Sepsis care 2023: Is it time to get personal?

John A. Kellum, MD, MCCM

Professor of Critical Care Medicine, Medicine,
Bioengineering and Clinical & Translational Science
University of Pittsburgh

Chief Medical Officer
Spectral Medical

Disclosures

Chief Medical Officer
- Spectral Medical

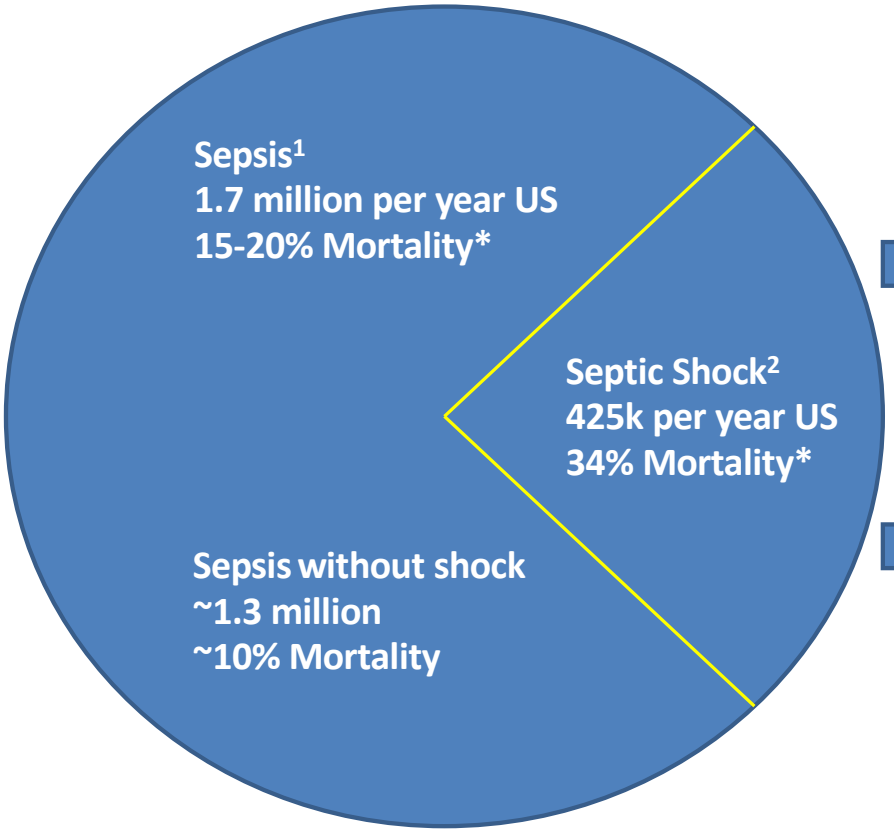
- Consultant
  - Astellas
  - Astute Medical
  - bioMérieux

- Intellectual Property
  - Astute Medical/bioMérieux
  - Cytosorbents
  - JƐRM
  - Klotho

Learning objectives

- Review the epidemiology of sepsis and inherent heterogeneity in the population
- Discuss the role of AI and molecular biology in subclassification of sepsis
- Review the role of endotoxin in pathophysiology of sepsis organ dysfunction.
- Understand how to measure endotoxin using the Endotoxin Activity Assay [EAA].
- Consider potential personized therapies for sepsis on the horizon

Sepsis Epidemiology



Endotoxemic Septic Shock[3]
140k per year US
>50% mortality

Other forms of Septic Shock
285k per year US
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

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

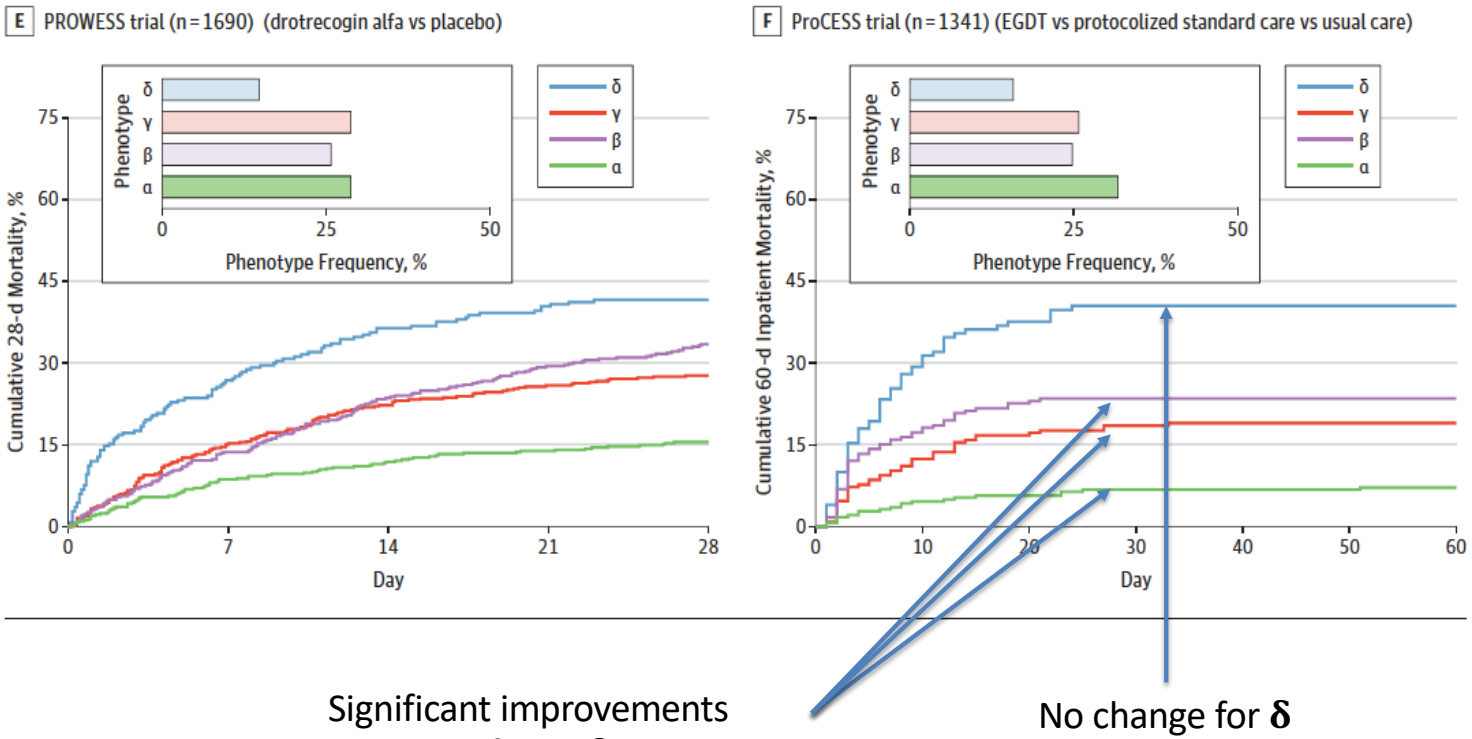
Acute Kidney Injury
Hepatic Dysfunction
Endothelial Dysfunction

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

Survival improving for most forms of sepsis . . .

2001

2014



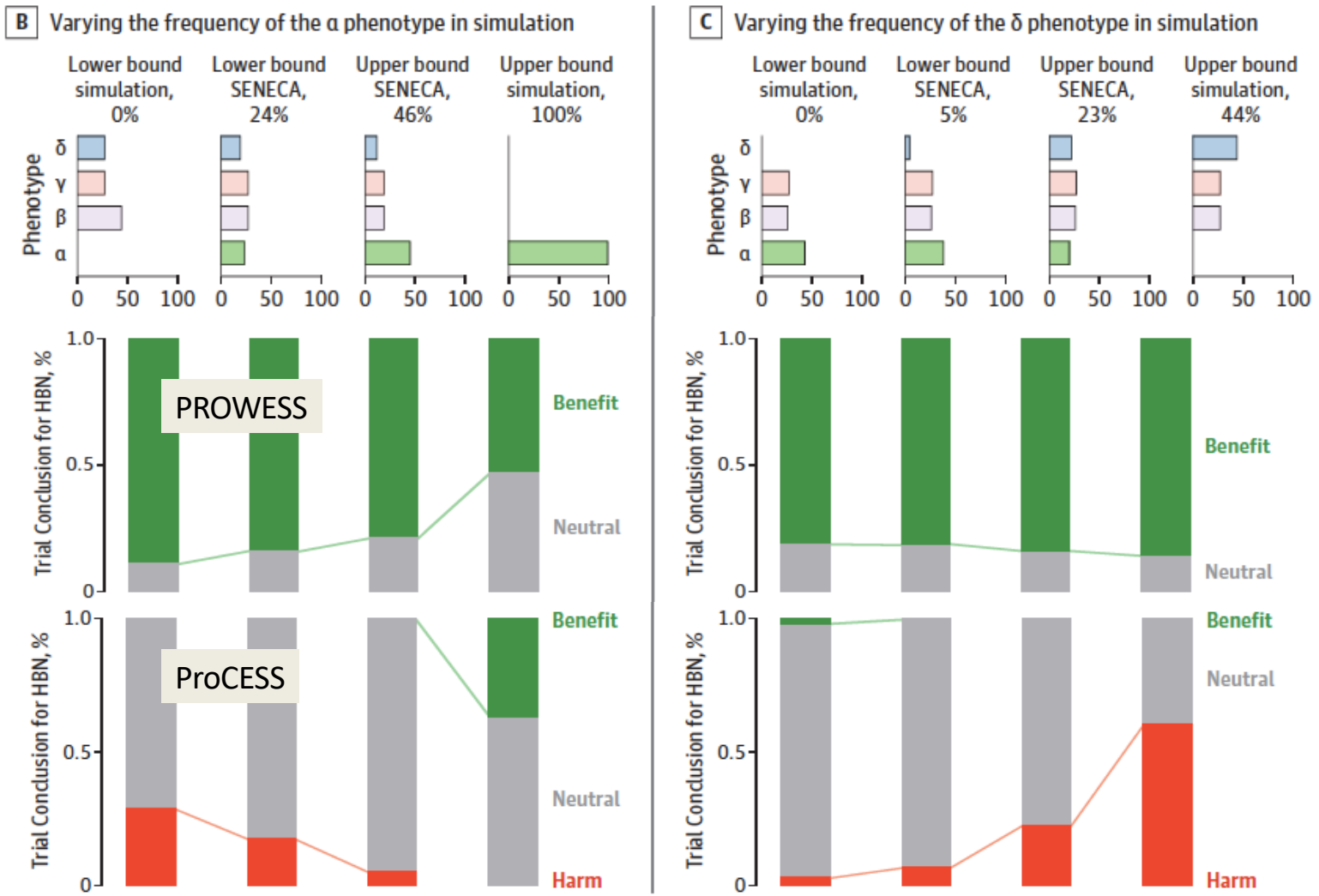
Significant improvements over time for **α**, **β**, and **γ** phenotypes

