THE 29TH INTERNATIONAL CONFERENCE ON
ADVANCES IN CRITICAL CARE NEPHROLOGY
AKI & CRRT 2024
MARCH 12-15, 2024 MANCHESTER GRAND HYATT SAN DIEGO, CALIFORNIA
Jointly Provided by
UC San Diego SCHOOL OF MEDICINE
and
CRRT, INC.

Plenary 4: Evolving Paradigms: Lessons from Ongoing Trials

Implementing Device Trials: What does it Require?

John A Kellum, MD

More specifically…
What about blood purification for sepsis?

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Chief Medical Officer
Spectral Medical

Tigris

a clinical trial for septic shock with endotoxemia

Disclosures

Chief Medical Officer

- Spectral Medical

Consultant

- Norvartis
- Astute Medical
- bioMérieux

Intellectual Property

- Astute Medical/bioMérieux
- Cytosorbents
- JεRM
- Klotho

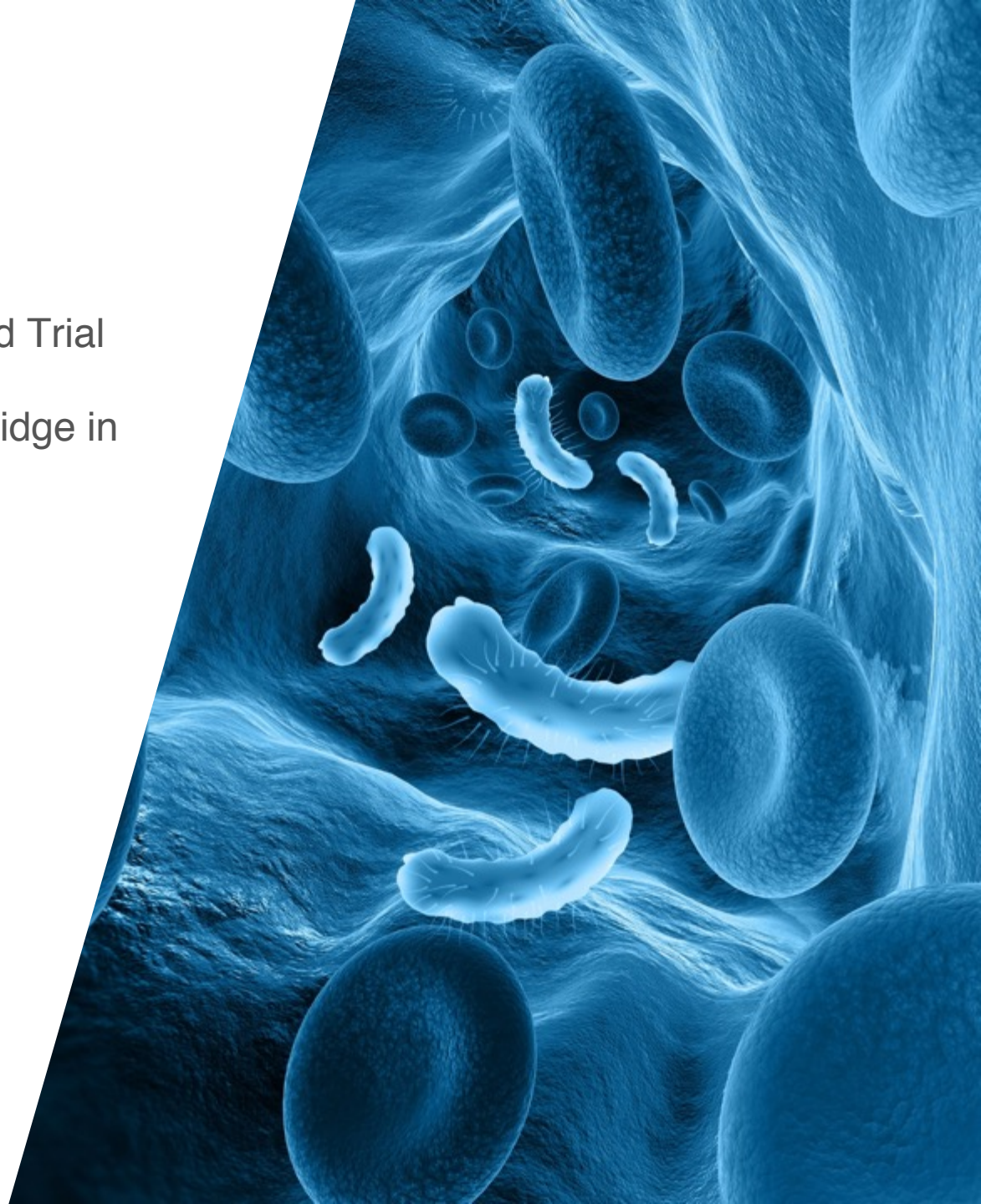
Updated March 2024

General considerations for trials of Blood Purification Therapy for US FDA

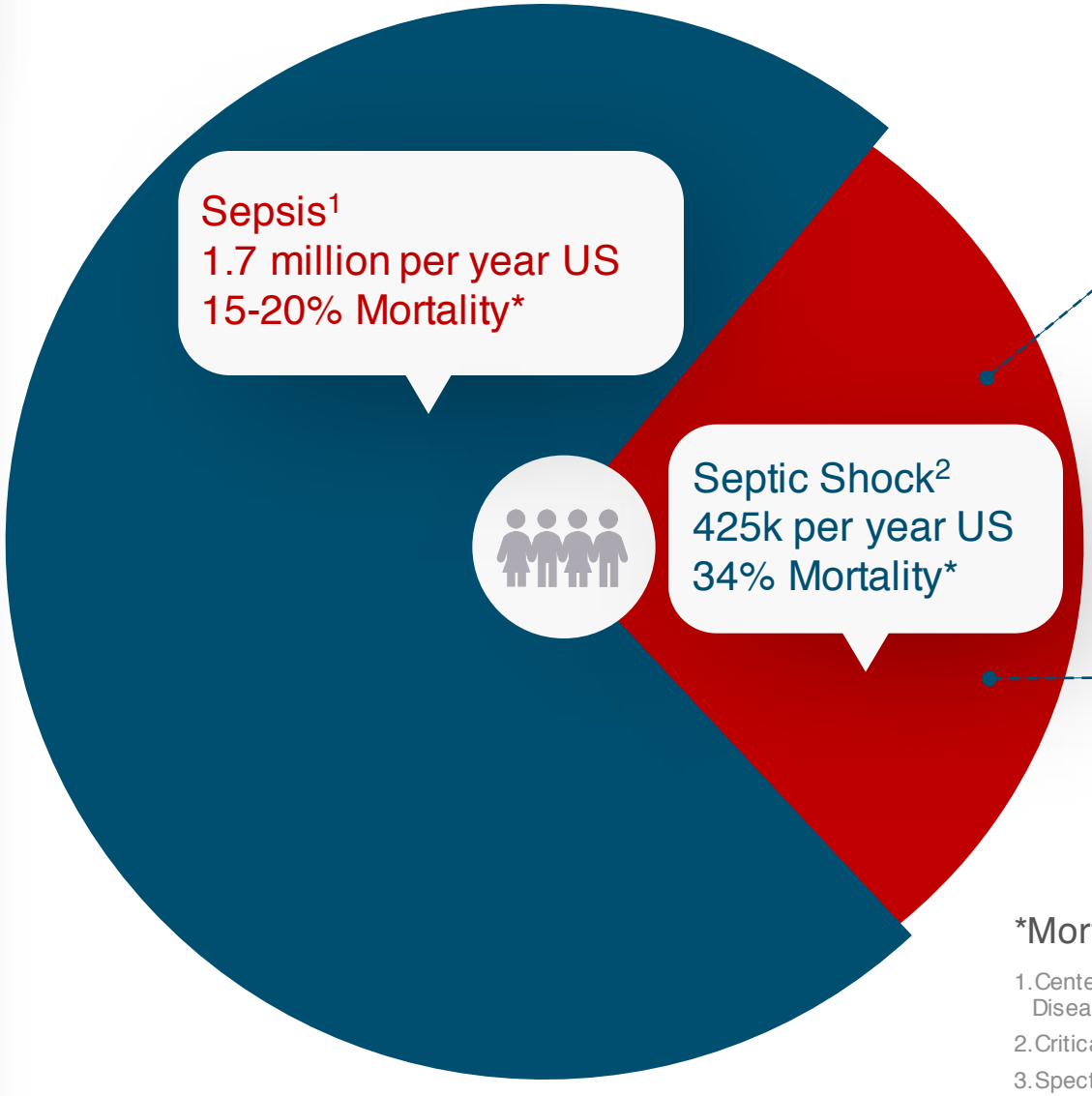
- FDA. Blood Purification Devices are generally reviewed by the Center for Devices and Radiological Health (CDRH), although some might be under the Center for Biologics Evaluation and Research (CBER). By contrast, most drugs are reviewed by Center for Drug Evaluation and Research (CDER).
  - In recent years most of the historical differences between centers on "requirements for approval" and policies have disappeared.
  - Rare exceptions: e.g. Orphan drugs (<200,000 people per year) Orphan devices (<10,000)
- Usually unblinded.
  - Endpoints other than mortality may be biased
- Staffing concerns –ICU and Nephrology research enterprises still wounded.
  - Weekend and evening coverage may be lacking
  - mITT

What is Tigris?

