extracorporeal therapeutic strategies in sepsis. *Abbreviations*: *TPE* therapeutic

David et al. Crit Care 2019

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Therapeutic plasma exchange in patients with life-threatening COVID-19: a randomised controlled clinical trial

Fahad Faqihi[a], Abdulrahman Alharthy[a], Salman Abdulaziz[a], Abdullah Balhamar[a], Awad Alomari[b], Zohair AlAseri[c], Hani Tamim[d], Saleh A. Alqahtani[e,f], Demetrios J. Kutsogiannis[g], Peter G. Brindley[g], Dimitrios Karakitsos[a,h,i], Ziad A. Memish[j,k,*]

[a] *Critical Care Department, King Saud Medical City, Riyadh, Kingdom of Saudi Arabia*
[b] *Department of Critical Care, Dr Sulaiman Al-Habib Group Hospitals, Riyadh, Saudi Arabia*
[c] *Departments of Emergency Medicine and Critical Care Medicine, King Saud University, Riyadh, Saudi Arabia*
[d] *Biostatistics Unit, Clinical Research Institute, American University of Beirut Medical Center, Beirut, Lebanon*
[e] *Division of Gastroenterology & Hepatology, Johns Hopkins University, Baltimore, MD, USA*
[f] *Liver Transplant Center, and Biostatistics, Epidemiology, and Scientific Computing Department, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[g] *Department of Critical Care, Faculty of Medicine and Dentistry, the University of Alberta, Alberta, Canada*
[h] *Department of Internal Medicine, South Carolina University, School of Medicine, Columbia, SC, USA*
[i] *Critical Care Department, Keck Medical School, University of Southern California, Los Angeles, CA, USA*
[j] *Research & Innovation Centre, King Saud Medical City, Riyadh, Saudi Arabia*
[k] *Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA*

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Survival

SOFA score

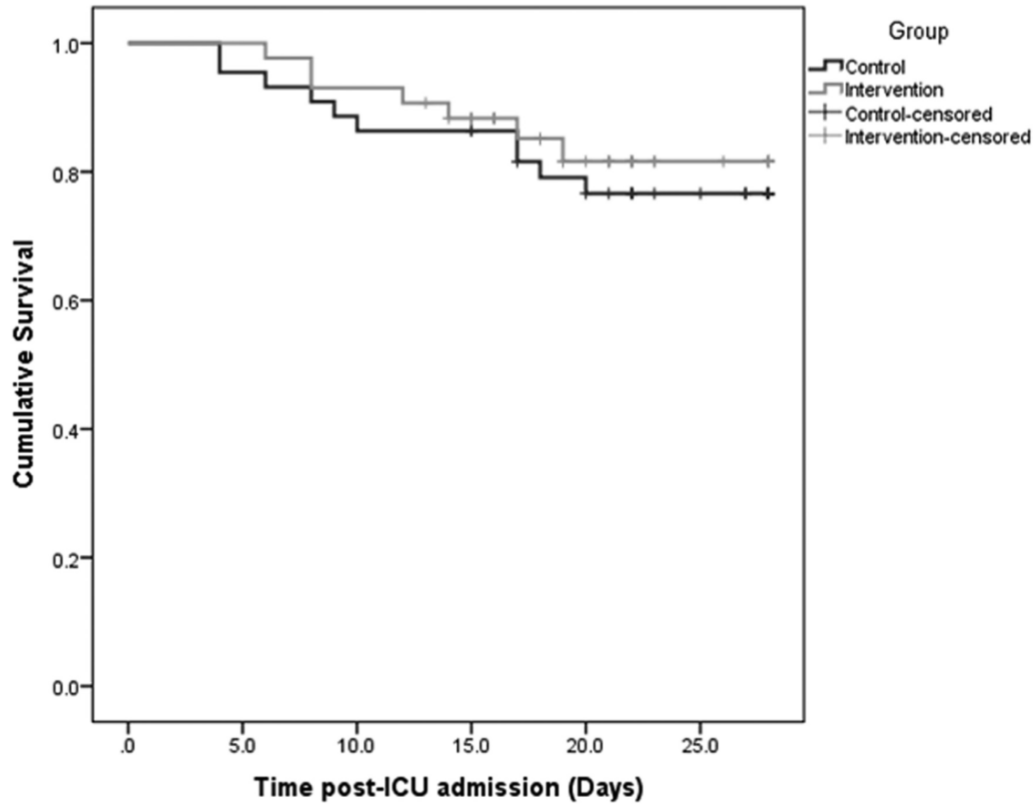

Fig. 2. Kaplan–Meier survival distributions in the intervention and control groups of critically-ill COVID-19 patients (log-rank test, $P = 0.582$; Cox regression model, HR = 0.81, 95% CI 0.35–1.87, $P = 0.62$). HR, hazard ratio; CI, confidence interval.

F. Faqihi, A. Alharthy, S. Abdulaziz et al. International Journal of Antimicrobial Agents 57 (2021) 106334

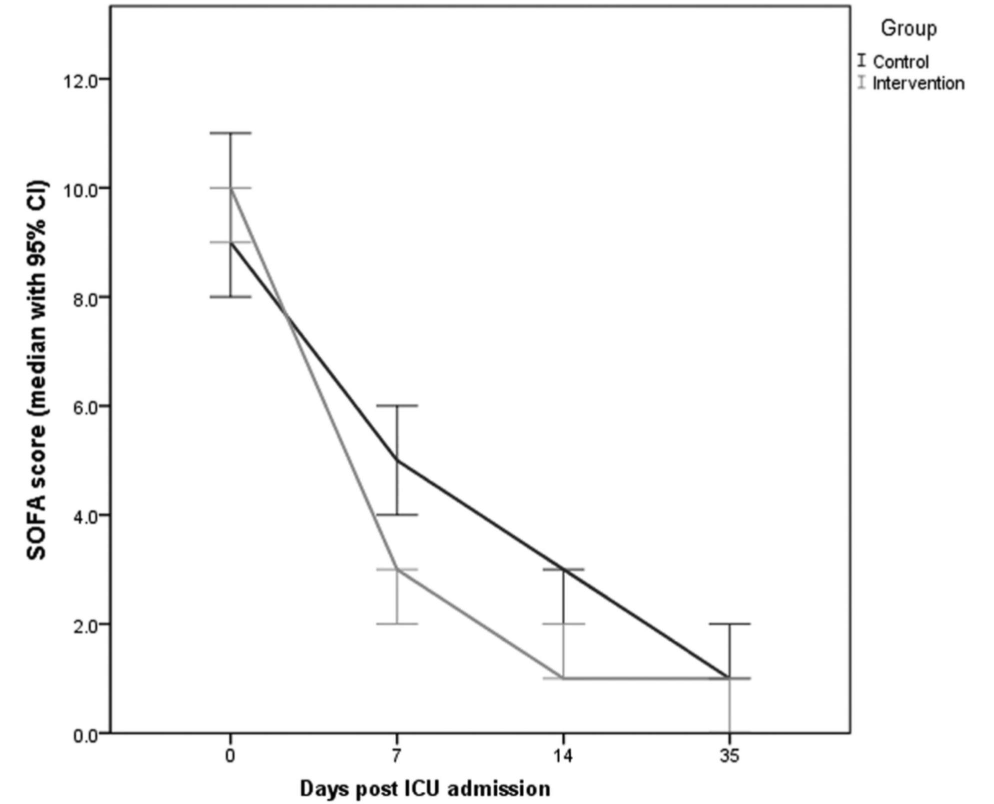

Fig. 3. Post-hoc (repeated measures) analysis of Sequential Organ Function Assessment (SOFA) score (median values with 95% CI) over time (days post ICU admission) for the intervention and control groups of critically ill COVID-19 patients. CI, confidence interval; ICU, intensive care unit.