No change for **δ**

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

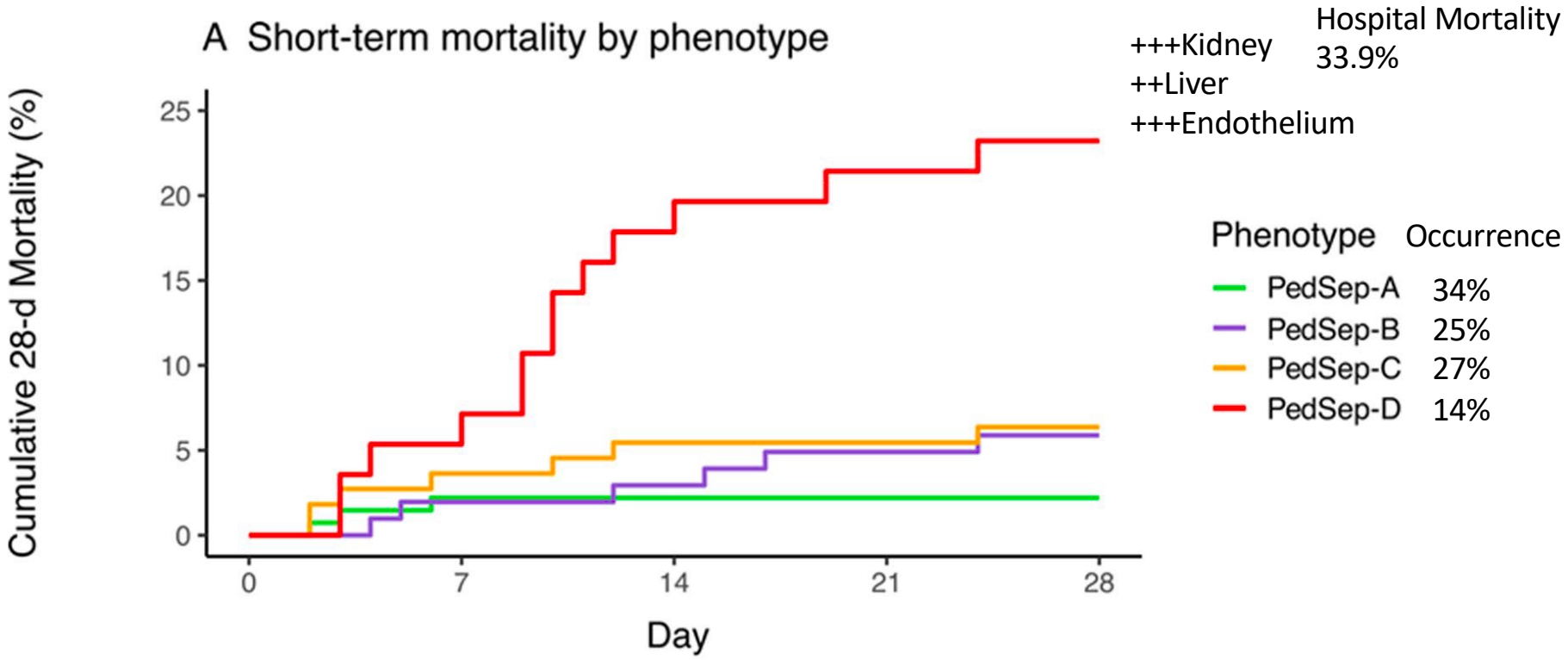
Why is sepsis mortality improving?

- No new interventions that improve survival
  - No new drugs
  - Not Fluids (EGDT trials and COVER were negative)
  - Not Vitamins (Vitamin C is actually harmful)
  - Maybe steroids for severe septic shock
- Better recognition?
  - Most important for cases that are mild or easily missed → usually these are less severe
  - Not all that causes fever is sepsis
- Emphasis on avoiding harm
  - Protective lung ventilation
  - Avoiding nephrotoxins (e.g. saline)



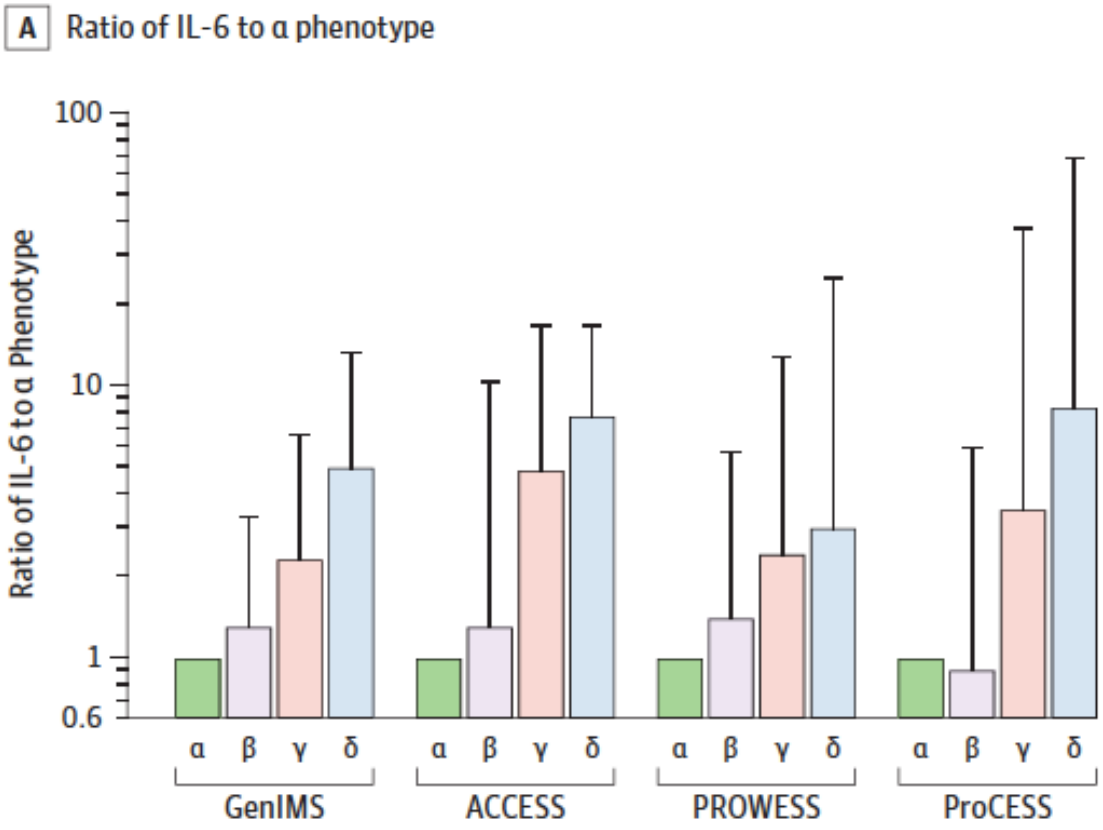
Seymour et al. JAMA. 2019;321(20):2003-2017.

Pediatrics



Qin *et al. Critical Care (2022) 26:128*

Phenotype is related to inflammatory mediator expression



…on average

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

Genetics

Phenotype

Environment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators

ABSTRACT

BACKGROUND

In a single-center study published more than a decade ago involving patients presenting to the emergency department with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT), in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to reach central hemodynamic targets, than among those receiving usual care. We conducted a trial to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.

The members of the writing committee (Donald M. Yealy, M.D., John A. Kellum, M.D., David T. Huang, M.D., Amber E. Barnato, M.D., Lisa A. Weissfeld, Ph.D., and Francis Pike, Ph.D., University of Pittsburgh, Pittsburgh; Thomas Terndrup, M.D., Ohio State University, Columbus; Henry E. Wang, M.D., University of Alabama at Birmingham, Birmingham; Peter C. Hou, M.D., Brigham and Women's Hospital, Boston; Frank LoVecchio, D.O., Maricopa

Genes & Immunity
https://doi.org/10.1038/s41435-018-0030-3

BRIEF COMMUNICATION

Adults with septic shock and extreme hyperferritinemia exhibit pathogenic immune variation

Kate F. Kernan[1,2] · Lina Ghaloul-Gonzalez[2,3,4] · Bita Shakoory · John A. Kellum[1] · Derek C. Angus[1] · Joseph A. Carcillo[1,2,3]

Table 1 Clinical phenotypes of subjects enrolled in the study

Subject	Age	Sex	SBP (mmHg)	Lactate (mmol/L)	WBC ($\times 10^9$/L)	Hgb (g/dL)	Plt ($\times 10^9$/L)	INR	PTT (s)	Tbili (mg/dL)	Cr (g/dL)	Ferritin (ηg/mL)	Infection	APACHE II	Dead at 30d
1	32	M	80	3.9	2.9	8.4	44	1.5		2.5	3.1	14,949	Culture negative	24	Yes
2	73	M	83	16	10.5	17.4	57	1.2	26.0	1.5	2.7	36,240	UTI/BSI	42	Yes
3	64	F	91	7.4	2.9	14.8	33			1.7	3.3	7,259	BSI	18	No
4	44	F	140	9.5	6.4	9.1	25	1.8		6.2	0.8	8,329	PNA/BSI	20	Yes
5	51	M	70	6.3	4.5	13.9	50		47.1	1.8	3.5	55,314	PNA/BSI	37	Yes
6	70	F	102	3.9	8.4	5.1	88	3.2	48.0	6.4	5.1	11,850	Culture negative	22	Yes