- A Prospective, Multicenter, Open-Label Randomized Trial
- Evaluating the Efficacy and Safety of the PMX Cartridge in Addition to Standard Medical Care for Patients with Endotoxic Septic Shock
- Two 2-hour treatments with PMX; 150 Patients, 2:1 randomization, 25 sites in US
- Primary endpoint: mortality at 28 days
- Bayesian statistical analysis



Sepsis Epidemiology



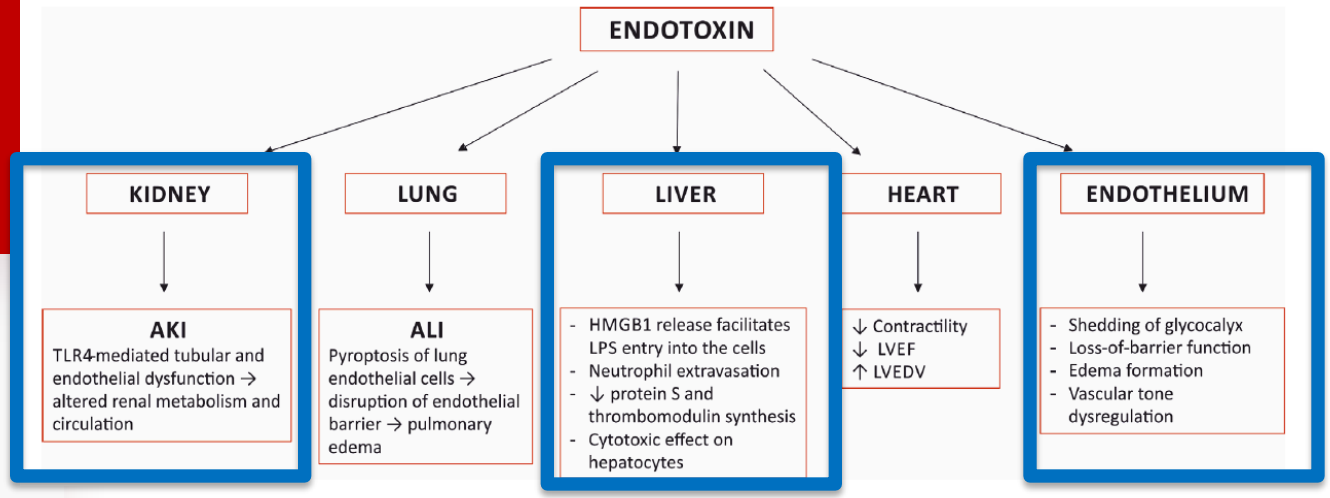
Endotoxic Septic Shock (ESS)[3]
140k per year US (3-4 million worldwide)
>50% mortality

<10% of sepsis **but**
>25% of deaths

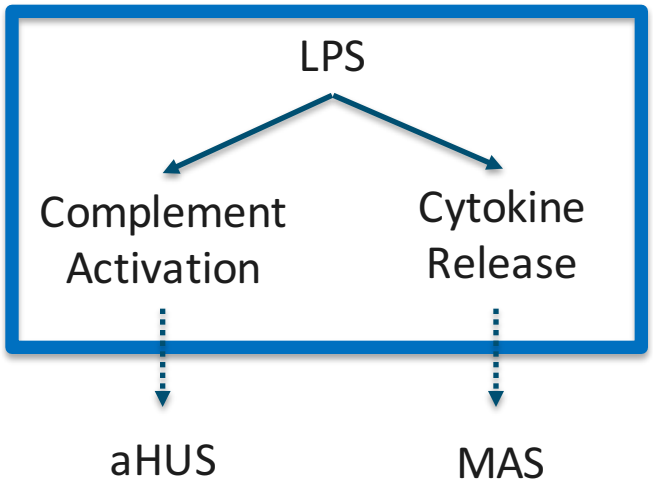
Other forms of Septic Shock
285k per year US (6-7 million worldwide)
25-30% mortality

*Mortality attributed to sepsis. Usually measured within 30-60 days.

1. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP) August 9, 2022
2. Critical Care Medicine 46(12):p 1889-1897, December 2018
3. Spectral Management estimates, based on Euphrates trial data



J Clin Med. 2022 Jan 26;11(3):619.



Vol. 328 No. 20 BRIEF REPORT —

BRIEF REPORT: SHOCK AND MULTIPLE-ORGAN DYSFUNCTION AFTER SELF-ADMINISTRATION OF SALMONELLA ENDOTOXIN

Angelo M. Taveira da Silva, M.D., Ph.D.,
Helen C. Kaulbach, M.D.,
Francis S. Chuidian, M.D.,
David R. Lambert, M.D.,
Anthony F. Suffredini, M.D.,
and Robert L. Danner, M.D.

Laboratory technician self-injected 1 mg of *Salmonella minnesota* LPS

Profound Shock
Vasodilatation
AKI
Thrombocytopenia
Increased PTT
Hepatic dysfunction
No Pulmonary or CNS

THE NEW ENGLAND JOURNAL OF MEDICINE May 20, 1993

More inflammation

Table 2. Characteristics of the 4 Phenotypes (continued)		33%	27%	27%	13%
		Phenotype			
Characteristic[a]	Total	α	β	γ	δ
Outcomes					
Mechanical ventilation, median (IQR), d[d]	5 (2-10)	4 (2-9)	4 (2-9)	6 (3-13)	4 (2-9)
Administration of a vasopressor, median (IQR), d[d]	3 (2-5)	2 (2-4)	3 (2-4)	3 (2-5)	3 (2-5)
Admitted to intensive care unit, No. (%)[d]	9063 (45)	1644 (25)	1778 (32)	3381 (63)	2260 (85)
In-hospital mortality, No. (%)	2082 (10)	126 (2)	286 (5)	818 (15)	852 (32)

More underlying comorbidity
Higher post-d/c mortality

More pulmonary involvement

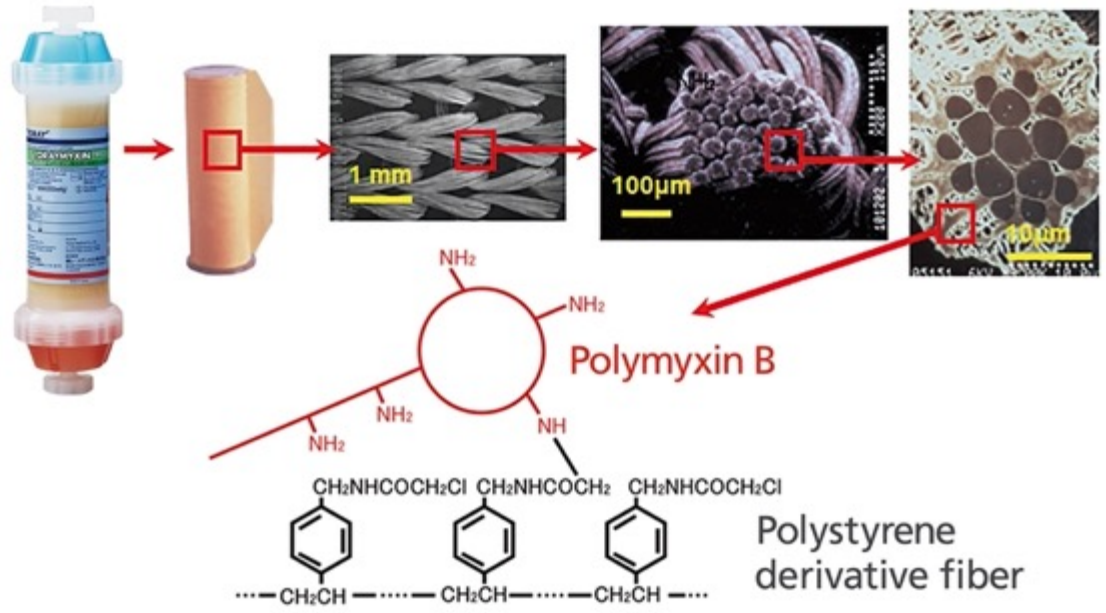
Acute Kidney Injury
Hepatic Dysfunction
Endothelial Dysfunction

Seymour et al. JAMA. 2019;321(20):2003-2017.