Faqihi et al. International Journal of antimicrobial agents 2021

Randomized controlled trial (EXCHANGE II)

Bi-centric HANNOVER – BONN, n=40, primary endpoint: hemodynamic after 6 h

LETTER

Adjuvant therapeutic plasma exchange in septic shock

Sascha David[1,2*], Christian Bode[3], Christian Putensen[3], Tobias Welte[4], Klaus Stahl[5] and The EXCHANGE study group

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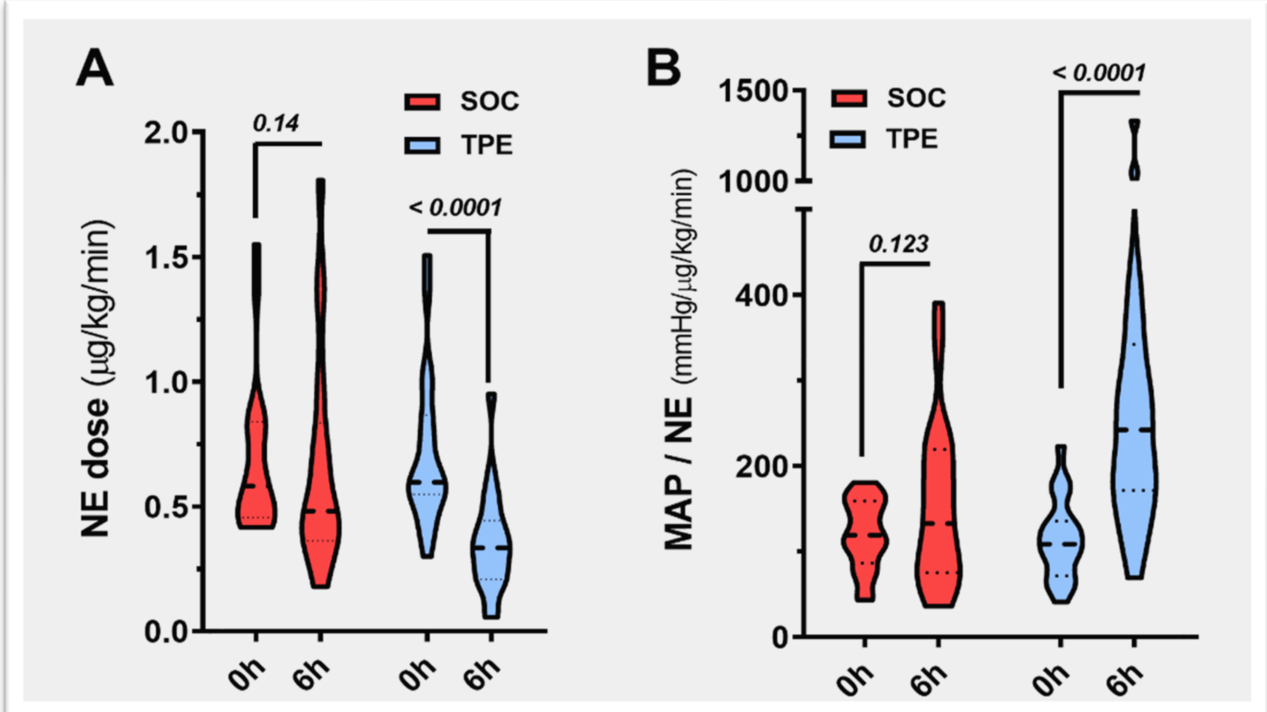
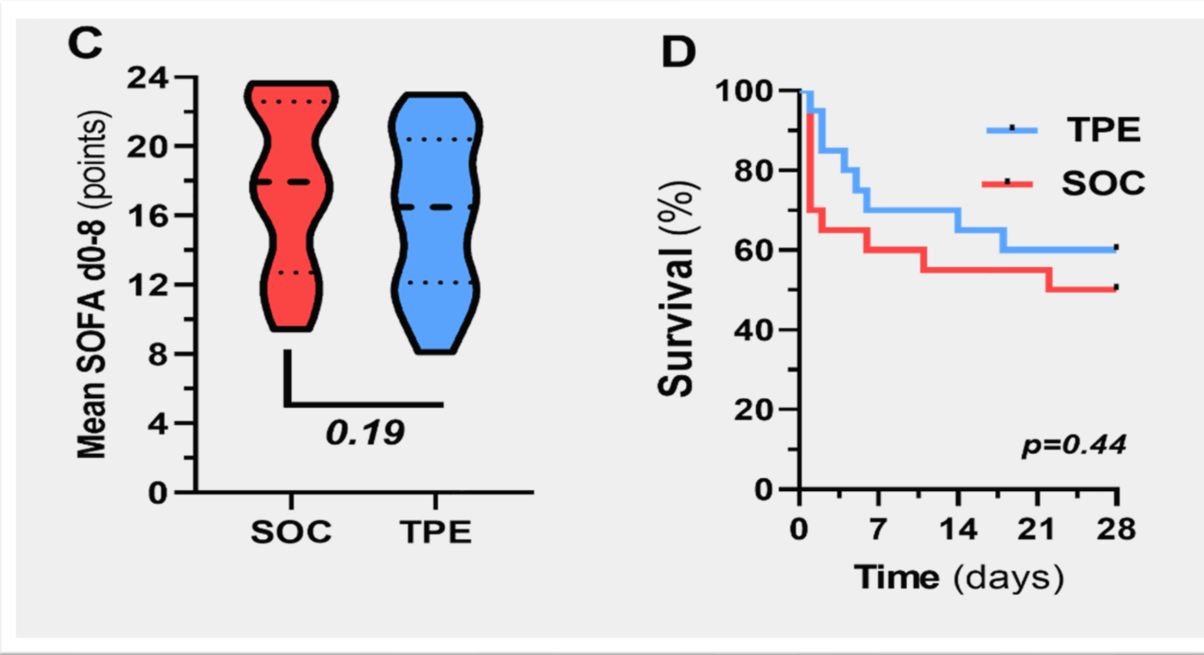




David et al. Intensive Care Med 2021

Stahl *et al. Critical Care* (2022) 26:134
https://doi.org/10.1186/s13054-022-04003-2

Critical Care

RESEARCH Open Access

Clinical and biochemical endpoints and predictors of response to plasma exchange in septic shock: results from a randomized controlled trial

Klaus Stahl[1†], Philipp Wand[2†], Benjamin Seeliger[3], Pedro David Wendel-Garcia[4], Julius J. Schmidt[2], Bernhard M. W. Schmidt[2], Andrea Sauer[5], Felix Lehmann[5], Ulrich Budde[6], Markus Busch[1], Olaf Wiesner[3], Tobias Welte[3], Hermann Haller[2], Heiner Wedemeyer[1], Christian Putensen[5], Marius M. Hoeper[3], Christian Bode[5†] and Sascha David[2,4*†]