Subject	Gene	Variant	Amino acid change	Disease	MAF
1	*C3*	c.1407G>C [52] NM_000064.2	p.Glu469Asp	aHUS	0.00394
	UNC13D	c.1579C>T [25, 26] NM_199242.2	p.Arg527Trp	HLH	0.00523
2	*CD46*	c.1058C>T [57] NM_172359.2	p.Ala353Val	aHUS	0.01532
	CFHR5	c.832G>A [58] NM_030787	p.Gly278Ser		0.00729
3	*UNC13D*	c.2782C>T [27, 28] NM199242.2	p.Arg928Cys	HLH	0.02986
4	*NLRP3*	c.2113C>A [35] NM_004895.4	p.Gln705Lys	CAPS	0.0495
	MEFV	c.250G>A [37] NM_000243.2	p.Glu84Lys	FMF	0.00012
5	*UNC13D*	c.2983G>C [27] NM_199242.2	p.Ala995Pro	HLH	0.00096
		c.2542A>C [27] NM_199242.2	p.Ile848Leu		0.00090
6	*CD46*	c.1058C>T [57] NM_172359.2	p.Ala353Val	aHUS	0.01532
	MEFV	c.2084A>G [60] NM_000243.2	p.Lys695Arg	FMF	0.00550

*

aHUS: atypical hemolytic uremic syndrome

HLH: Hemophagocytic Lymphohistiocytosis—a.k.a. Macrophage activation Syndrome (MAS)

*Minor Allele Frequency

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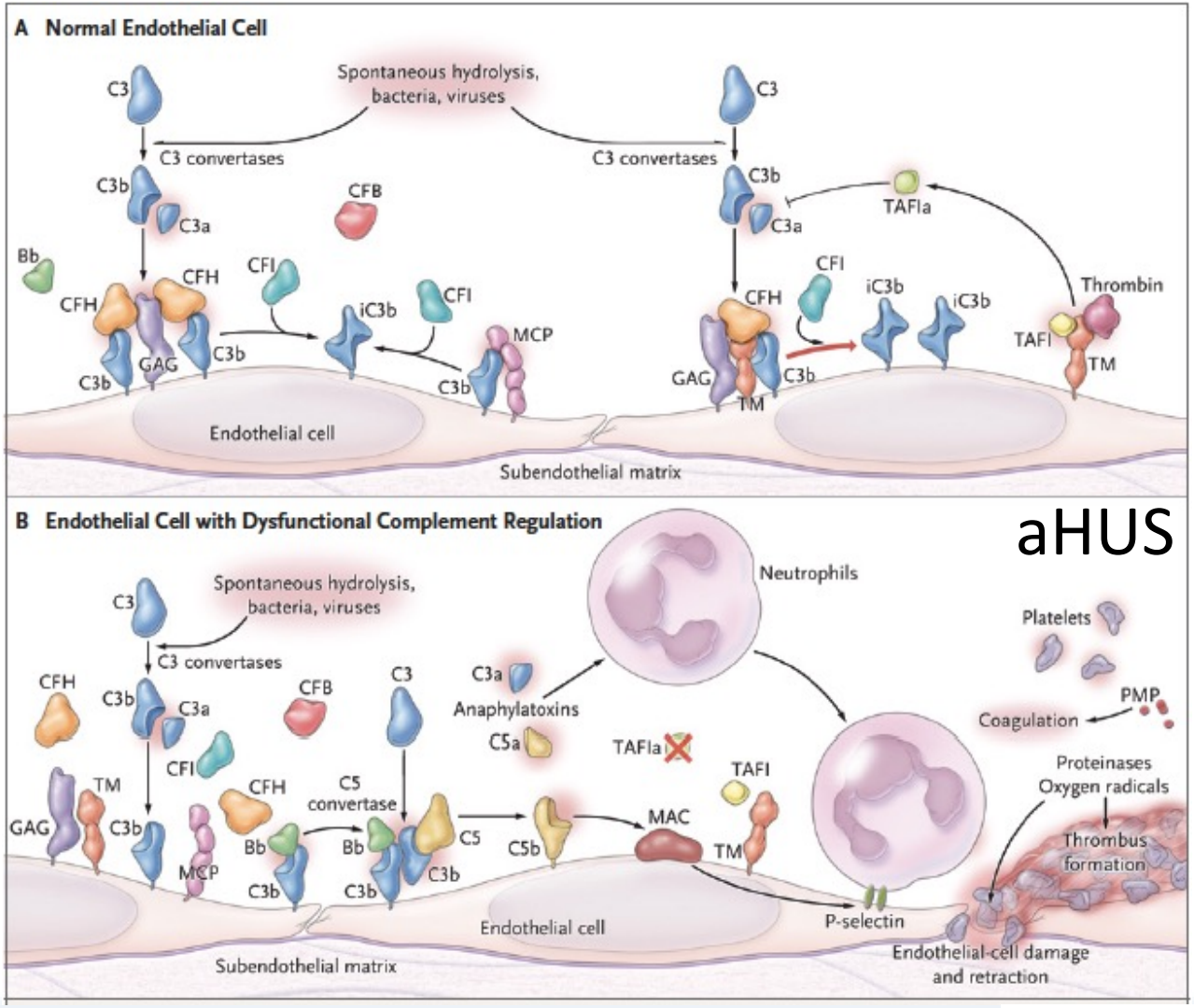


aHUS

N Engl J Med 2009;361:1676-87.

Known genetic defects

Table 2. Genetic Abnormalities and Clinical Outcome in Patients with Atypical Hemolytic–Uremic Syndrome.*

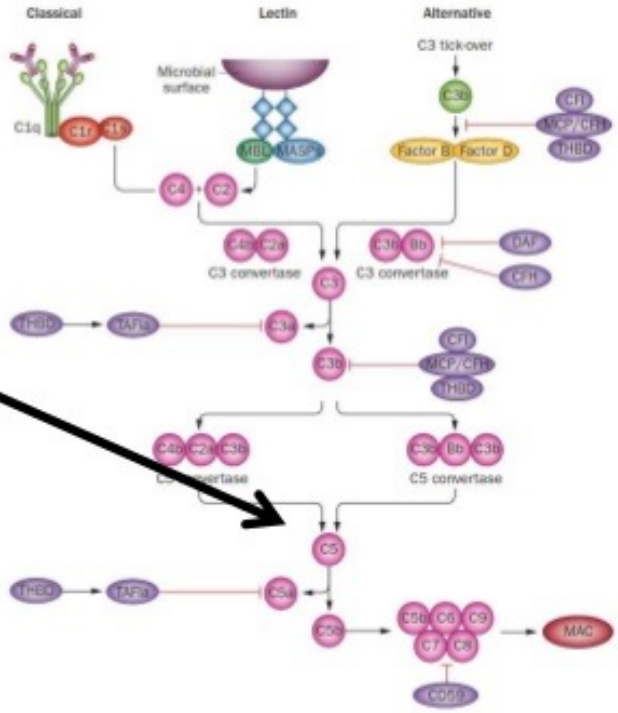
Gene	Protein Affected	Main Effect	Frequency	Response to Short-Term Plasma Therapy†	Long-Term Outcome‡	Outcome of Kidney Transplantation
			%			
CFH	Factor H	No binding to endothelium	20–30	Rate of remission: 60% (dose and timing dependent)	Rate of death or ESRD: 70–80%	Rate of recurrence: 80–90%§
CFHR1/3	Factor HR1, R3	Anti–factor H antibodies	6	Rate of remission: 70–80% (plasma exchange combined with immunosuppression)	Rate of ESRD: 30–40%	Rate of recurrence: 20%¶
MCP	Membrane cofactor protein	No surface expression	10–15	No definitive indication for therapy	Rate of death or ESRD: <20%	Rate of recurrence: 15–20%¶
CFI	Factor I	Low level or low cofactor activity	4–10	Rate of remission: 30–40%	Rate of death or ESRD: 60–70%	Rate of recurrence: 70–80%§
CFB	Factor B	C3 convertase stabilization	1–2	Rate of remission: 30%	Rate of death or ESRD: 70%	Recurrence in one case
C3	Complement C3	Resistance to C3b inactivation	5–10	Rate of remission: 40–50%	Rate of death or ESRD: 60%	Rate of recurrence: 40–50%
THBD	Thrombomodulin	Reduced C3b inactivation	5	Rate of remission: 60%	Rate of death or ESRD: 60%	Recurrence in one case

N Engl J Med 2009;361:1676-87.

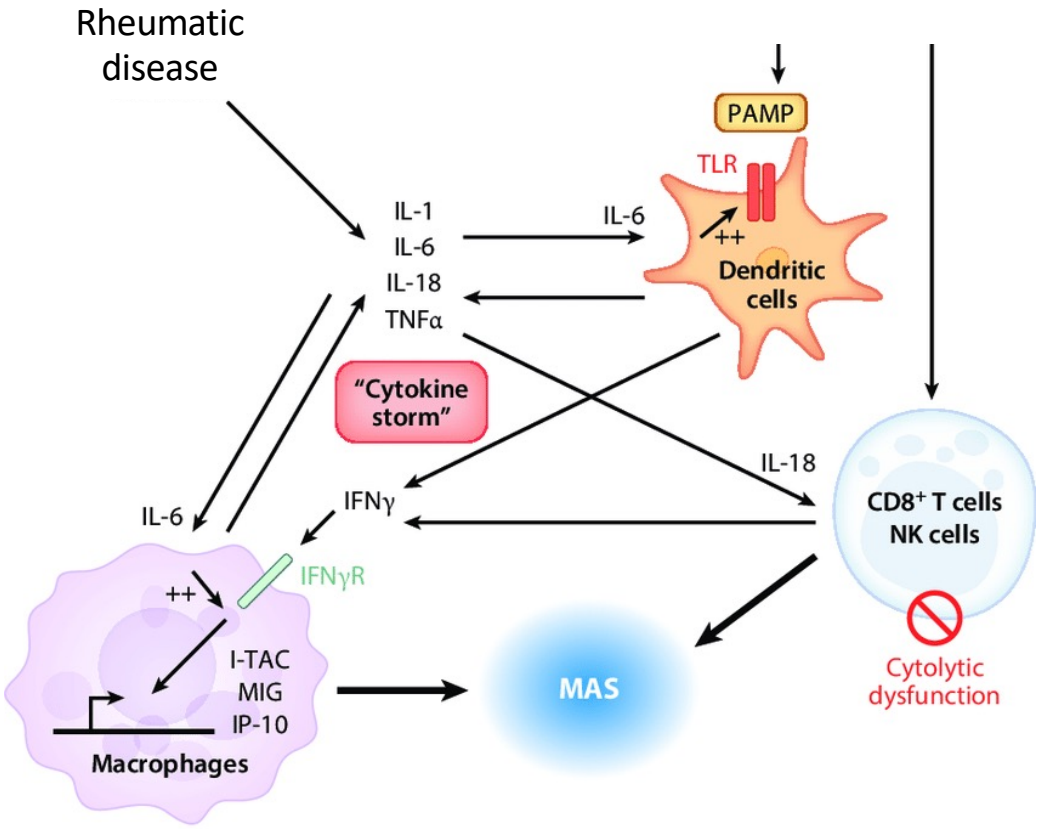
Treatment

Eculizumab

- C5 Inhibitor



MAS/HLH



Clinical features
Nonremitting fever
Hepatomegaly
Splenomegaly
Lymphadenopathy
Hemorrhagic manifestations
Encephalopathy