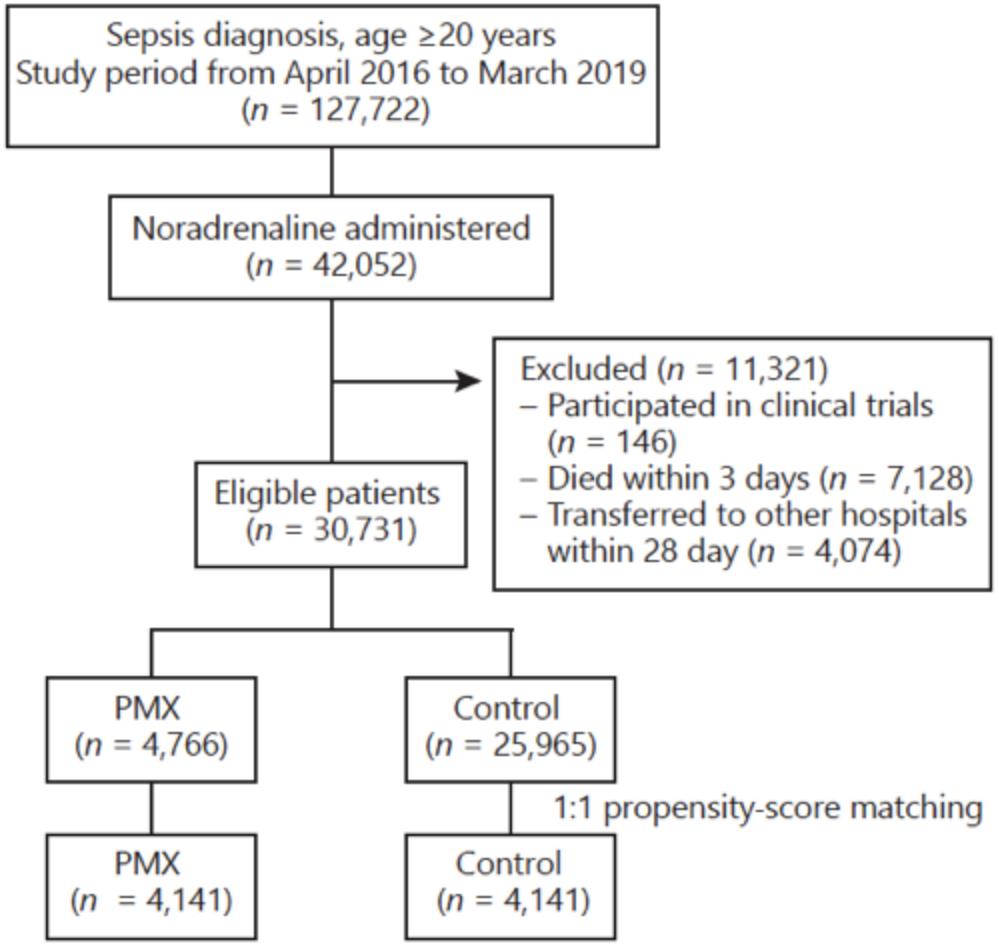
Treatment: Endotoxin adsorption

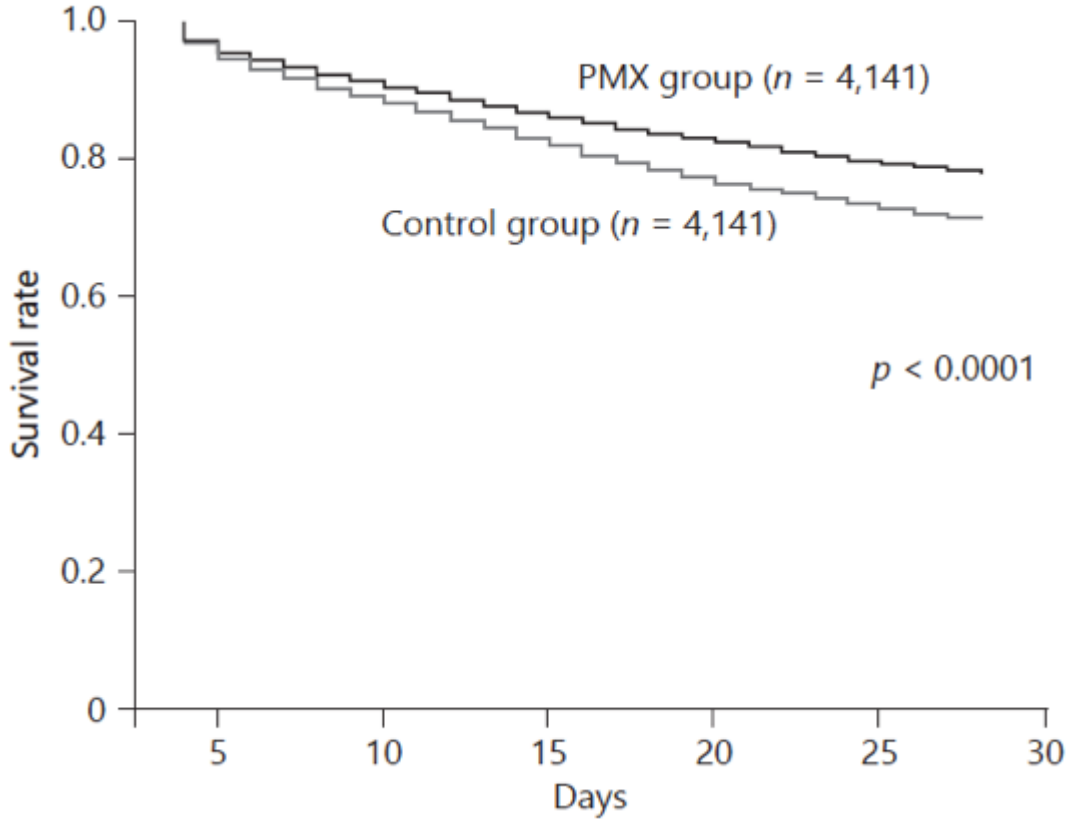
- Polymyxin B (PMX) has intrinsic endotoxin-binding capacity; it is covalently bound to a membrane used for hemoadsorption.

- Each PMX cartridge is used for 2 hours and can remove approximately 5-10 µg of endotoxin.



Survival benefit with PMX-hemoperfusion



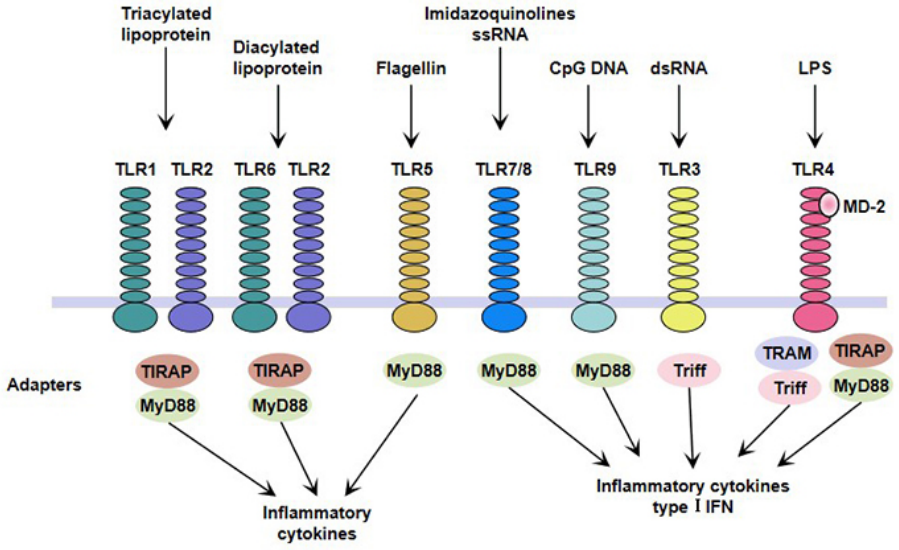


Survival at day 28 was 77.9% with PMX vs. 71.1% with SOC ($p < 0.0001$)
OR 1.433 (95% CI, 1.298–1.584)
ARR 6.8%

Fujimori, et al. Blood Purif. 2021 Feb 12;1-6.