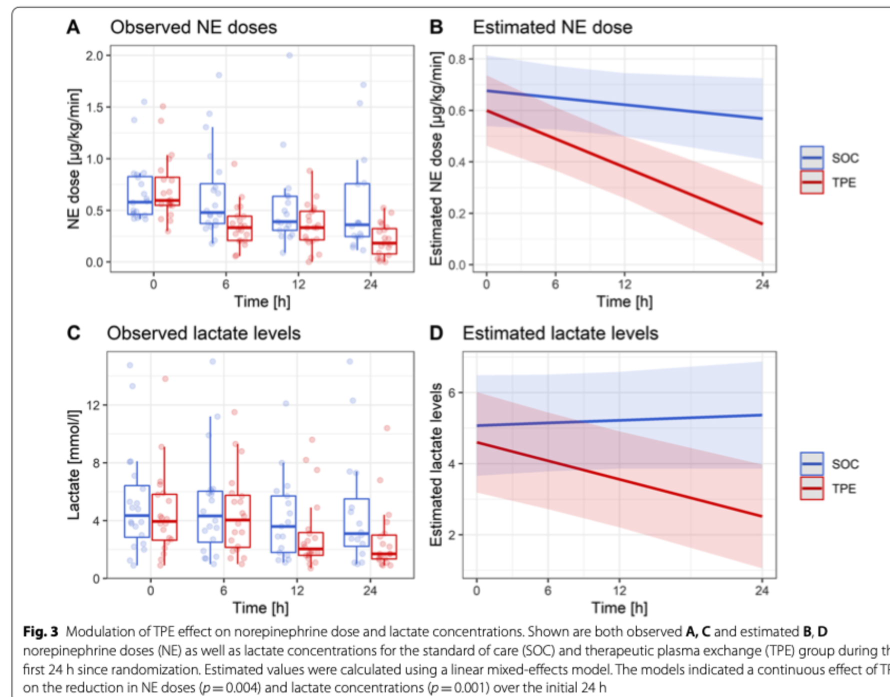


Fig. 3 Modulation of TPE effect on norepinephrine dose and lactate concentrations. Shown are both observed **A, C** and estimated **B, D** norepinephrine doses (NE) as well as lactate concentrations for the standard of care (SOC) and therapeutic plasma exchange (TPE) group during the first 24 h since randomization. Estimated values were calculated using a linear mixed-effects model. The models indicated a continuous effect of TPE on the reduction in NE doses ($p = 0.004$) and lactate concentrations ($p = 0.001$) over the initial 24 h

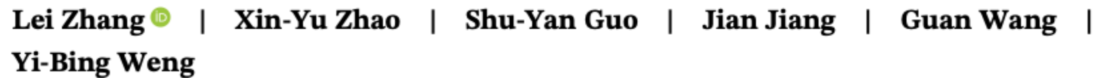
Stahl et al. Crit Care 2022

Received: 15 September 2022 | Accepted: 6 December 2022
DOI: 10.1111/iwj.14059

ORIGINAL ARTICLE

IWJ WILEY

An inquiry into the treatment of sepsis using plasma exchange therapy: A systematic review and meta-analysis


Lei Zhang | Xin-Yu Zhao | Shu-Yan Guo | Jian Jiang | Guan Wang | Yi-Bing Weng

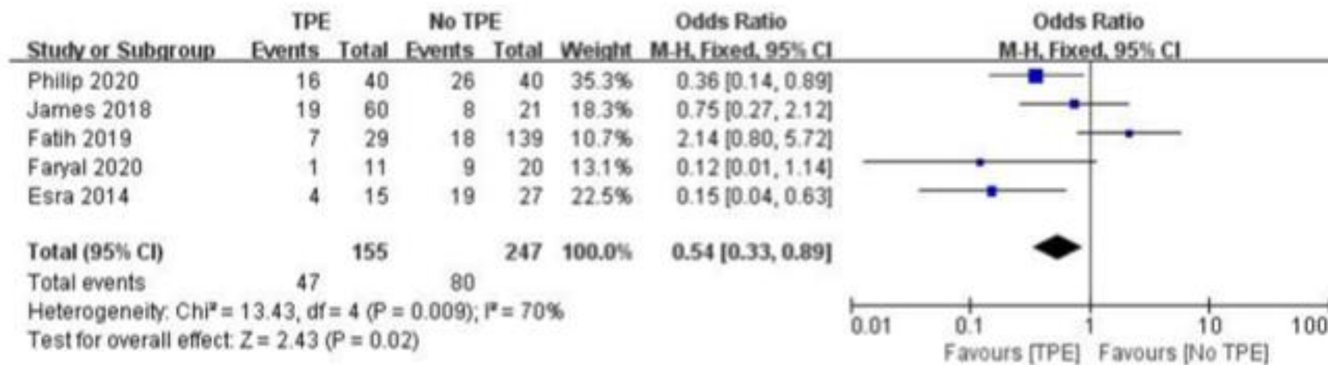


FIGURE 2 Mortality associated with plasma exchange. Boxes and horizontal lines represent point estimates, varying in size according to the weight in the analysis, and 95% confidence intervals. Chr2 = Chi-squared; df = degrees of freedom; CI = Confidence interval; I^2 = I-squared.

5 | CONCLUSION

Plasmapheresis appears to be an effective treatment for patients with sepsis, but a large number of RCTs are still needed to confirm this notion.

Zhang et al. Int Wound J 2023

C = Extracorporeal blood purification techniques ?

HEMOPERFUSION (Sorbents)

PMX-B (Toray/Estor)
Cytosorb (Cytosorbents)
LPS adsorber (Alteco)
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MG350 (Biosun)

CRRT filters

high adsorptive hemofiltration (oXiris, Baxter – PMMA, Toray)

high cut-off membranes (Emic2, Fresenius Medical Care)

NEW BLOOD PURIFICATION THERAPIES

(capable of leukocyte or bacteria or virus removal)

Seraph® (Exthera Medical)
FcMBL protein (Opsonix)
Hemopurifier® (Aethlon Medical)
other selective cytapheresis technology…