Laboratory features
Cytopenias
Abnormal liver function tests
Coagulopathy (DIC)
Decreased ESR
Hypertriglyceridemia
Increased lactate dehydrogenase level
Hyperferritinemia

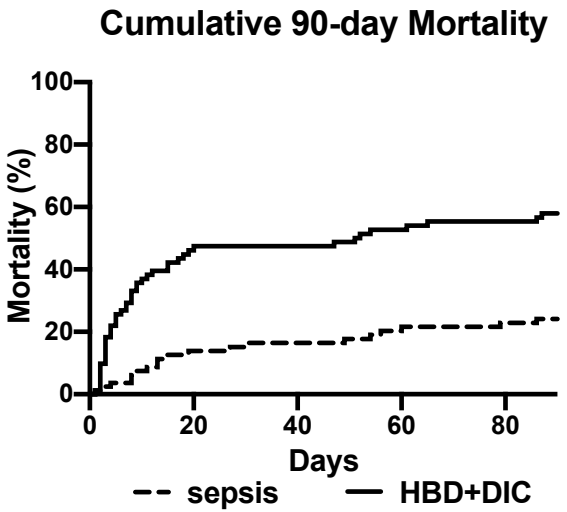
Histopathologic features
Bone marrow: Macrophage hemophagocytosis
Increased CD163 staining

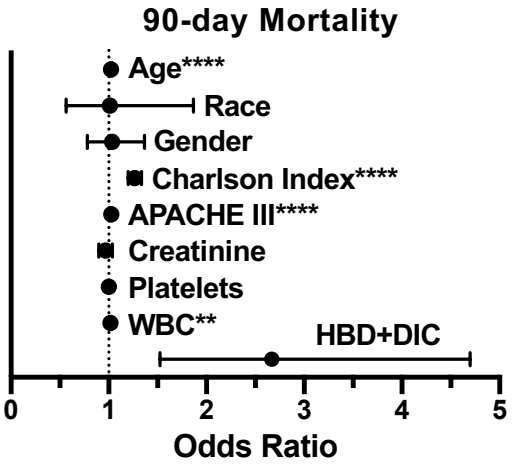
Schulert, Grant & Grom, Alexei. (2014). Annual review of medicine. 66.

Hematol Oncol Clin N Am 29 (2015) 927–941

MAS: ProCESS

HBD (T Bili ≥ 1.2 mg/dL)
DIC (Plts ≤ 100 and INR >1.5)
N = 82/1341 (6%)

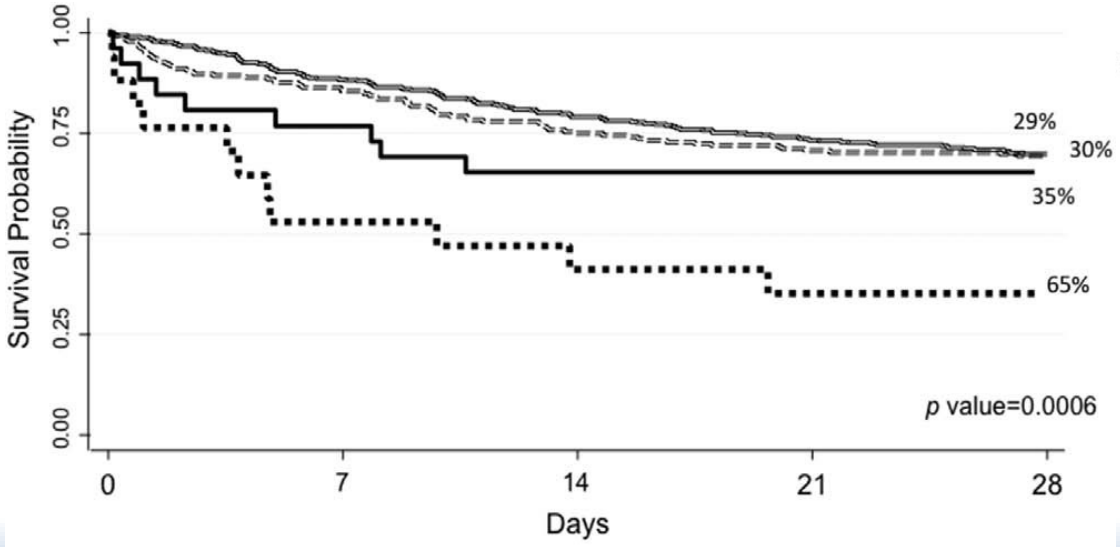




Anderko et al. ICMx. 2022;10(1):6.

Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial*

Bita Shakoory, MD[1]; Joseph A. Carcillo, MD[2]; W. Winn Chatham, MD[3]; Richard L. Amdur, PhD[4]; Huaqing Zhao, PhD[4]; Charles A. Dinarello, MD[5]; Randall Q. Cron, MD, PhD[6]; Steven M. Opal, MD[7]



Non-HBD/DIC+ rIL-1Ra (n=484); Mortality (%): 145 (29)

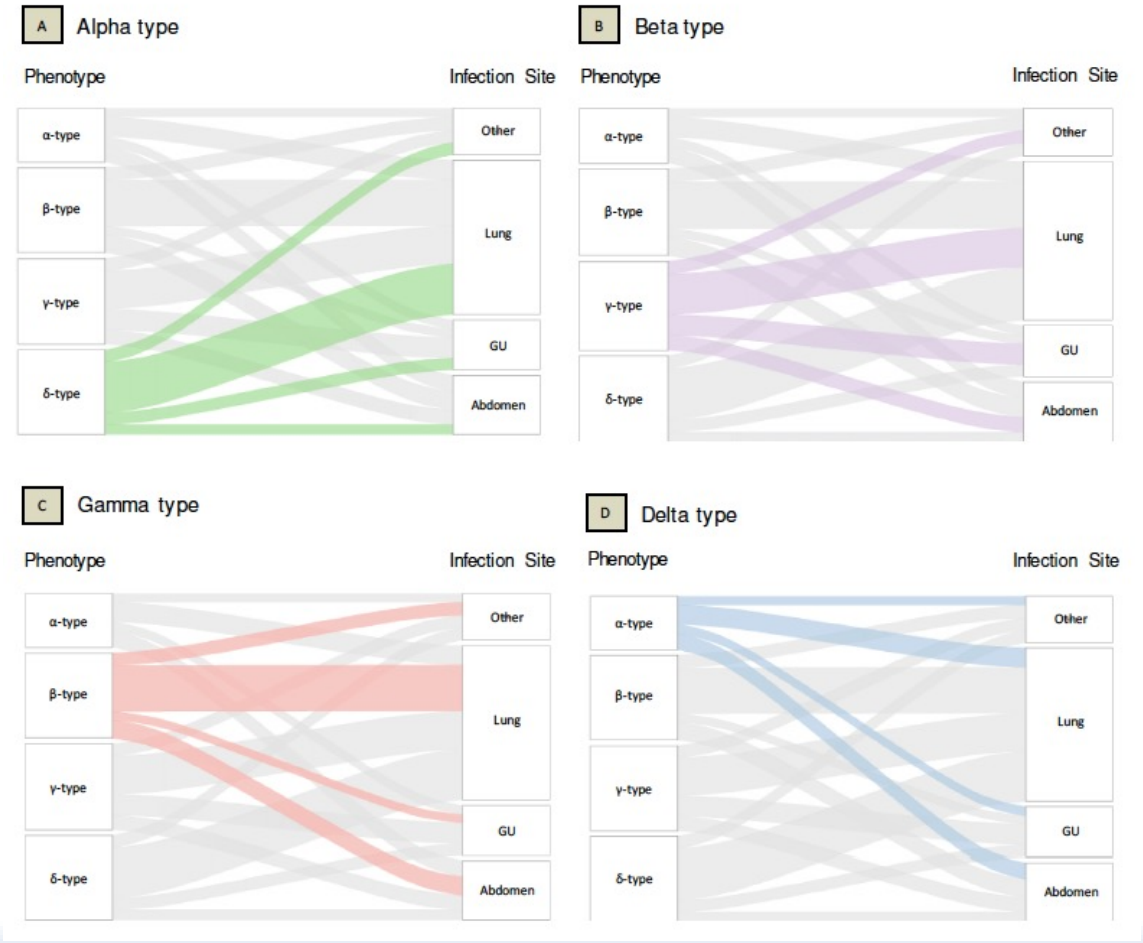
Non-HBD/DIC+ placebo (n=236); Mortality (%): 72 (30)

HBD/DIC+ rIL-1Ra (n= 26); Mortality (%): 9 (35)