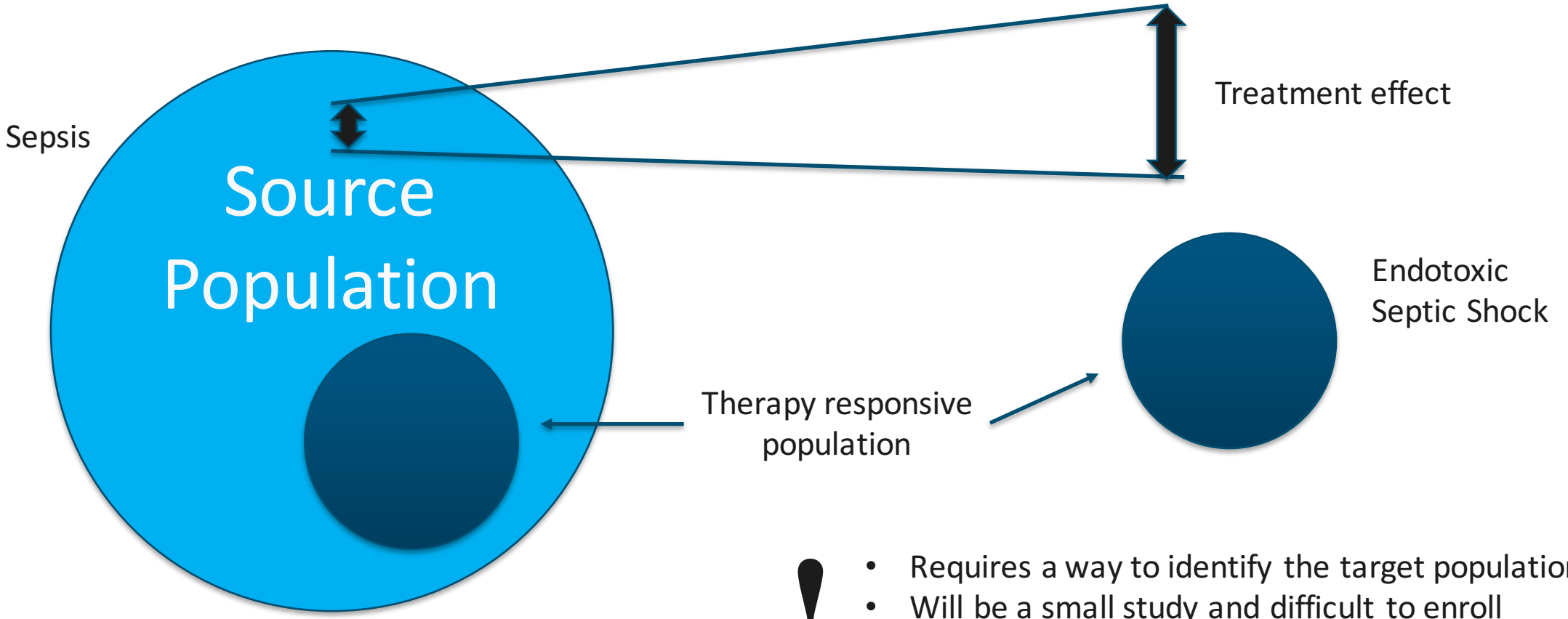
DAMPs and PAMPs

- Damage-Associated Molecular Patterns
  - HMGB1
  - Heat-shock Proteins
  - Hyaluronan fragments
  - Uric acid
  - Heparin sulfate
  - DNA



- Pathogen-Associated Molecular Patterns
  - Endotoxin
  - Flagellin
  - Lipoteichoic acid (gram-positive bacteria)
  - Peptidoglycan
  - Nucleic acid variants (viruses) e.g. double-stranded RNA (dsRNA), unmethylated CpG motifs

Effect size vs. Addressable Population



- Requires a way to identify the target population
- Will be a small study and difficult to enroll
- Alternative trial designs may be required
- Precision medicine NOT pragmatic failures

Effects of Dilution and Attenuation on Sample Size

Hypothetical treatment targeting 5% of patients with AKI (or sepsis)

Proportion of Patients who can respond	Placebo Event Rate	Treatment Event rate	RRR	ARR	Proportion of overall population	Sample size required for 80% Power
100%	60%	30%	50%	30%	5%	84
50%	30%	15%	50%	15%	10%	240
25%	15%	7.5%	50%	7.5%	20%	554
10%	6%	3%	50%	3.0%	50%	1496
5%	3%	1.5%	50%	1.5%	100%	3066

The NEW ENGLAND JOURNAL of MEDICINE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

Djillali Annane, M.D., Ph.D., Alain Renault, M.Sc., Christian Brun-Buisson, M.D., Bruno Megarbane, M.D., Jean-Pierre Quenot, M.D., Shidasp Siami, M.D., Alain Cariou, M.D., Xavier Forceville, M.D., Ph.D., Carole Schwebel, M.D., Claude Martin, M.D., Jean-François Timsit, M.D., Benoît Misset, M.D., et al., for the CRICS-TRIGGERSEP Network*

- Mortality benefit: @90 day RR 0.88 (95% CI, 0.78 to 0.99), P=0.03.
- Vasopressor-free days: 17 vs. 15 days, P<0.001
- Organ-failure–free days: 14 vs. 12 days, P=0.003
- Vent-free days were similar: 11 vs. 10 days P=0.07

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

Balasubramanian Venkatesh, M.D., Simon Finfer, M.D., Jeremy Cohen, M.D., Ph.D., Dorrilyn Rajbhandari, R.N., Yaseen Arabi, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., M.Res., Maryam Correa, Ph.D., Parisa Glass, Ph.D., Meg Harward, R.N., Christopher Joyce, M.D., Ph.D., Qiang Li, M.Sc., et al., for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

- No mortality benefit: OR, 0.95; 95% CI, 0.82 to 1.10; P=0.50
- Shorter duration of shock: 3 days [IQR, 2 to 5] vs. 4 days [2 to 9]; hazard ratio, 1.32; 95% CI, 1.23 to 1.41; P<0.001).
- No difference in vent-free or organ failure-free days

Was ADRENAL too broad (i.e. included patients that were not as sick)?

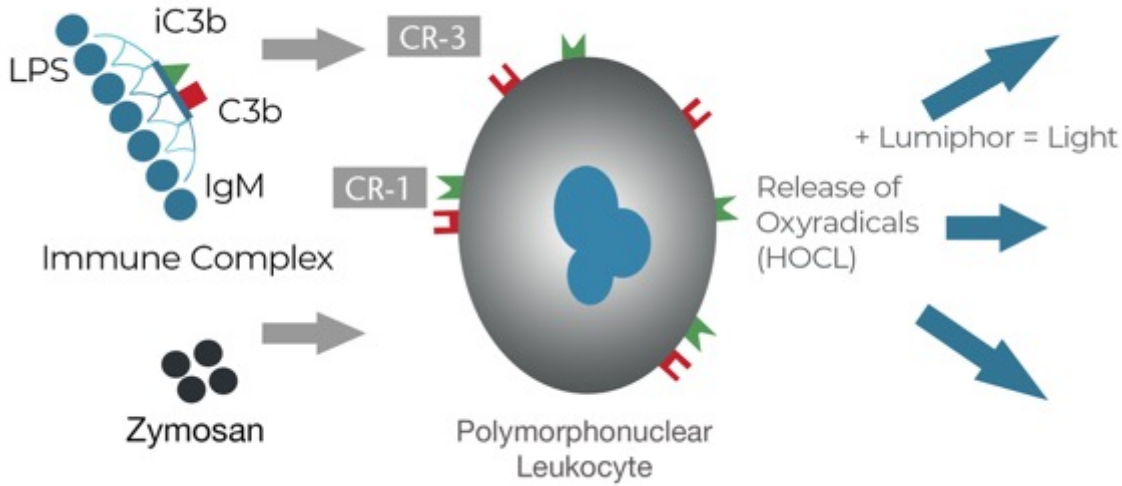
- Placebo mortality 28% (compared 49% in APROCCHSS
- NE dose 30 mcg/min (vs 70 in APROCHSS)

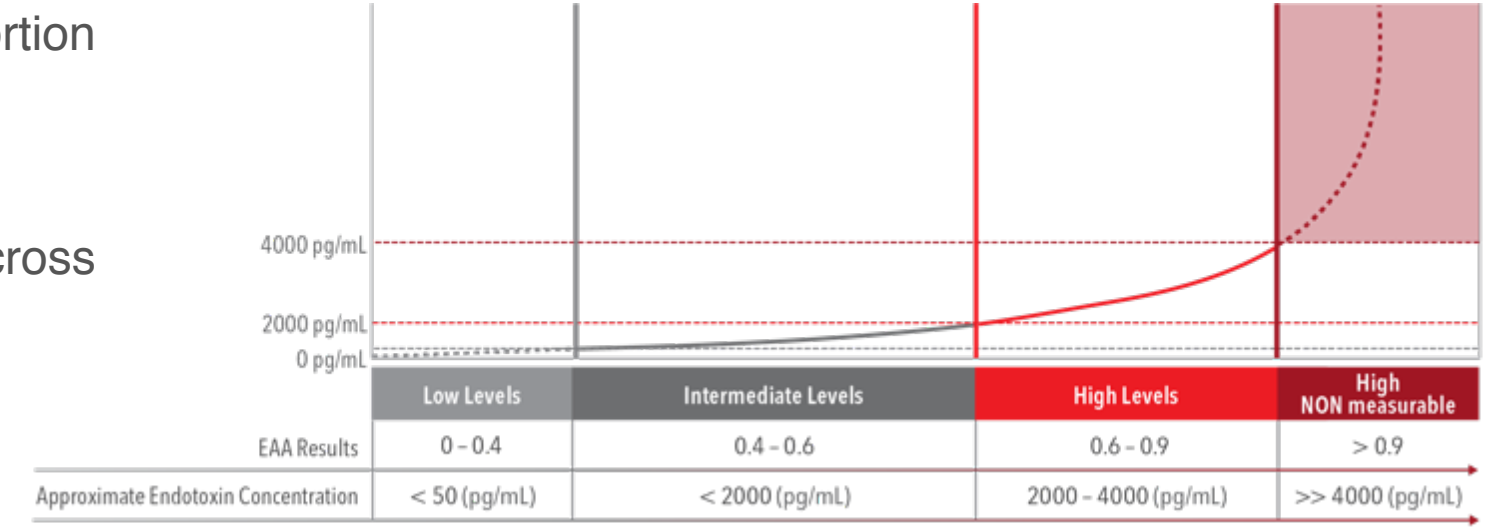
Was ADRENAL too “pragmatic”?