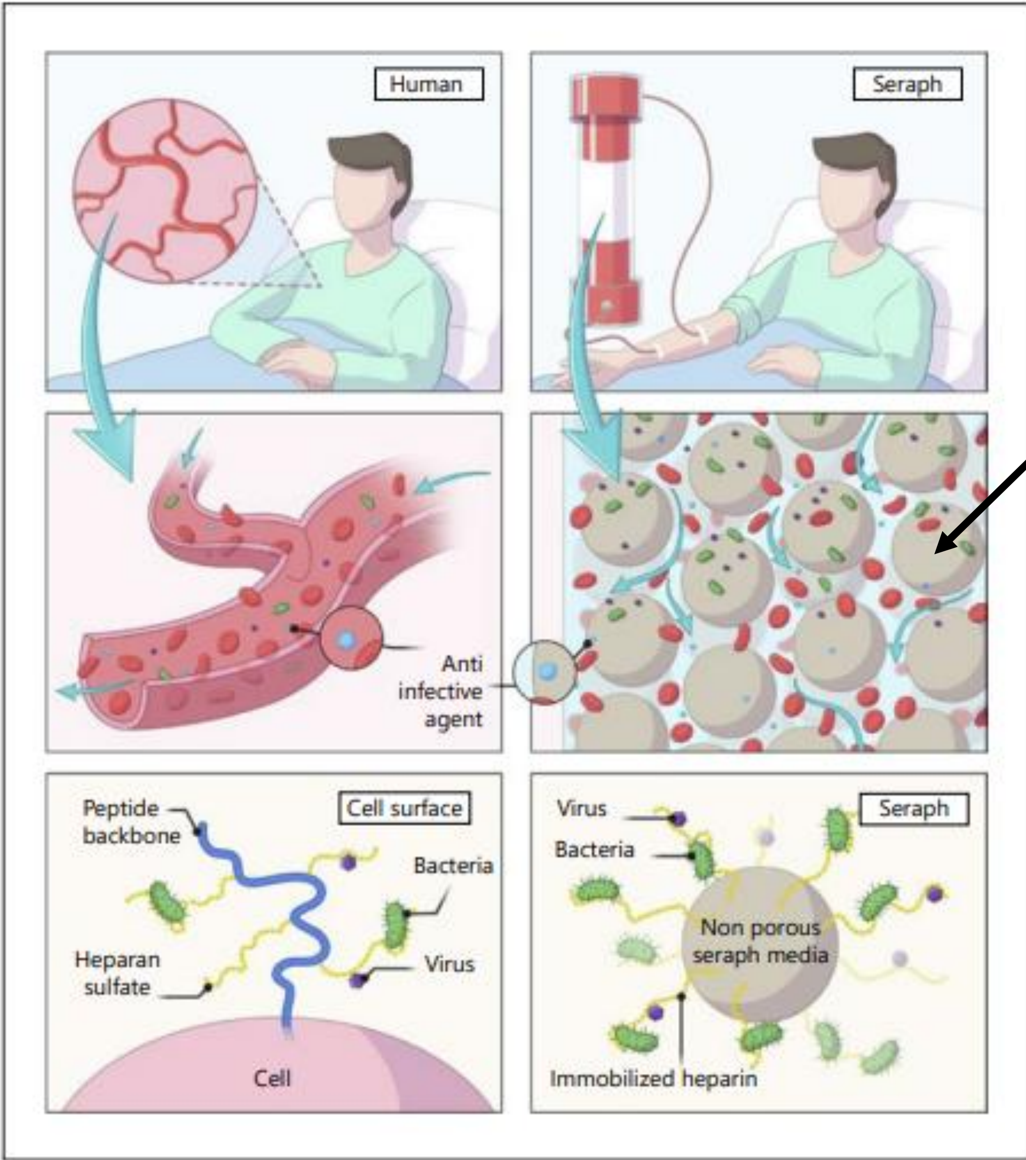
MISCELLANEOUS, OTHER TECHNIQUES

High-volume hemofiltration/Cascade hemofiltration

Plasma exchanges

Coupled Plasma Filtration Adsorption

Removing Pathogens : the Seraph® 100 Microbind Affinity adsorber



Polyethylene beads

Seffer et al. Blood Purif 2021

Removing Pathogens : the Seraph® 100 Microbind Affinity filter

Binding Results from Independent Laboratories

Drug-Resistant Bacteria	Gram Positive Bacteria	Gram Negative Bacteria	Viruses, Fungi, and Toxins
MRSA	*S. aureus*	*E. coli*	HSV-1, HSV-2, CMV, Adenovirus, Ebola
CRE - *E. coli* and *K. pneumoniae*	*S. pneumoniae*	*K. pneumoniae*	*C. albicans*
ESBL - *K. pneumoniae*	*E. faecalis*	*Acinetobacter. baumannii*	LPS/Endotoxin*
VRE - *E. faecalis*	*E. faecium*	*P. aeruginosa**	*S. a.* α-hemolysin, Anthrax 'protective antigen'

Considered "URGENT THREAT" by CDC | Considered "SERIOUS THREAT" by CDC

Removal of Carbapenem-Resistant Enterobacteriaceae

	Test Medium	Starting Concentration (CFU/ml)	% Removed by 0.6 grams of media	Adsorbed Bacteria (CFU/g media)
E. coli ATCC 8739	2 ml Defibrinated Blood	6.15E+05	99.75	2.04E+06
K. pneumoniae ATCC 13883		4.02E+05	36.43	4.88E+05
E. coli ATCC BAA-2469 (CRE)		2.57E+05	99.93	8.56E+05
K. pneumoniae ATCC BAA-2146 (CRE)		1.40E+05	99.94	4.66E+05

Mc Crea et al. Plos One 2014

Seraph® 100 PURIFY OBS Preliminary COVID-19 Outcome Data (US): April 26, 2021

A Multicenter Evaluation of Blood Purification with Seraph-100 Microbind Affinity Blood Filter for the Treatment of Severe COVID-19: A Preliminary Analysis

Stephen A. Chitty, MD[1]; Sarah Mobbs, FNP-BC[1]; Brian S. Rifkin, MD[2]; Steven W. Stogner, MD[2]; Andrew M. Wilhelm, DO[3]; Michael S. Lewis, MD[4]; Jaime Betancourt, MD[4]; Jeffrey DellaVolpe, MD[5]; Fadi Abouzahr, MD[5]; Harold M. Szerlip, MD[6]; Robert M. Gaeta, DO[7]; Ian Rivera, MD[7]; James D. Oliver, MD, PhD[8]; Stephen W. Olson, MD[8]; Subrata Debnath, MBBS, MPH, PhD[9]; Sean P. Barnett, MD[9]; Amay Parikh, MD[10]; Robert J. Walter, MD[11]; Mai T. Nguyen, MD[11]; Breandan Sullivan, MD[12]; Karl C. Alcover, PhD[13]; Ian J. Stewart, MD[13]; Kathleen P. Pratt, PhD[13]; Kumar Sharma, MD[9]; Kevin K. Chung, MD[13] for the PURIFY Investigators

Design: Prospective observational patient registry[3]

- Primary Endpoint: Time spent on medications used to increase blood pressure
- Secondary Endpoints: Time on mechanical ventilation, ICU LOS, Hospital LOS, Time spend on dialysis, Mortality
- 99 patients included in preliminary preprint publication
- **Mortality was much lower in the Seraph 100 treated group compared to the historical controls: 37.7% vs. 67.4% respectively (p=0.003)**
- Multivariable logistic regression analysis yielded an odds ratio of 0.27 (95% confidence interval 0.09- 0.79, p=0.016): **Nearly 4X improvement in survivability odds when severely ill COVID-19 patients are treated with Seraph 100**
- **Significant reduction of 10.5 median ICU LOS compared to matched controls (p = 0.052)**
- These results support the 2021 launch of a US multicenter randomized controlled feasibility trial of the Seraph 100 for septic shock due to any pathogen