HBD/DIC+ placebo (n=17); **Mortality (%): 11 (65)**

Total N = 43/763 5.6%

Environment: Phenotype is not related to site of infection



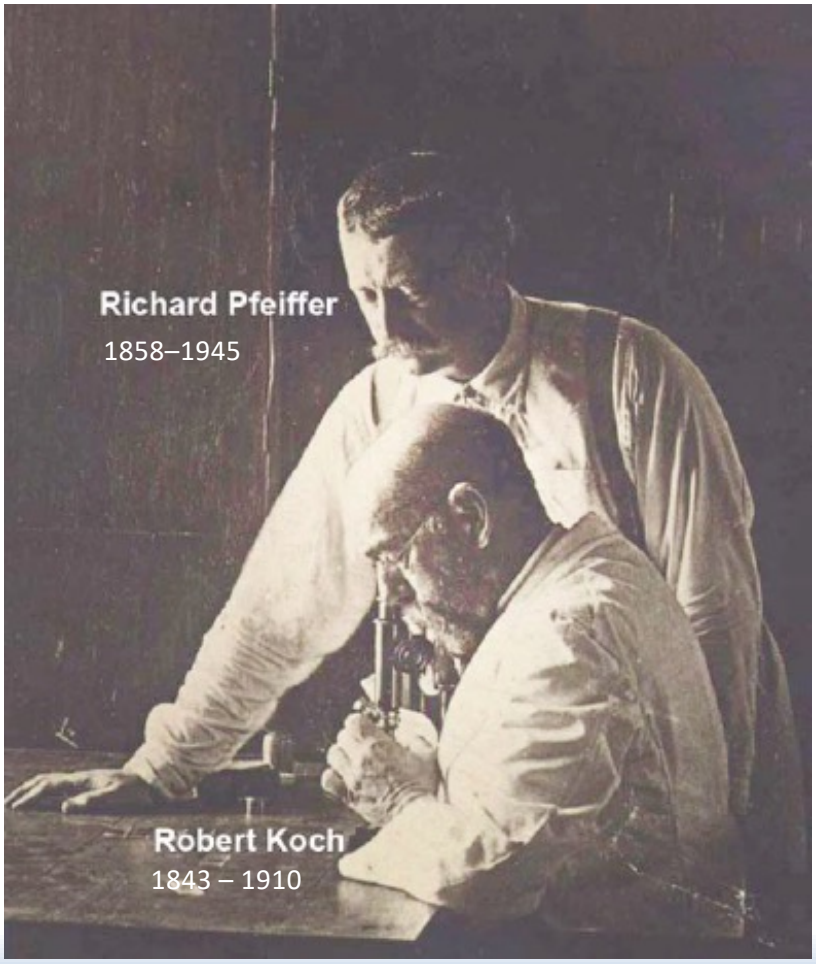
Seymour et al. JAMA. 2019;321(20):2003-2017.

Environment: (Bacteria)

Infection (and contagion) were concepts known in ancient times

Microbes were only discovered in the 17th century

And the association between microbes and infection was not known until the 19th century



- Soon after microbes were discovered it was appreciated that animals recognize them as foreign and mount an inflammatory response

- 1892 Richard Pfeiffer noticed that bacterial cell wall induced a picture of bacterial infection without viable bacteria present

- By the 1920-30s it was recognized as a contaminant in parenteral fluids and drugs

- Hypothesized as a driver of inflammation

Defective LPS Signaling in C3H/HeJ and C57BL/10ScCr Mice: Mutations in *Tlr4* Gene

Alexander Poltorak, Xiaolong He,* Irina Smirnova, Mu-Ya Liu,† Christophe Van Huffel,‡ Xin Du, Dale Birdwell, Erica Alejos, Maria Silva, Chris Galanos, Marina Freudenberg, Paola Ricciardi-Castagnoli, Betsy Layton, Bruce Beutler§

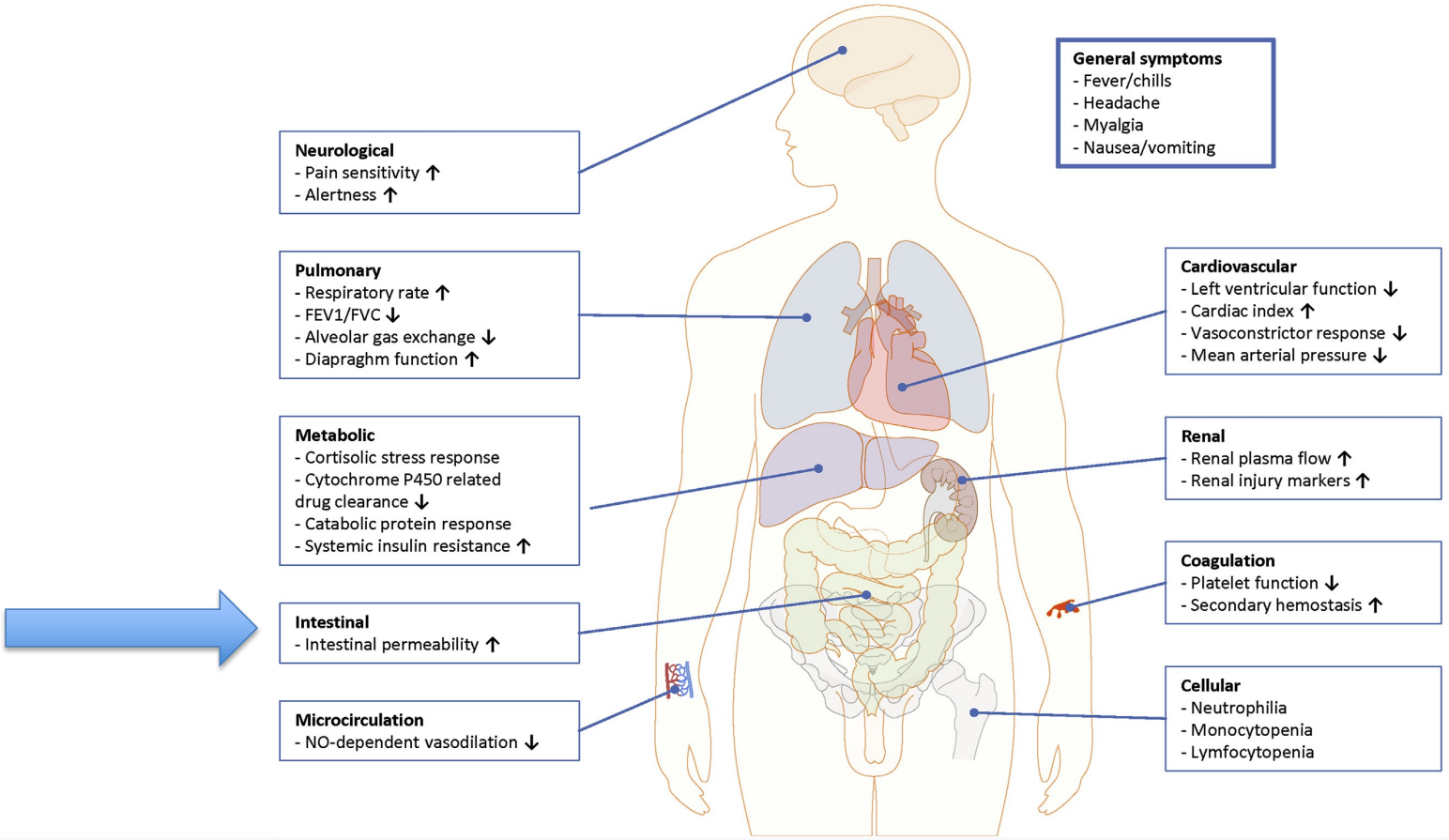
Mutations of the gene *Lps* selectively impede lipopolysaccharide (LPS) signal transduction in C3H/HeJ and C57BL/10ScCr mice, rendering them resistant to endotoxin yet highly susceptible to Gram-negative infection. The codominant Lps^d allele of C3H/HeJ mice was shown to correspond to a missense mutation in the third exon of the Toll-like receptor-4 gene (*Tlr4*), predicted to replace proline with histidine at position 712 of the polypeptide chain. C57BL/10ScCr mice are homozygous for a null mutation of *Tlr4*. Thus, the mammalian Tlr4 protein has been adapted primarily to subserve the recognition of LPS and presumably transduces the LPS signal across the plasma membrane. Destructive mutations of *Tlr4* predispose to the development of Gram-negative sepsis, leaving most aspects of immune function intact.

Conservative estimates hold that in the United States alone, 20,000 people die each year as a result of septic shock brought on by Gram-negative infection (*1*). The lethal effect of a Gram-negative infection is linked, in part, to the biological effects of bacterial lipopolysaccharide (endotoxin), which is produced by all Gram-negative organisms. A powerful activator of host mononuclear cells, LPS prompts the synthesis and release of tumor necrosis factor (TNF) and other toxic cytokines that ultimately lead to shock in

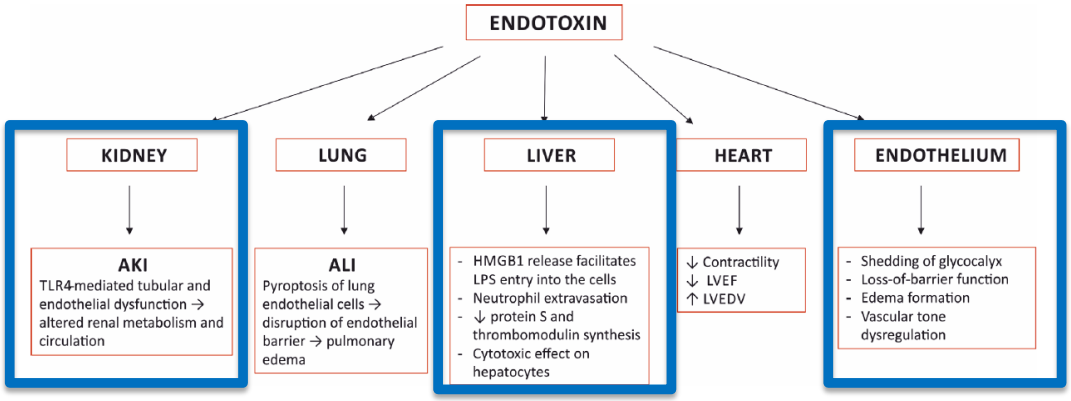
www.sciencemag.org SCIENCE VOL 282 11 DECEMBER 1998