- Randomization 20 +/- 90hrs from start of shock
- Bolus dosing (vs continuous infusion used in other trials)

What is Endotoxin Activity Assay (EAA)?

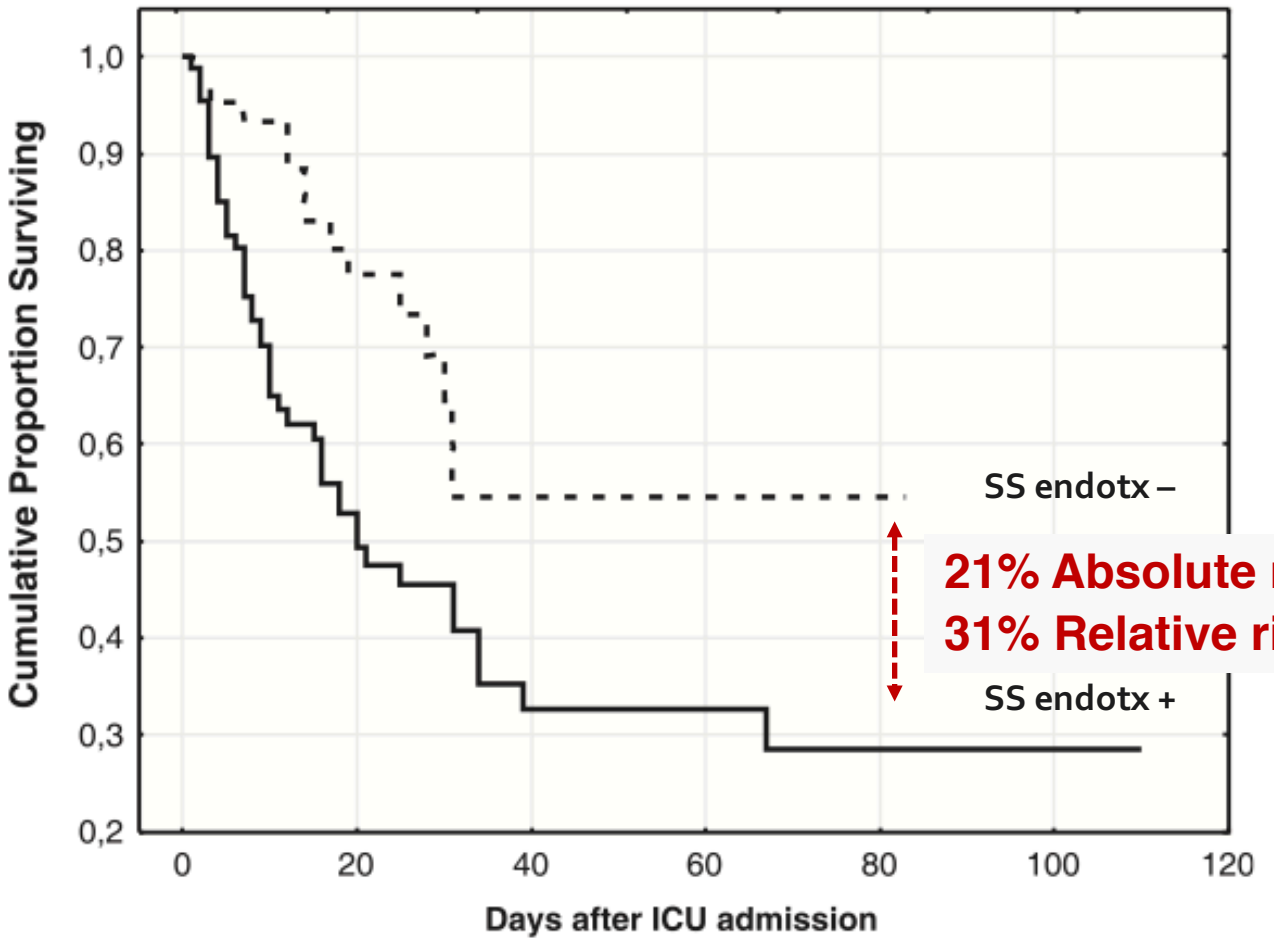
- EAA is a Chemiluminescent assay based on the oxidative burst reaction of neutrophils in combination with a complement coated antibody-antigen (LPS-IgM) complex.
- The antibody is specific for the Lipid A portion of endotoxin (LPS). This portion was selected due to the highly conserved nature of the structure allowing for the robust response across Gram Negative endotoxins.





Foster, Kellum. IJMS 2023

Survival from ESS



Prognosis this poor → w/d of care

Adamik, et al. Medicine 2015;94:e1085

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

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

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

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

Overall, no benefit from PMX in the EUPHRATES trial. HOWEVER. . .