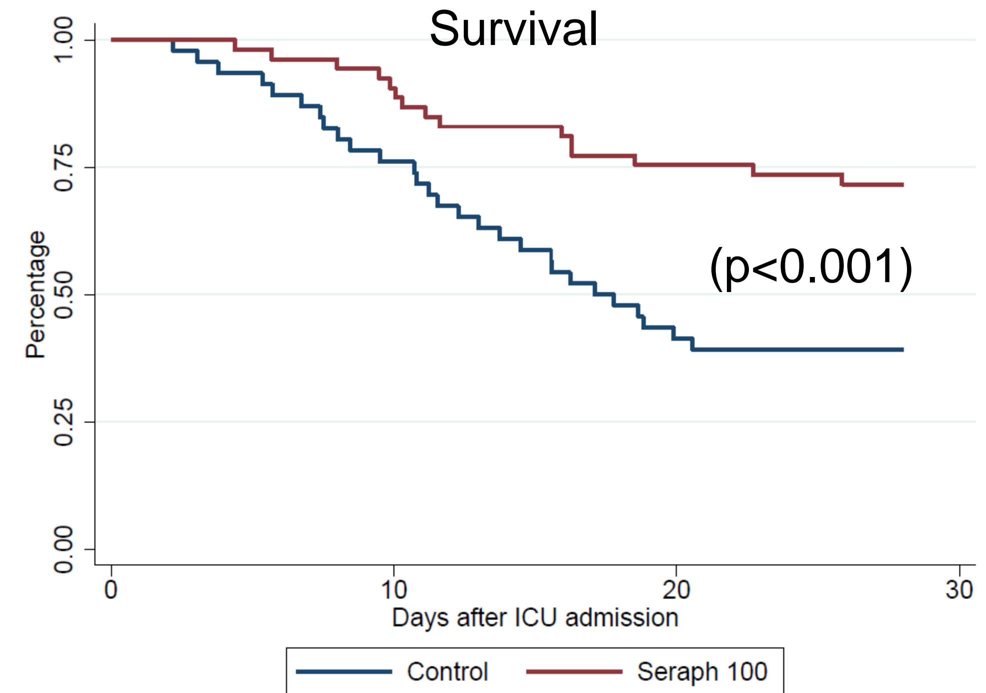


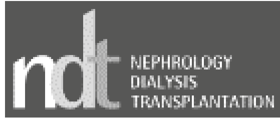
Table 2. Outcomes stratified by study cohort

	Treatment	Control	P value
Mortality (%)	37.7	67.4	0.003
ICU-free days, Median (IQR)[a]	10.5 (0-19.5)	0 (0-12.5)	0.052
RRT dependent at discharge (%)[b]	0	9.4	0.541
Hospital length of stay (day), Median (IQR)[b]	17 (10-35.5)	15 (5-32)	0.170

RRT= renal replacement therapy
[a]Data available for 88 subjects
[b]Among survivors, data missing for one study subject

9. Chitty et al, A Multicenter Evaluation of Blood Purification with Seraph 100 Microbind Affinity Blood Filter for the Treatment of Severe COVID-19: A Preliminary Report, (2021);

Seraph® 100 Prelimanary Outcome Data COVID-19: COSA COVID-19 Patient Registry (EU)



Interim-analysis of the COSA (COVID-19 patients treated with the Seraph® 100 Microbind® Affinity filter) registry

Julius J Schmidt, Dan Nicolae Borchina, Mariet van ´t Klooster, Khalida Bulhan-Soki, Reuben Okioma, Larissa Herbst, Diego Sandoval Rodríguez, Vedran Premužić, Stefan Büttner, Birgit Bader, Wojciech Serednicki, Ewa Zasada, Michael Schmitz, Ralf A Quabach, Maria Hrincheva, Thomas Führer, Jan T Kielstein ✉

Nephrology Dialysis Transplantation, gfab347, https://doi.org/10.1093/ndt/gfab347

Published: 07 December 2021

Design: Prospective multicenter observational study[20]

- Primary Endpoint: Overall 30-day survival after Seraph 100 therapy session
- Secondary Endpoints: Adverse events, clotting rates, time to ICU discharge
- 82 Patients documented to-date (Median SOFA Score: 9)
- **Significant survival improvement for Seraph treatment(s) initiated <60 hrs (2.5 days) after ICU admission** (1.73 [1.5-3.2] vs. 4.58 [2.05-11.4] days p=0.0023)
  - → 34.5% vs. 62.5% ICU mortality (p=0.04)
- 66.7% Patients treated on mechanical ventilation
- 43.1% Hemoperfusion (HP) modality/stand-alone treatment
- Seraph 100 treatments well tolerated, low rate of clotting, no serious adverse events

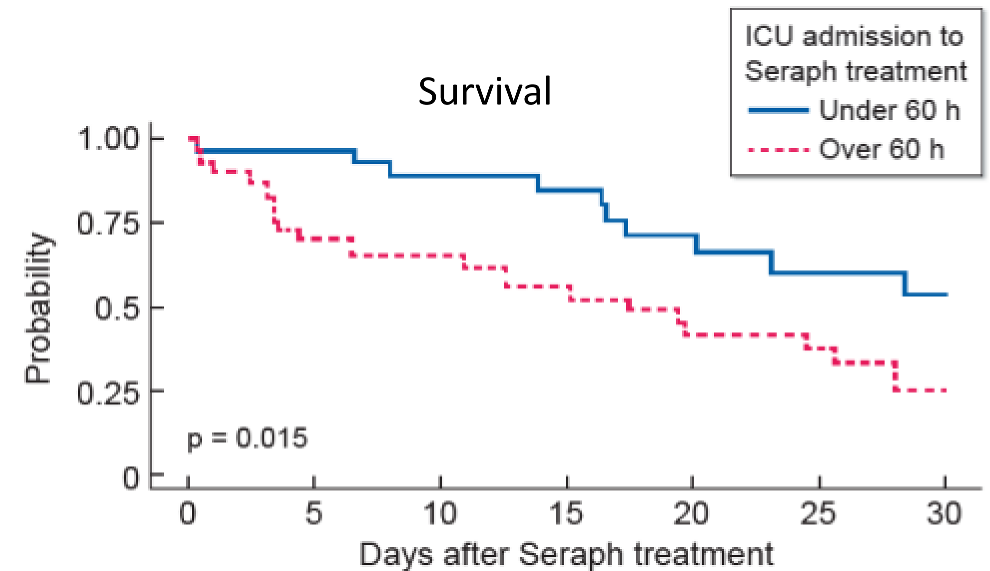
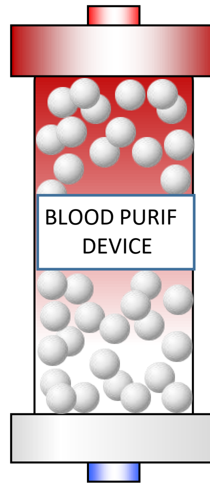


Figure 2: Kaplan-Meier analysis of survival in patients stratified for ICU admission < and > 60 hrs during 30 days (p log-rank test < 0.015).

Schmidt et al. NDT 2021

The extracorporeal blood purification concept in sepsis

SEPSIS + 

= Improved patient outcomes ?

Intensive Care Med
https://doi.org/10.1007/s00134-021-06506-y

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Laura Evans[1*], Andrew Rhodes[2], Waleed Alhazzani[3], Massimo Antonelli[4], Craig M. Coopersmith[5], Craig French[6], Flávia R. Machado[7], Lauralyn Mcintyre[8], Marlies Ostermann[9], Hallie C. Prescott[10], Christa Schorr[11], Steven Simpson[12], W. Joost Wiersinga[13], Fayez Alshamsi[14], Derek C. Angus[15], Yaseen Arabi[16], Luciano Azevedo[17], Richard Beale[9], Gregory Beilman[18], Emilie Belley-Cote[19], Lisa Burry[20], Maurizio Cecconi[21,22], John Centofanti[23], Angel Coz Yataco[24], Jan De Waele[25], R. Phillip Dellinger[11], Kent Doi[26], Bin Du[27], Elisa Estenssoro[28], Ricard Ferrer[29], Charles Gomersall[30], Carol Hodgson[31], Morten Hylander Møller[32], Theodore Iwashyna[33], Shevin Jacob[34], Ruth Kleinpell[35], Michael Klompas[36,37], Younsuck Koh[38], Anand Kumar[39], Arthur Kwizera[40], Suzana Lobo[41], Henry Masur[42], Steven McGloughlin[43], Sangeeta Mehta[44], Yatin Mehta[45], Mervyn Mer[46], Mark Nunnally[47], Simon Oczkowski[3], Tiffany Osborn[48], Elizabeth Papathanassoglou[49], Anders Perner[50], Michael Puskarich[51], Jason Roberts[52,53,54,55], William Schweickert[56], Maureen Seckel[57], Jonathan Sevransky[5], Charles L. Sprung[58,59], Tobias Welte[60], Janice Zimmerman[61] and Mitchell Levy[62]

Evans et al. *Intensive Care Med* 2021

K. BLOOD PURIFICATION

1. **We make no recommendation regarding the use of blood purification techniques.**

Rationale Blood purification includes various techniques, such as high-volume hemofiltration and hemoadsorption (or hemoperfusion), where sorbents, removing either endotoxin or cytokines, are placed in contact with blood; plasma exchange or plasma filtration, through

because of clotting of the circuit, which raises doubts about CPFA feasibility.