Nobel Prize, 2011
Together with
Jules Hoffman

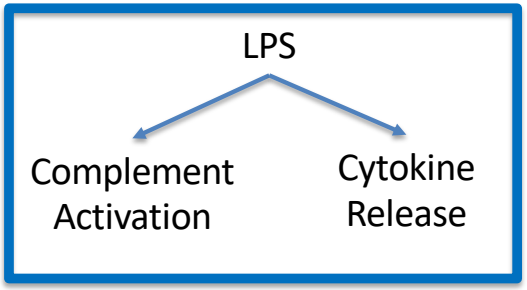
Low-dose endotoxin administration



D. van Lier et al. / Biochimie 159 (2019) 99e106



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

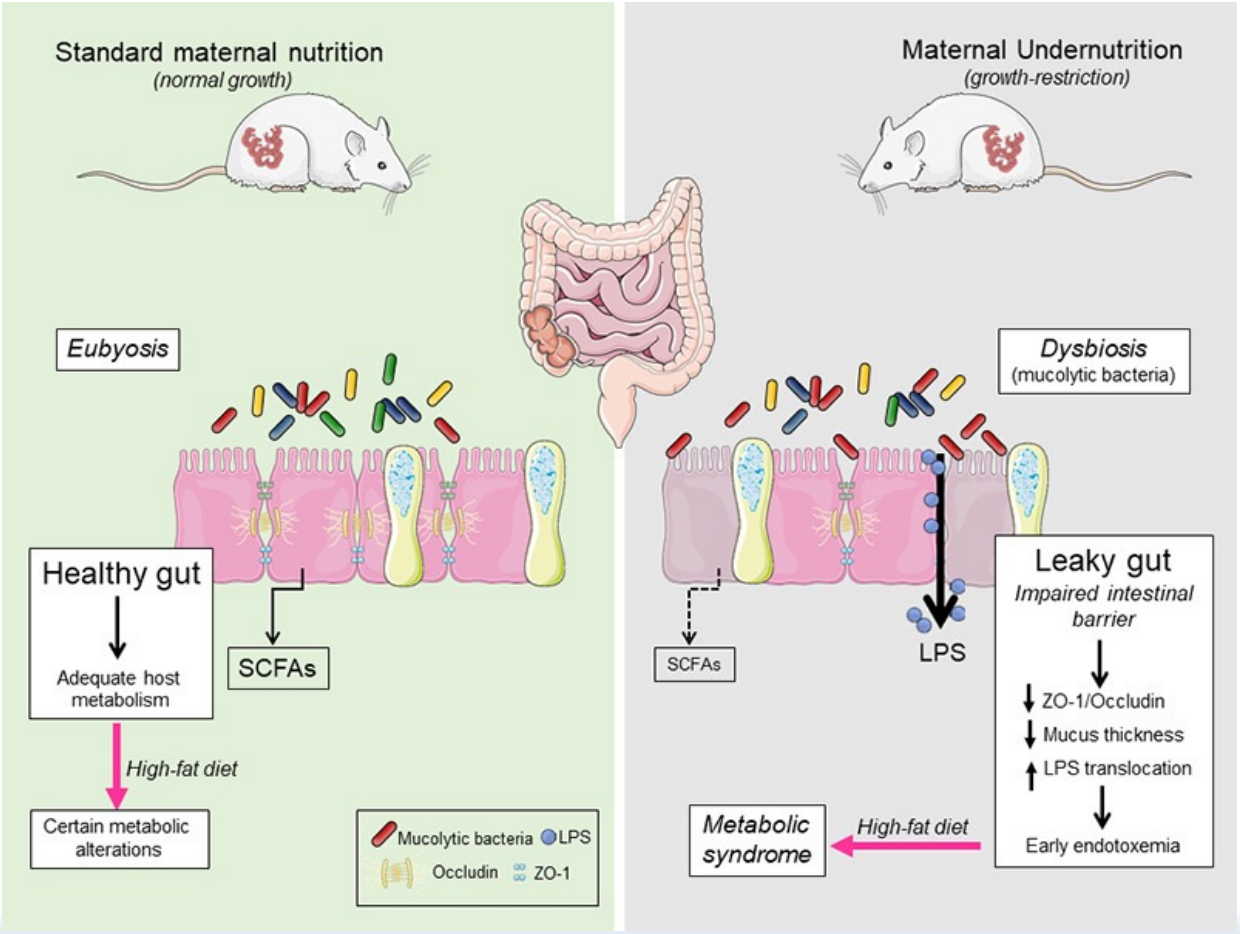
THE NEW ENGLAND JOURNAL OF MEDICINE May 20, 1993

Endotoxemia ≠ bacteremia

- Endotoxin in bloodstream does not equate to primary or secondary blood stream infections.
- >70% of patients with sepsis with high endotoxin activity have negative blood cultures.[1]
- Endotoxemia can result from…
  - Active infections gram negative bacteria
  - Infections with various types of organisms (including COVID-19) that compromise gut barrier function (resulting in translocation of endotoxin)[2]
  - Antibiotics can release endotoxin as they kill bacteria[3]

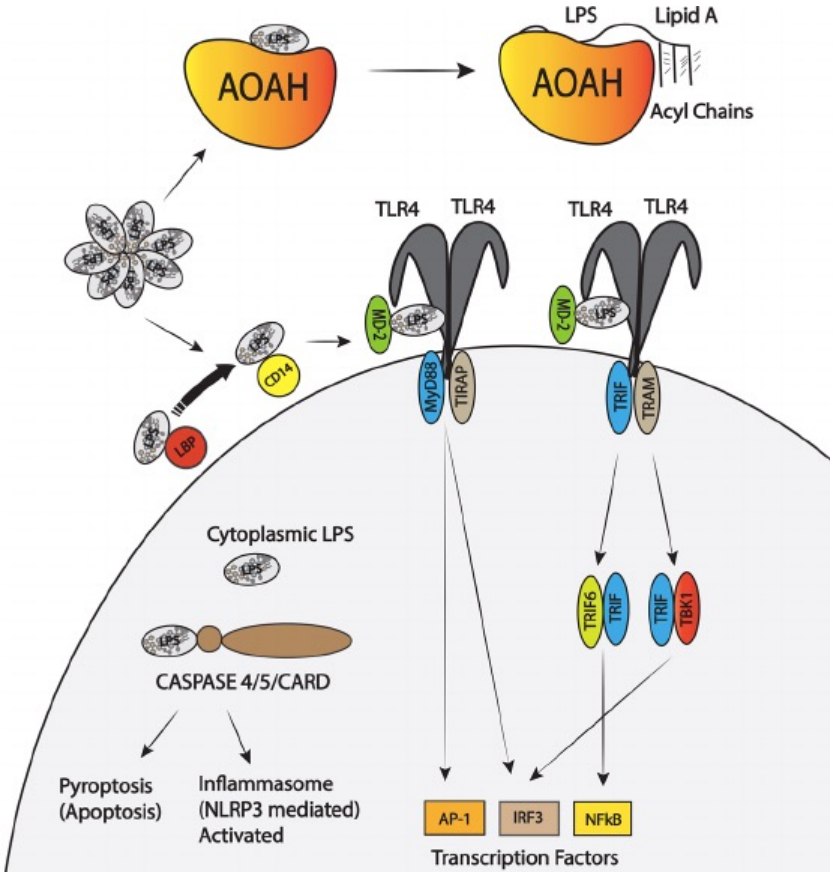
[1]Dellinger RP et al. JAMA. 2018;320(14):1455-1463
[2]Sirivongrangson P et al. Intensive Care Med Exp. 2020;8(1):72.
[3]Dofferhoff AS et al. *Scand. J. Infect. Dis. 1991;*23, 745–754.

Mucolytic bacteria → loss of barrier function



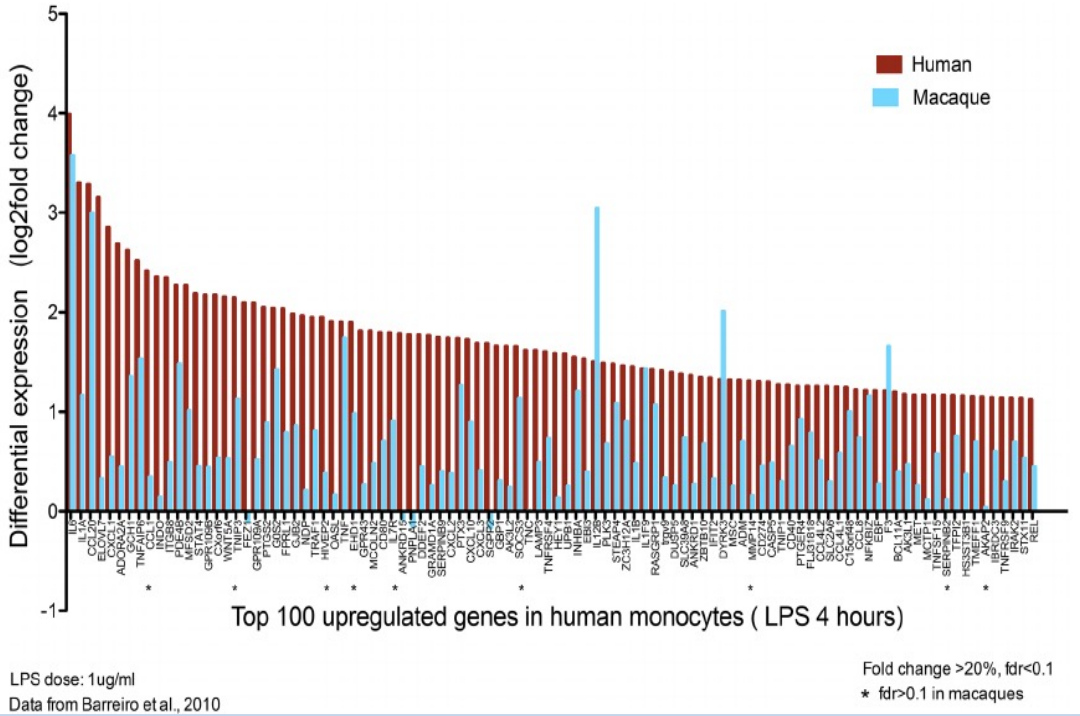
Martínez-Oca et al.
J Nutr Biochem, 81: 2020