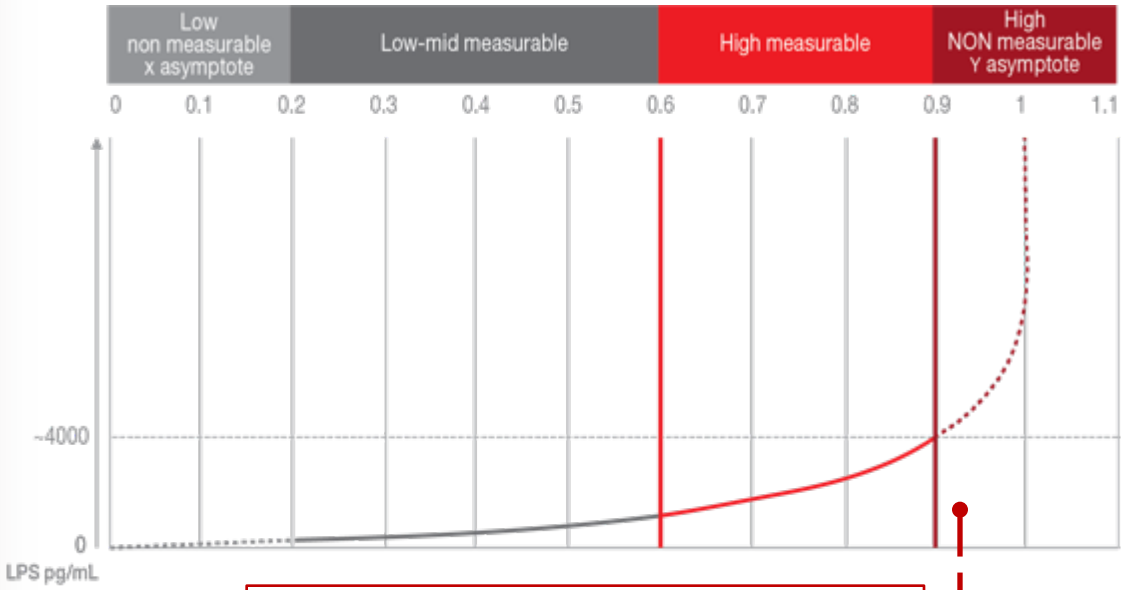
JAMA. 2018;320(14):1455-1463

Tigris

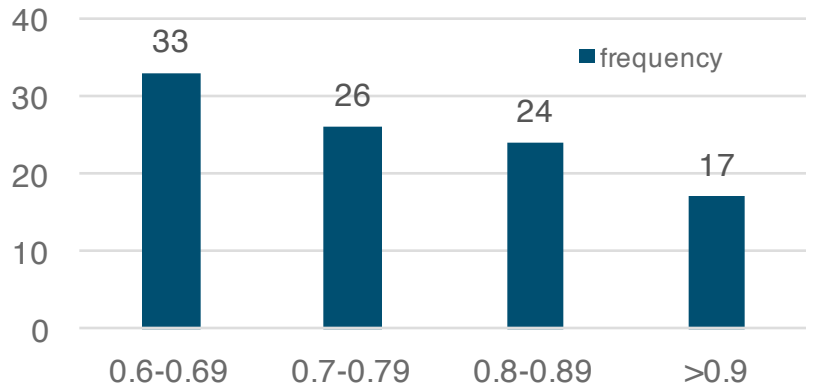
ORIGINAL

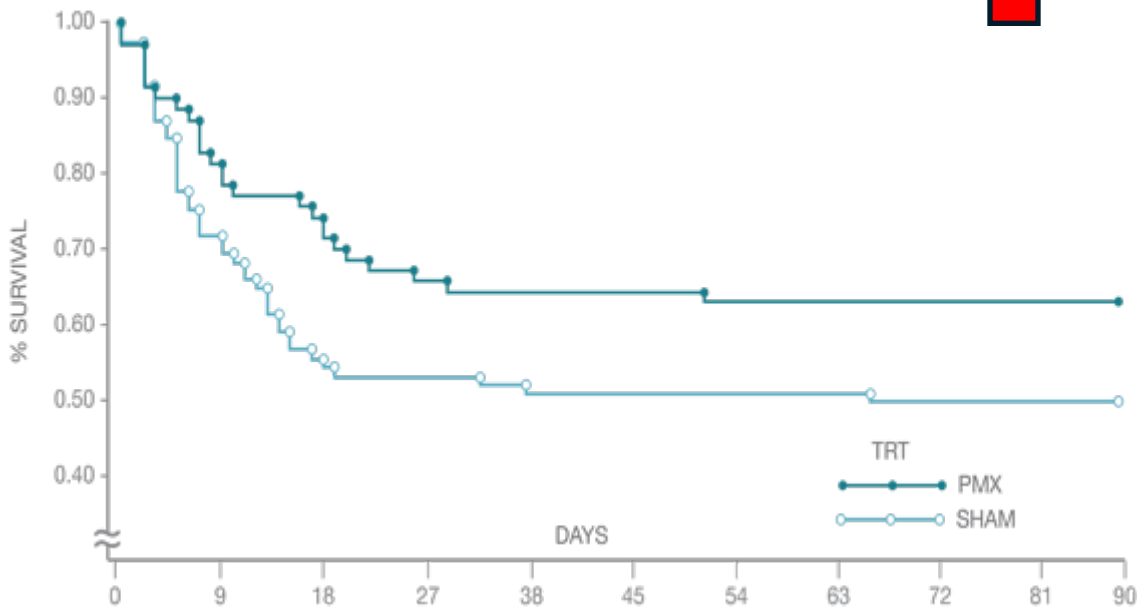
Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

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



A survival benefit emerges after excluding patients with >0.9 EAA





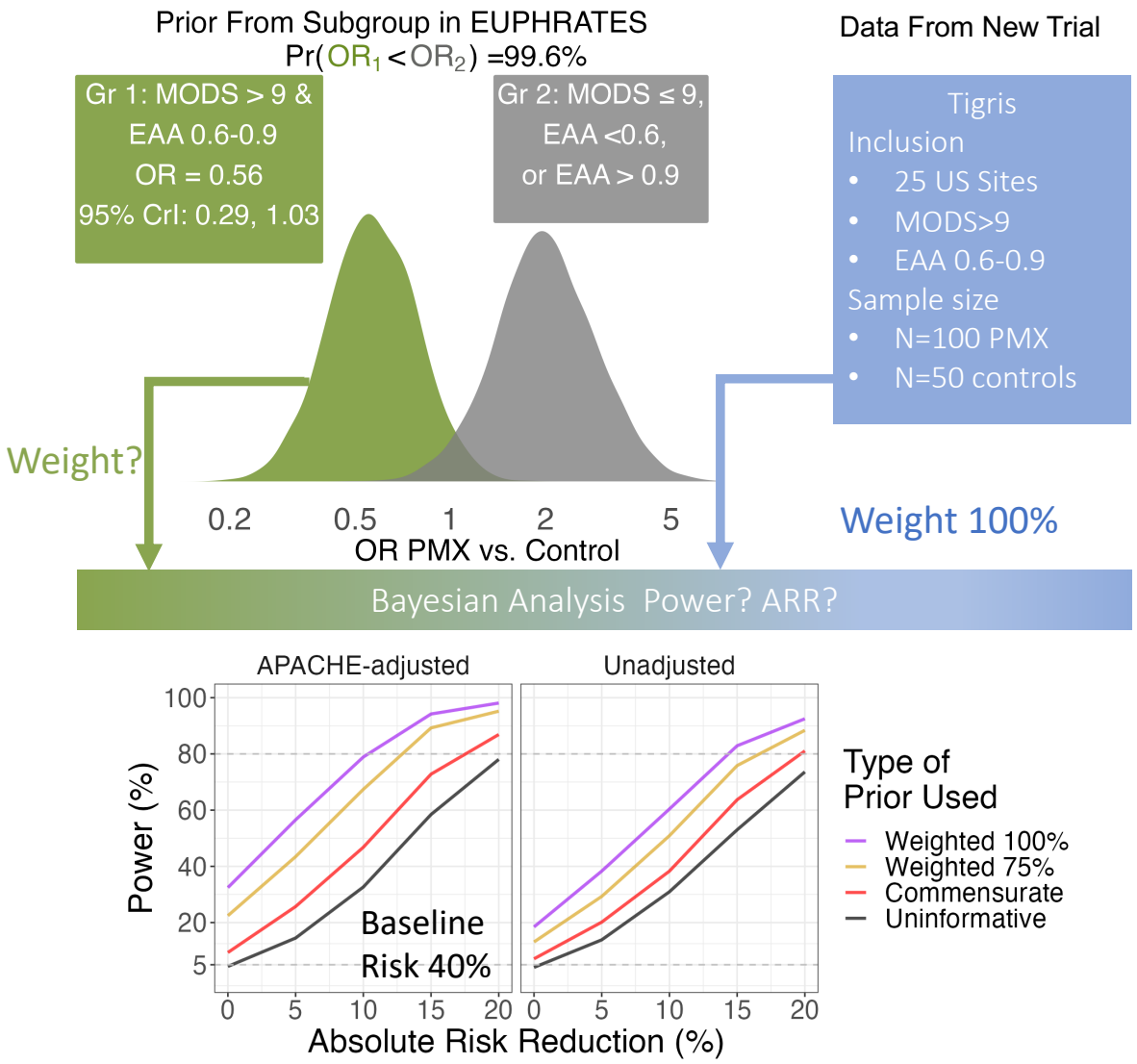
Time	Risk Reduction %	HR and p-value
14 Days	52%	HR 0.48, p= 0.0189
28 Days	42%	HR 0.585, p = 0.0429
90 Days	41%	HR 0.594, p=0.0373

Intensive Care Med. 2018 Dec;44(12):2205-2212

Bayesian Analysis:

Tomlinson et al. Crit Care (2023) 27:432

- **Question:** How will different uses of historical data (e.g. weighting) through a prior distribution, and type of analysis influence results of a proposed trial that will be analyzed using Bayesian statistical methods?
- **Methods:** Simulation study incorporating historical data from EUPHRATES.
  - Historical data come from a 179-patient subgroup of the previous trial of adult critically ill patients with septic shock, multiple organ failure and an EAA 0.60 to 0.89.
  - The trial intervention consisted of two polymyxin B hemoadsoption treatments (2hrs each) completed within 24 hours of enrollment.
  - Simulations were run 2000 times per scenario