In consideration of all these limitations, our confidence in the evidence is very low either in favor of or against blood purification techniques; therefore, we do not provide a recommendation. Further research is needed to clarify the clinical benefit of blood purification techniques.

Rhodes et al. *Intensive Care Med* 2017

Blood Purification

Recommendations

59. For adults with sepsis or septic shock, we **suggest against** using polymyxin B haemoperfusion

Weak recommendation; low quality of evidence

60. There is **insufficient evidence to make a recommendation** on the use of other blood purification techniques

Further research is needed to determine the effect of various blood purification techniques on patient outcomes.

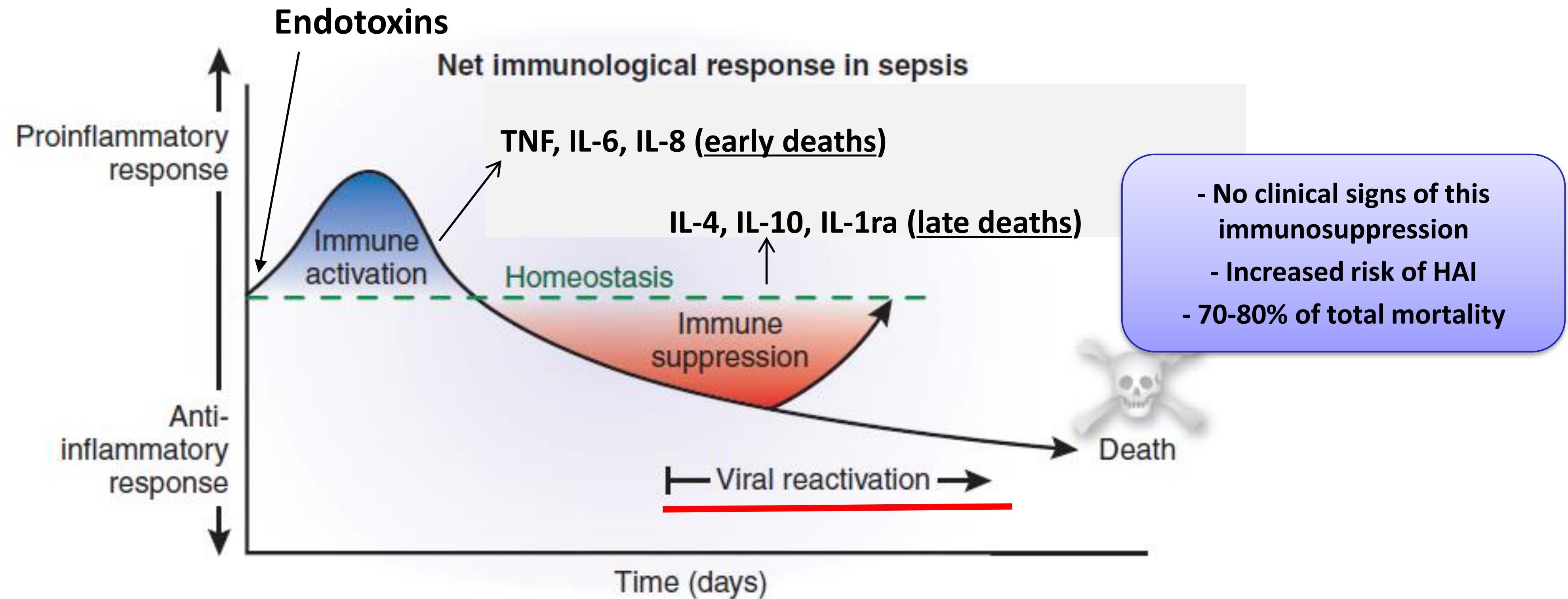
Evans et al. *Intensive Care Med* 2021

What about the villains?

HEROES	VILLAINS
A	D
B	E
C	F

D = Sepsis-induced immunosuppression

Septic shock = Hyperinflammation followed by severe immunosuppression



- No clinical signs of this immunosuppression
- Increased risk of HAI
- 70-80% of total mortality