Endotoxin signaling

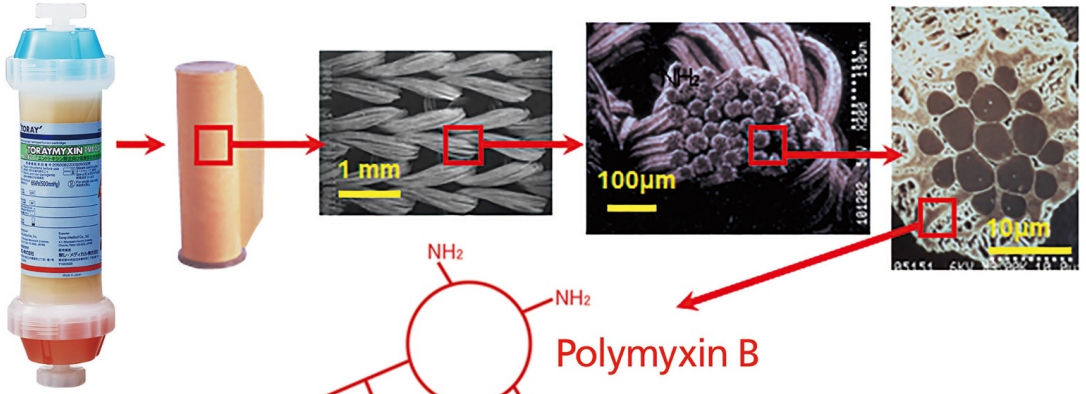


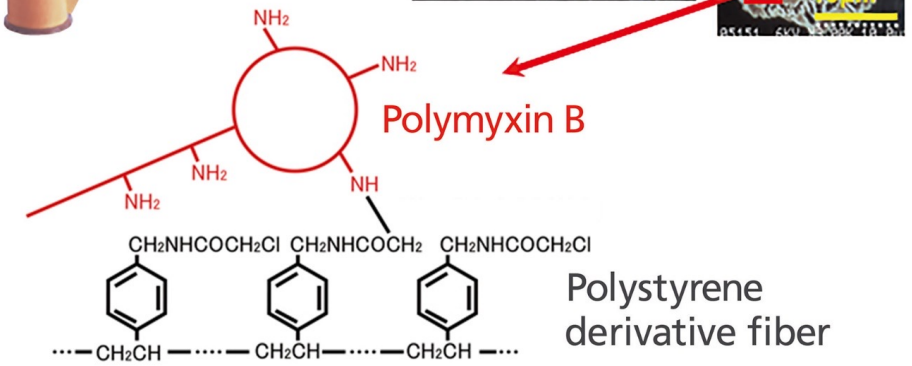
Evolutionary Anthropology. 2021;1–17.

Humans are exquisitely sensitive to endotoxin

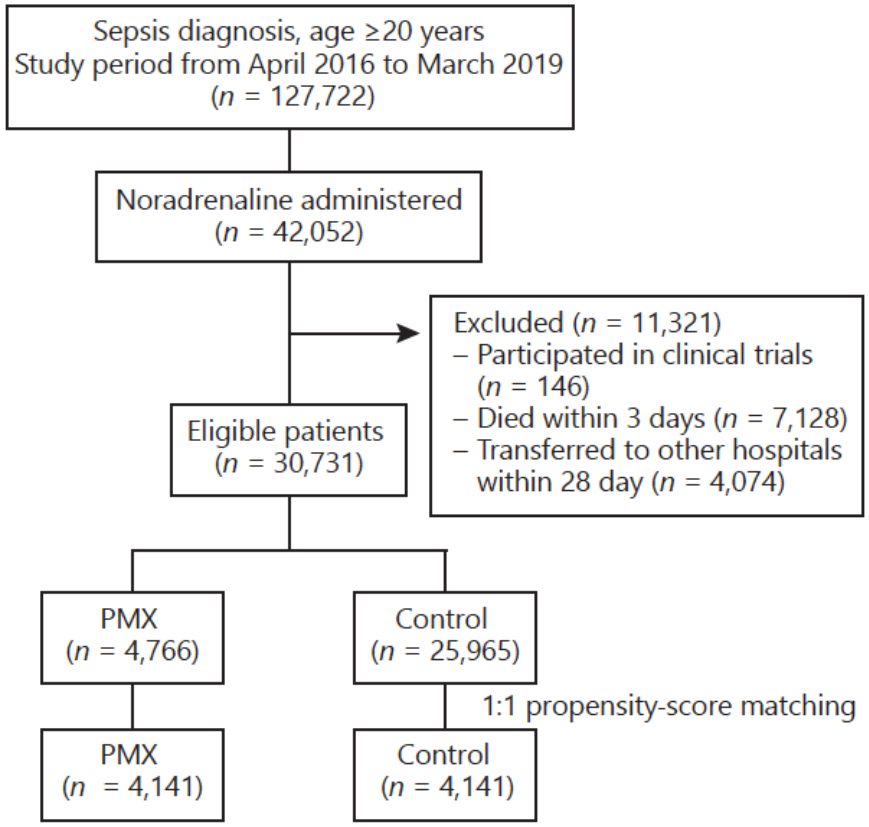


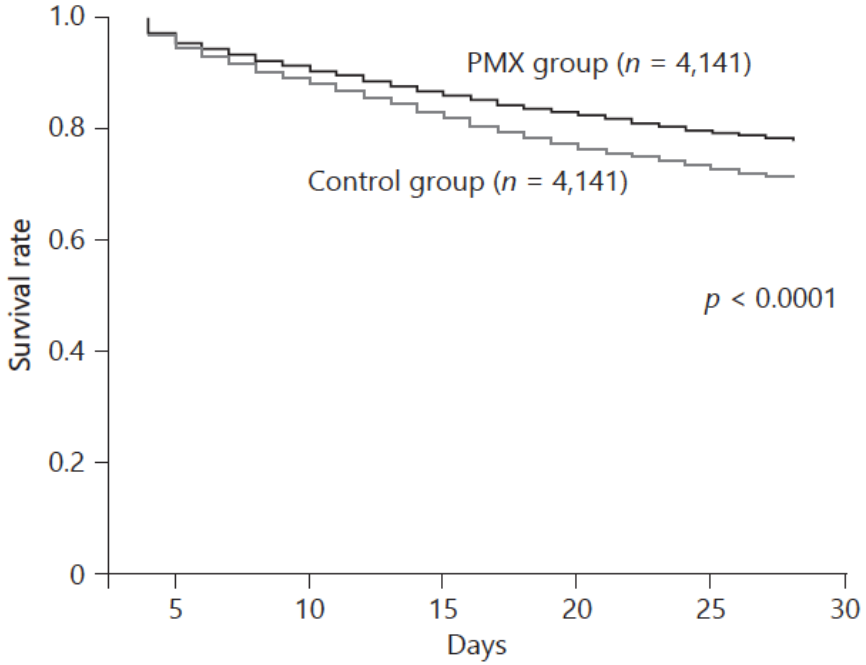
Treatment: Endotoxin adsorption





Survival benefit with PMX-hemoperfusion



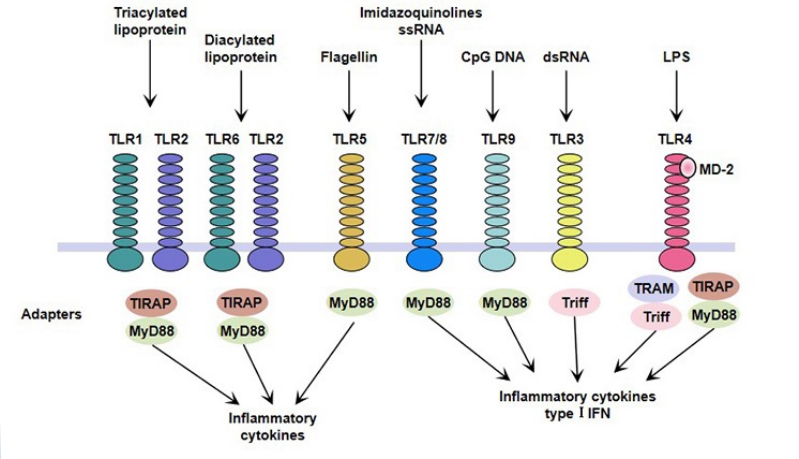


Survival at day 28 was 77.9% with PMX
Vs. 71.1% with SOC (p < 0.0001)
OR 1.433 (95% CI, 1.298–1.584)
ARR 6.8%