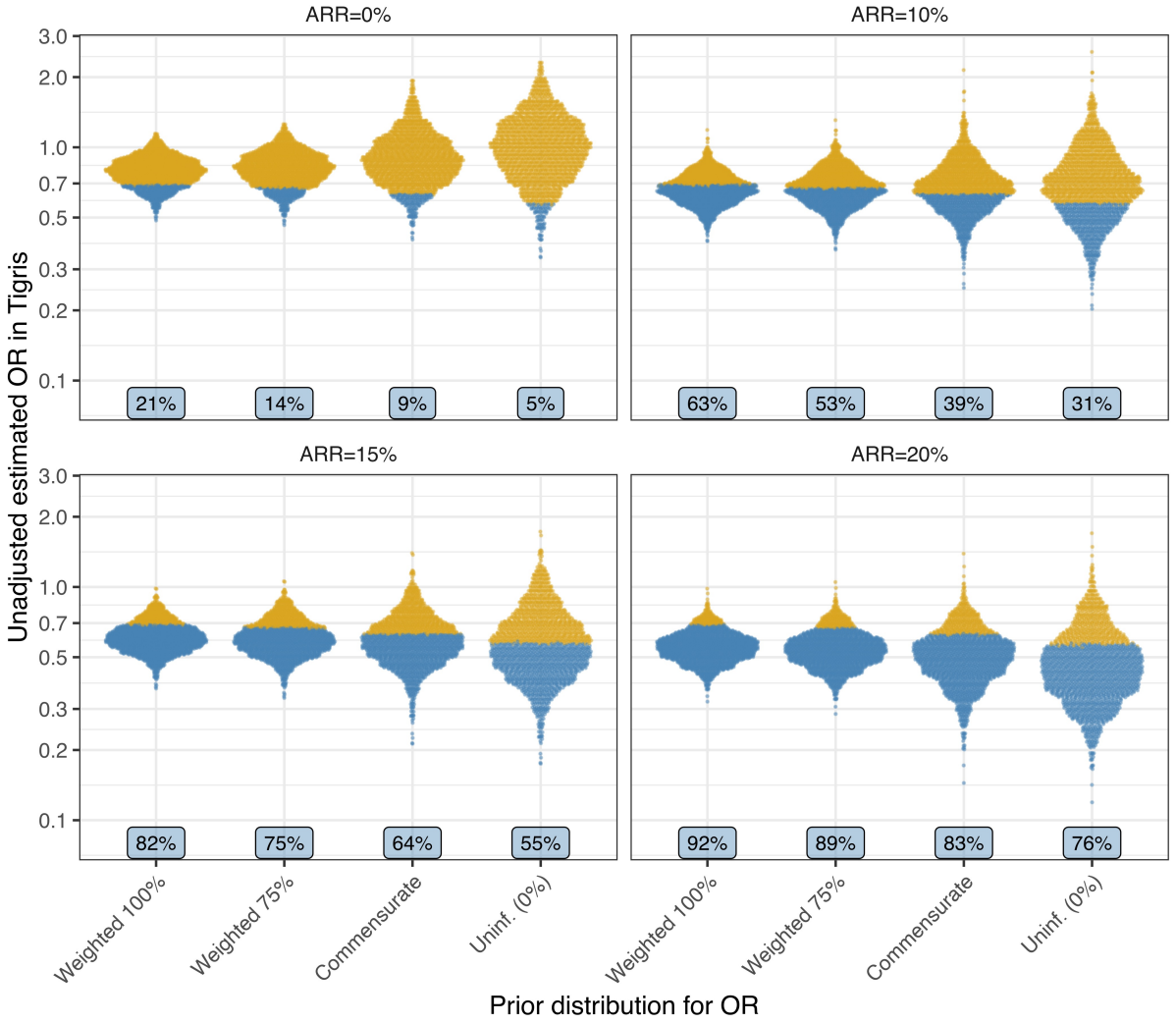
Bayesian Analysis: Unadjusted

Tomlinson et al. Crit Care (2023) 27:432

Simulations of 2000 potential trial results where the true ARR varies from 0% to 20%

Prior distribution (From EUPHRATES):
179 patients, 90 PMX/89 control,
28-day mortality was 36.7% vs 47.2%.

New Confirmatory Trial (Tigris)
Planned 150 patients, 2:1 Randomization



Bayesian Analysis: Adjusted by APACHE III

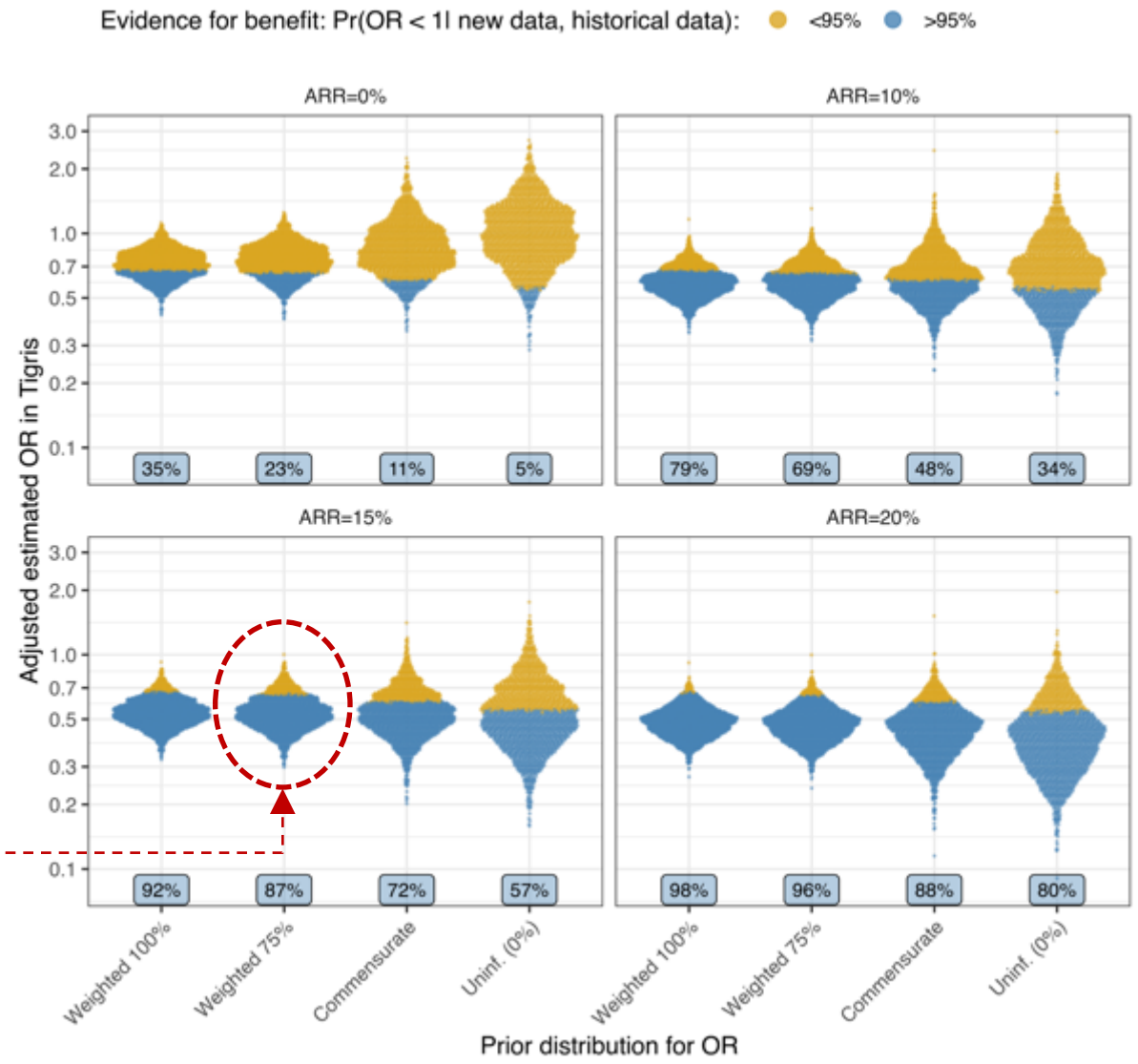
Tomlinson et al. Crit Care (2023) 27:432

Simulations of 2000 potential trial results where the true ARR varies from 0% to 20%

Prior distribution (From EUPHRATES):
179 patients, 90 PMX/89 control,
28-day mortality was 36.7% vs 47.2%.

New Confirmatory Trial (Tigris)
Planned 150 patients, 2:1 Randomization

One scenario uses a 75% weight on the prior and considers a 15% "True" ARR from new data, yields an 87% likelihood of achieving >95% probability of benefit.



Bayesian Analysis: Concerns

Critics of Bayesian statistics are mainly concerned about two issues

- Type 1 error (finding an effect when it doesn't exist) also known as false discovery
  - → "When using prior information, it may be appropriate to control type I error at a less stringent level than when no prior information is used. For example, if the prior information is favorable, the current trial may not need to provide as much information regarding safety and effectiveness.
    The degree to which we might relax the type I error control is a case-by-case decision that depends on many factors, primarily the confidence we have in the prior information."

FDA Guidance of Bayesian analysis

- Justification for use of an informative prior

Analysis set	Adjusted by APACHE II?	Interaction effect [exp(b3)] Posterior Mean and 95% CrI	Posterior Pr (Interaction effect <1)
All EUPHRATES (USA and Canada)	No	0.51 [0.22, 1.02]	97.1%
	Yes	0.48 [0.19, 0.99]	97.6%
USA EUPHRATES	No	0.36 [0.13, 0.81]	99.3%
	Yes	0.32 [0.11 ,0.73]	99.6%

>99% probability that our Prior population (USA Pts with EAA 0.6-0.9 and with MODS >9) is different (responds better) from the EUPHRATES cohort in toto.

Tomlinson et al. Crit Care (2023) 27:432

The way forward for Critical Illness?