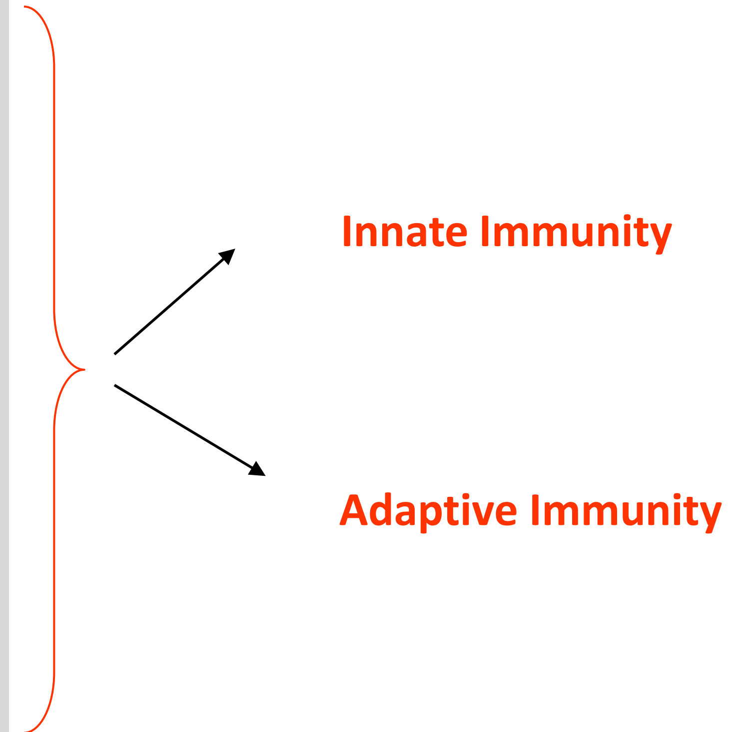
Hotchkiss et al. *Nat Med* 2009

Pathophysiology: Main mechanisms of sepsis-induced immunosuppression

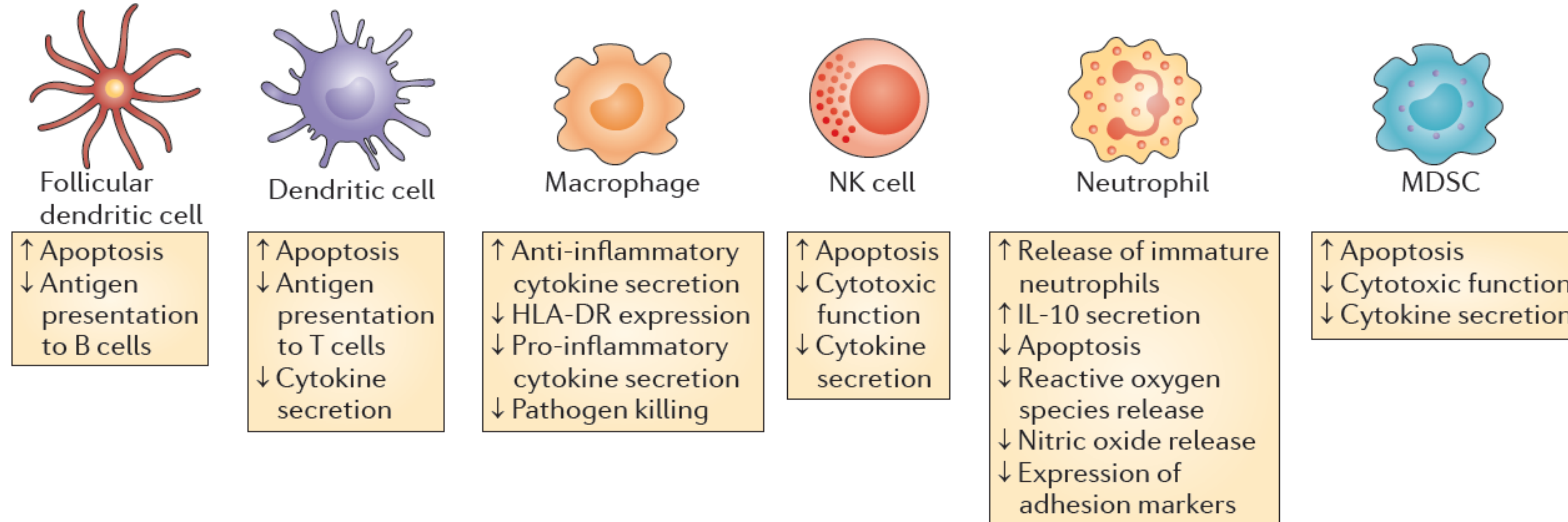
Table 1

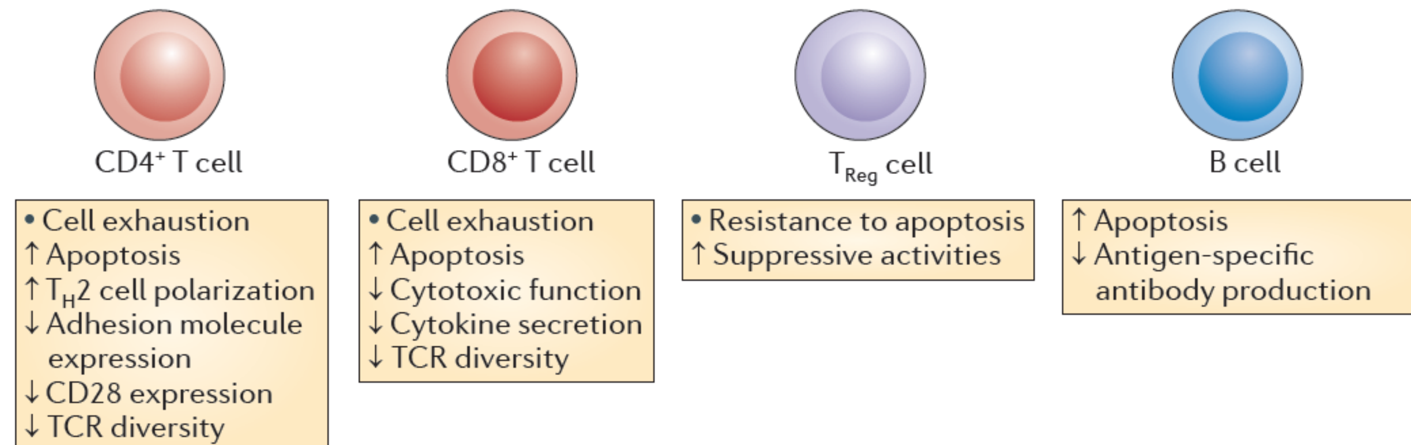
Sepsis-induced immune dysfunctions: pathophysiology at a glance

Mechanisms	Features of sepsis-induced immune alterations
Endotoxin tolerance	↓ pro-inflammatory ↑ anti-inflammatory cytokine production ↓ Ag presentation capacity
Apoptosis	↓ cell number Cell anergy
Energetic failure	Cell anergy Apoptosis Mitochondrial dysfunction
Anti-inflammatory mediators	↓ activating co-receptor expressions ↑ inhibitory co-receptor expressions Cell anergy Endotoxin tolerance
Epigenetic regulation	↓ pro-inflammatory gene expressions Cellular reprogramming
Central and endocrine Regulations	↓ pro-inflammatory cytokine production



Venet et al. Curr Opin Immunol 2013





Hotchkiss et al. Nat Rev Immunol 2013

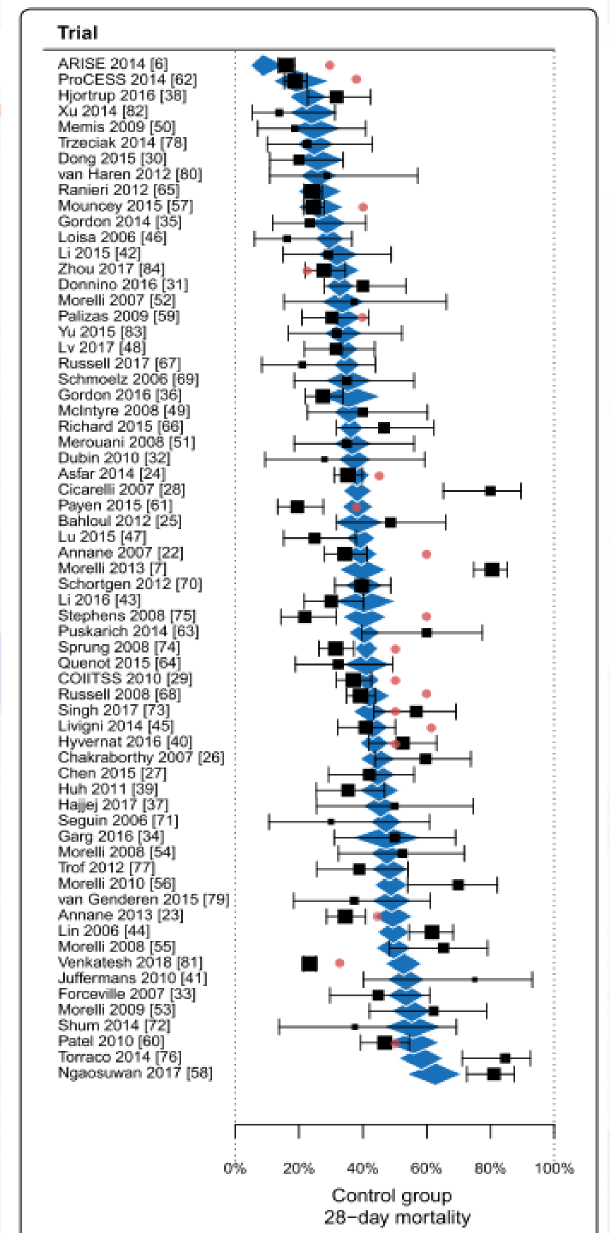
E = Sepsis heterogeneity

Sepsis is a very heterogeneous syndrome!

SYSTEMATIC REVIEW

Unexplained mortality differences between septic shock trials: a systematic analysis of population characteristics and control-group mortality rates

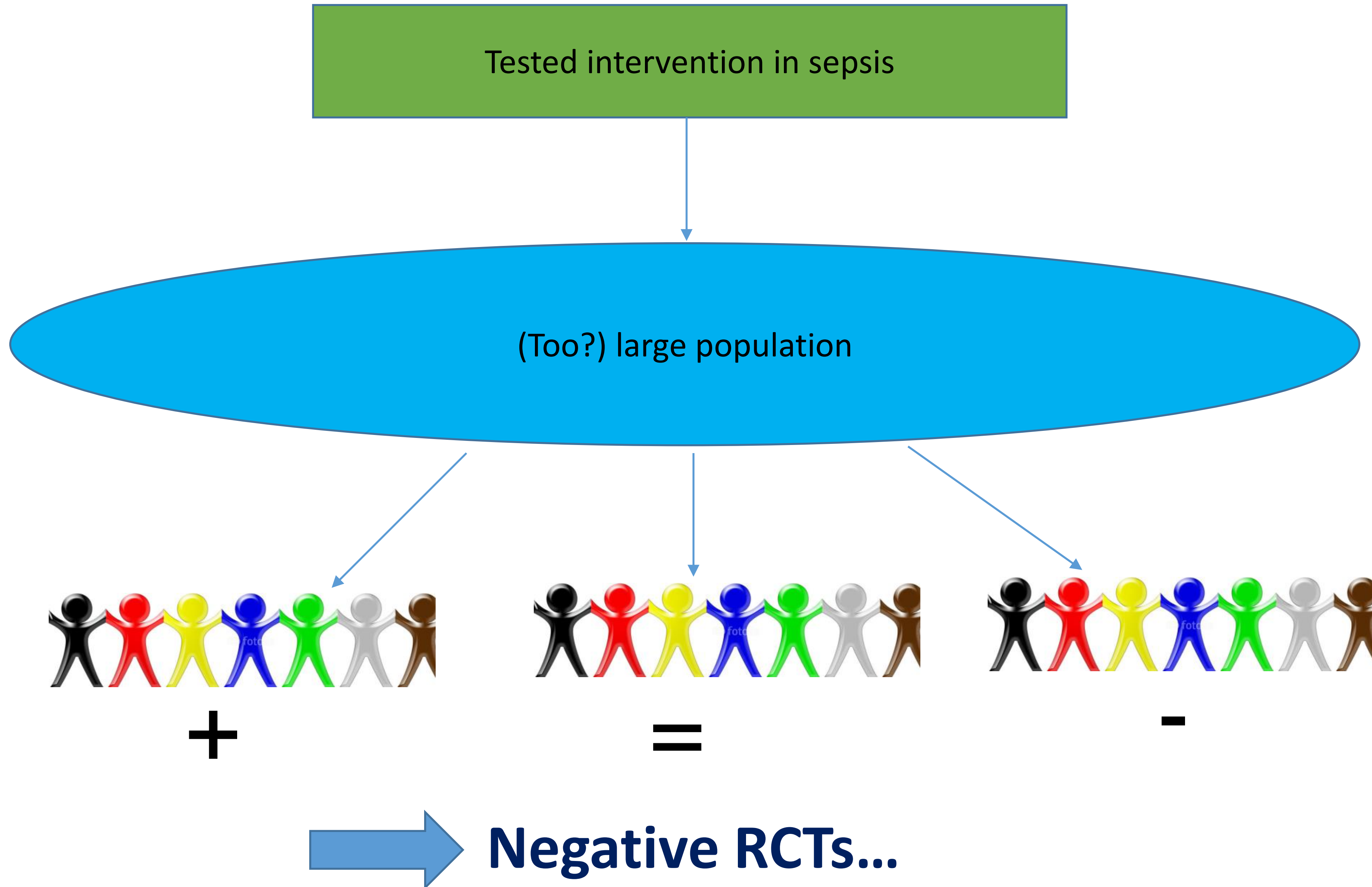
Harm-Jan de Grooth[1,2*], Jonne Postema[2], Stephan A. Loer[2], Jean-Jacques Parienti[3,4], Heleen M. Oudemans-van Straaten[1] and Armand R. Girbes[1]



- <u>Blue Diamond</u> – predicted mortality rate
- <u>Black Square</u> – observed real mortality
- <u>Control-group mortality</u> demonstrates rate significant variability

De Grooth *Intensive Care Med* 2018

F = Methodological issues of sepsis trials = Insufficient patient selection!



Negative RCTs…

To pick the right patient to study is key: not sick enough, sick enough, too sick… ?

RESEARCH **Open Access**

Effectiveness of polymyxin B hemoperfusion for sepsis depends on the baseline SOFA score: a nationwide observational study

Kenji Fujimori[1*], Kunio Tarasawa[1] and Kiyohide Fushimi[2]

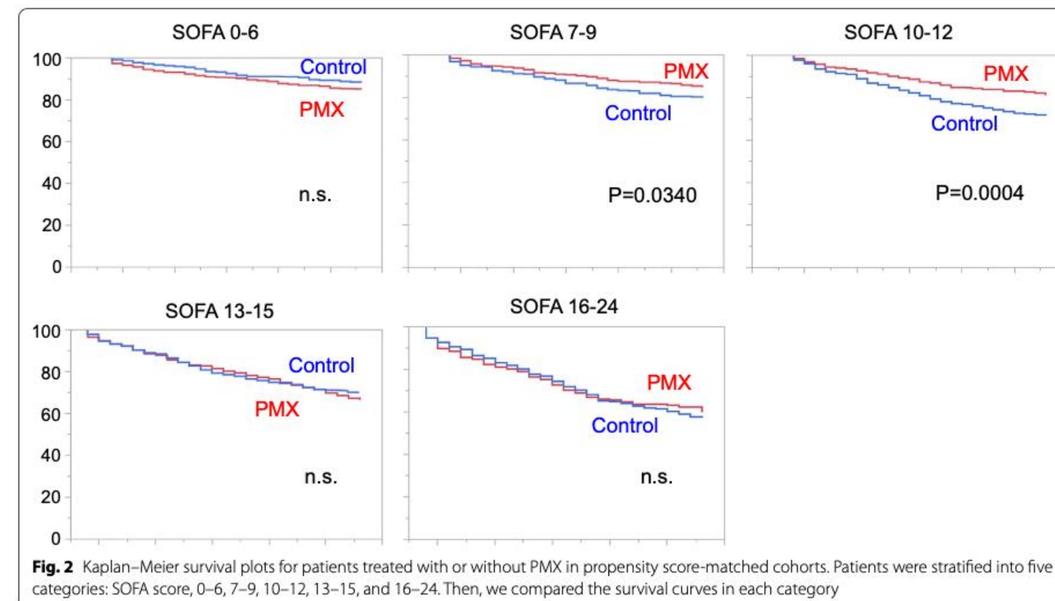


Fig. 2 Kaplan–Meier survival plots for patients treated with or without PMX in propensity score-matched cohorts. Patients were stratified into five categories: SOFA score, 0–6, 7–9, 10–12, 13–15, and 16–24. Then, we compared the survival curves in each category

Fujimori et al. *Ann Intensive Care* 2021

Outline

1) Introduction

2)

HEROES	VILLAINS
A	D
B	E
C	F

3) Conclusion

Conclusions / Take-home messages

HEROES	VILLAINS
Early antibiotics	Sepsis-induced immunosuppression
Antibiotics / Source control / Organ support	Sepsis heterogeneity
Extracorporeal blood purification techniques?	Insufficient patient selection for sepsis trials