Personalized interventions analyzed using novel trial designs

nature medicine

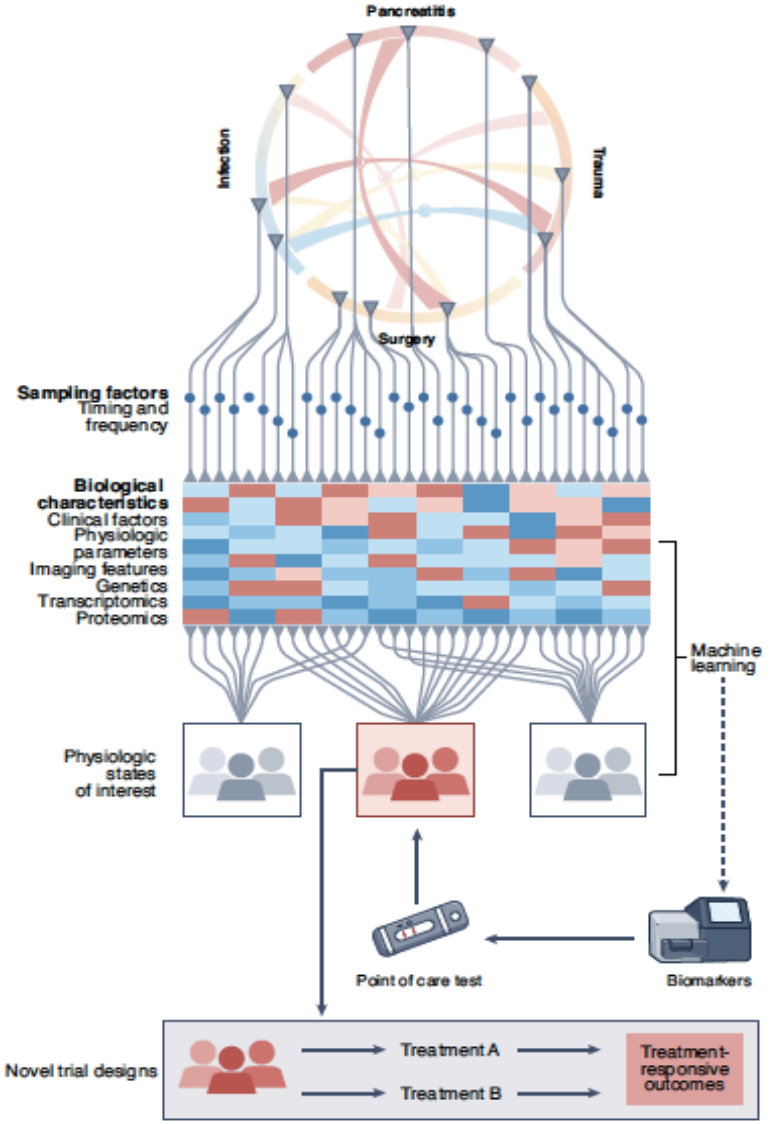
PERSPECTIVE

https://doi.org/10.1038/s41591-022-01843-x

Check for updates

Redefining critical illness

David M. Maslove[1,2,45], Benjamin Tang[3,45], Manu Shankar-Hari[4,5], Patrick R. Lawler[6,7], Derek C. Angus[8,9], J. Kenneth Baillie[5,10,11], Rebecca M. Baron[12,13], Michael Bauer[14,15], Timothy G. Buchman[16,17], Carolyn S. Calfee[18], Claudia C. dos Santos[7,19], Evangelos J. Giamarellos-Bourboulis[20], Anthony C. Gordon[21], John A. Kellum[8], Julian C. Knight[22], Aleksandra Leligdowicz[23,24], Daniel F. McAuley[25,26], Anthony S. McLean[3], David K. Menon[27], Nuala J. Meyer[28], Lyle L. Moldawer[29], Kiran Reddy[25,26], John P. Reilly[28], James A. Russell[30], Jonathan E. Sevransky[16,31], Christopher W. Seymour[8], Nathan I. Shapiro[13,32], Mervyn Singer[33], Charlotte Summers[34], Timothy E. Sweeney[35], B. Taylor Thompson[13,36], Tom van der Poll[37], Balasubramanian Venkatesh[38,39], Keith R. Walley[30], Timothy S. Walsh[40], Lorraine B. Ware[41], Hector R. Wong[42,46], Zsolt E. Zador[43] and John C. Marshall[7,43,44]



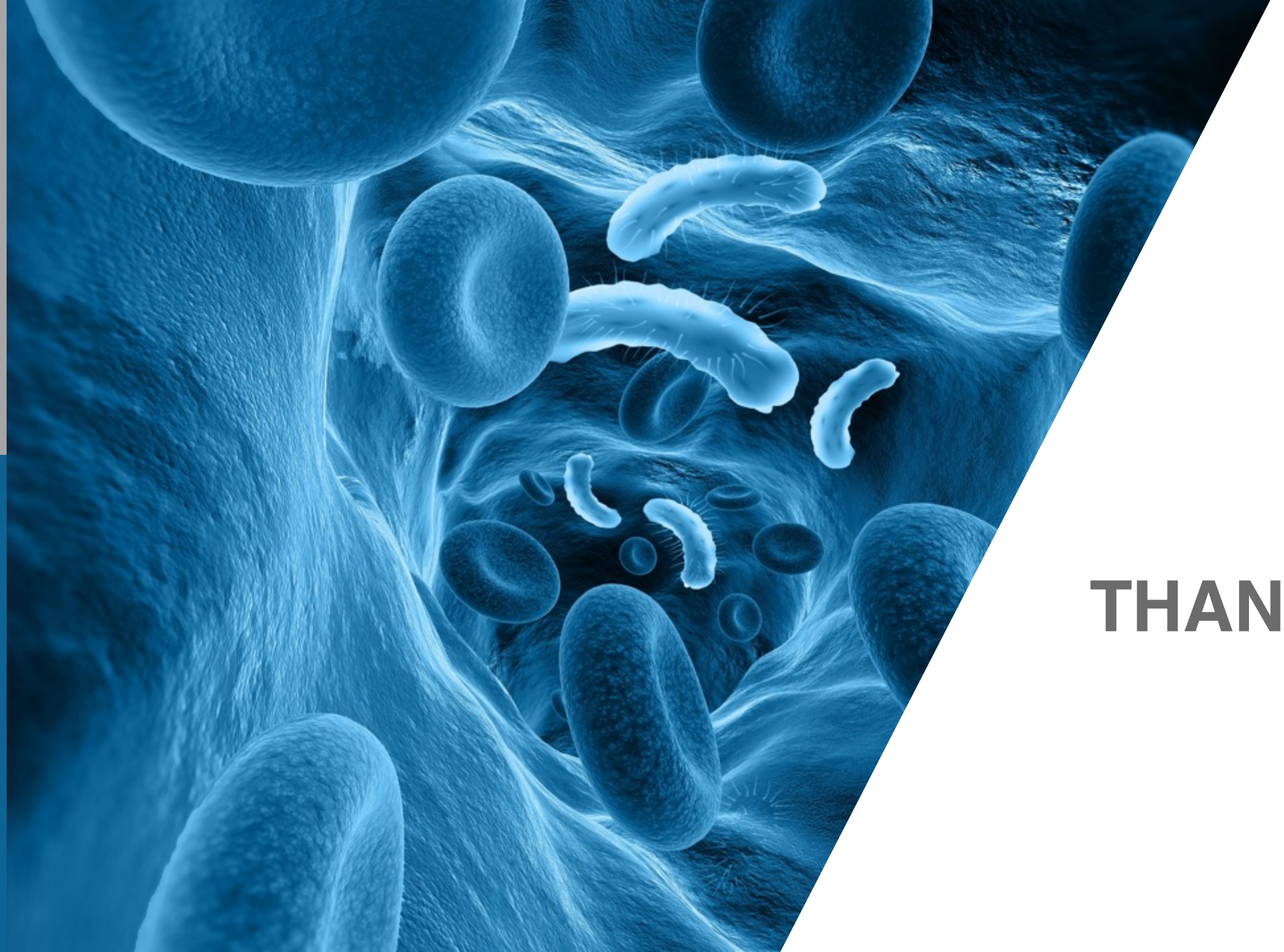
Maslove et al. Nat Med 2022 Jun;28(6):1141-1148.

Conclusions

- Clinical trials for ICU syndromes (e.g. sepsis, AKI) will fail without precision medicine
  - Endotyping, predictive and/or prognostic enrichment
  - Expect small and slow; Pragmatic trials = failed trials
- Blood purification trials carry additional burdens
  - ICU and nephrology staffing; wounded research enterprise post-COVID
  - Impracticality of Blinding; devices can breakdown post-randomization → mITT?
- Endotoxic Septic Shock (ESS) is an endotype of sepsis
  - ESS is a particularly malignant form of septic shock defined by multi-organ failure and EAA >0.6. It effects about 1 in 3 patients with septic shock or 10% of sepsis (but is responsible for a >25% of deaths) –mortality rate >50%
- Bayesian methods may be a viable option (reducing sample size requirements) for trials in Sepsis and AKI where beneficial treatments have been elusive.

TIGRIS CLINICAL TRIAL

JOHN A KELLUM, MD



THANK YOU