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

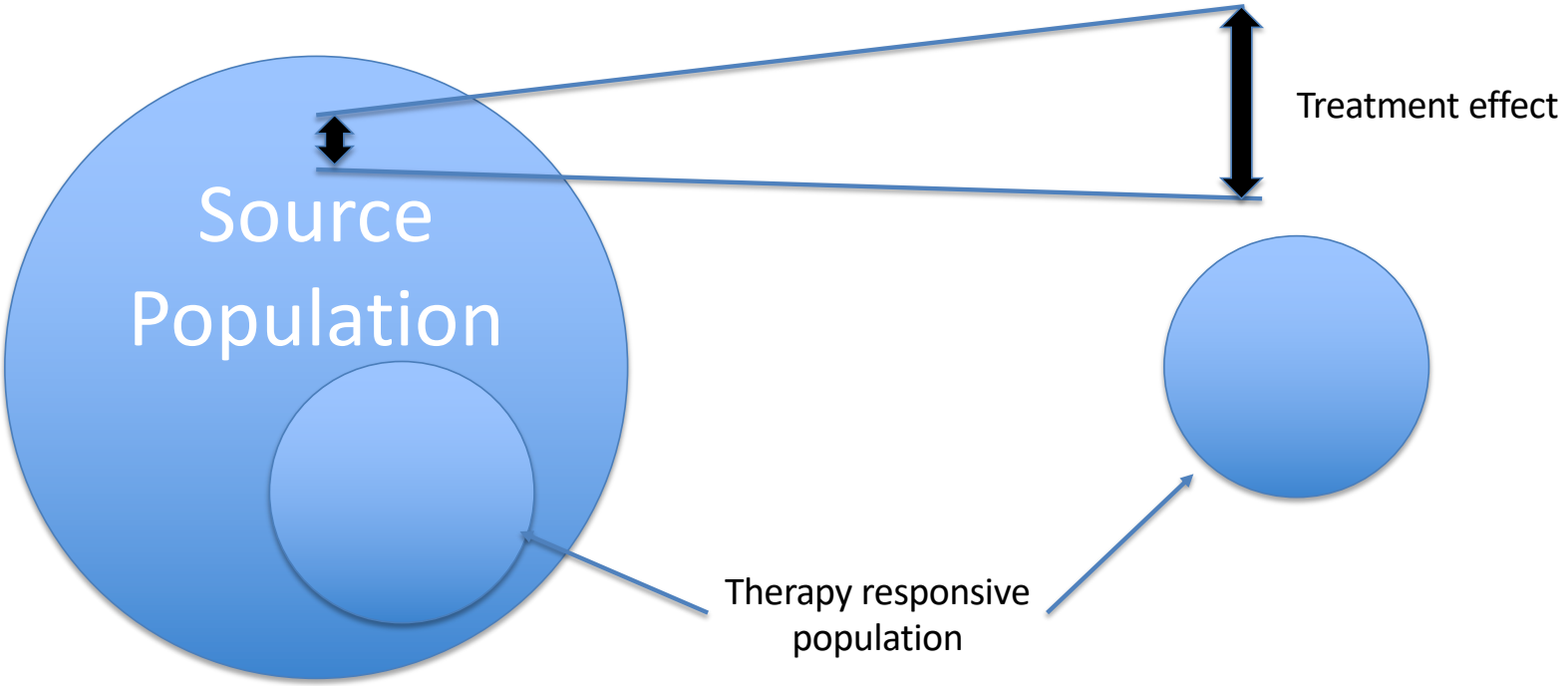
Environment: DAMPs and PAMPs

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

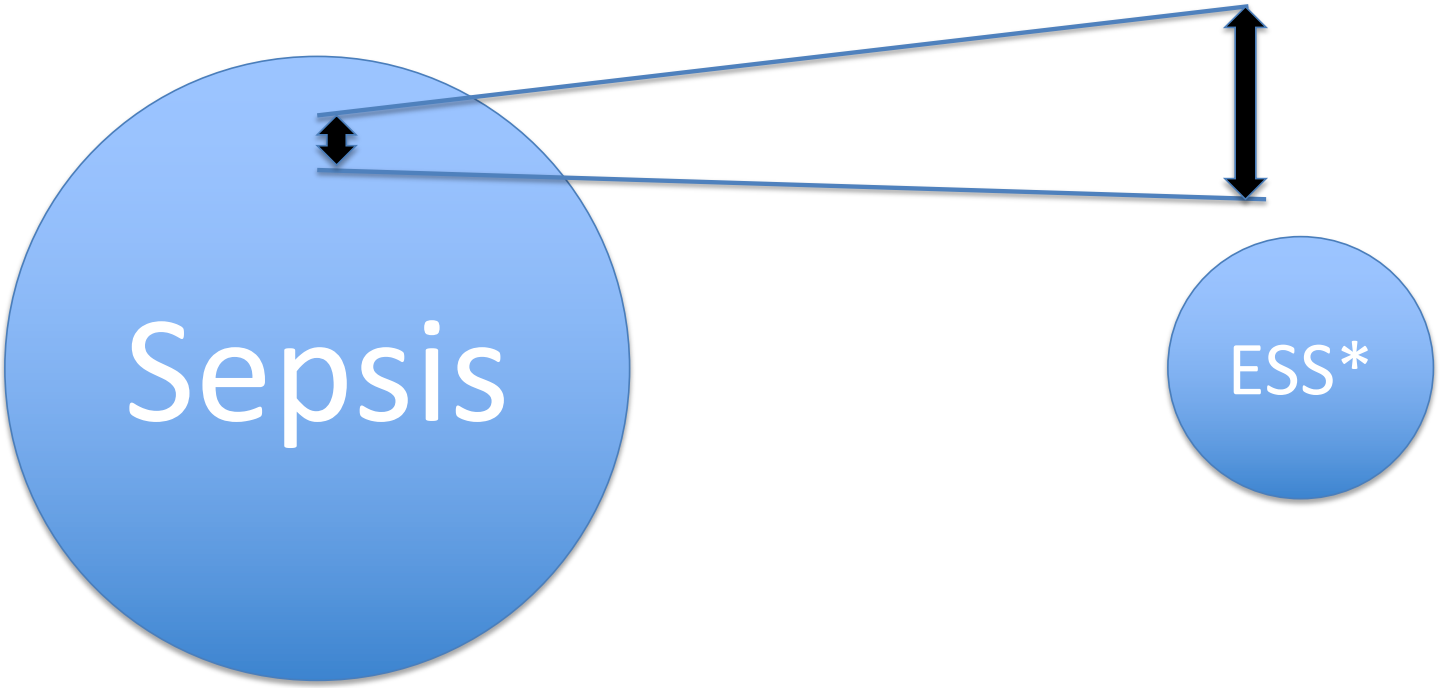


- Pathogen-Associated Molecular Patterns
  - Endotoxin
  - Flagellin
  - Lipoteichoic acid (gram-positive bacteria)
  - Peptidoglycan
  - Nucleic acid variants (viruses) e.g. double-stranded RNA (dsRNA), unmethylated CpG motifs

Effect size vs. Addressable Population



Effect size vs. Addressable Population



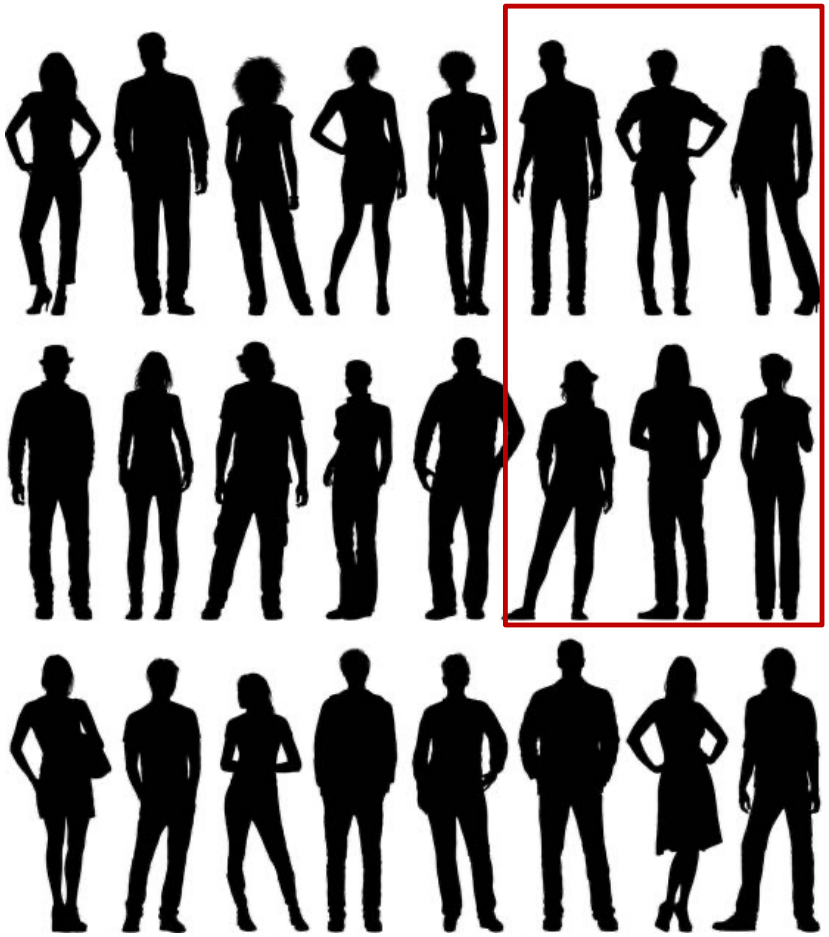
*Endotoxemic Septic Shock

Patient Selection

Lipoteichoic acid

Peptidoglycan

HMGB1



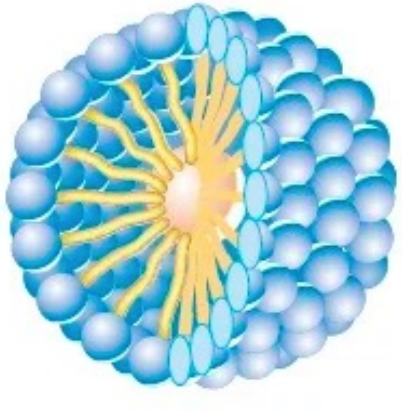
Endotoxin

Enrichment

dsDNA

Flagellin

Enrichment: Measuring Endotoxin



- Endotoxin is difficult to measure in blood
- Endotoxin is carried in the blood by. . .
  - LBP—#lipopolysaccharide binding protein
  - HDL— high density lipoproteins
    - Micelles due to its hydrophobic and hydrophilic portions
  - Adheres to albumin and cell walls
  - Very little exists as "free endotoxin"

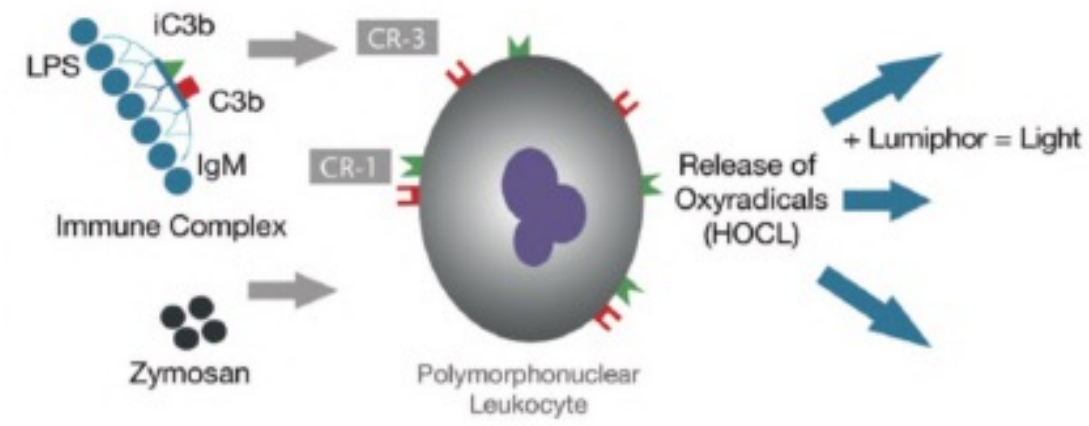
- Limulus Amebocyte Lysate (LAL)
  - Endolymph from a horseshoe crabs agglutinates when exposed to endotoxin --cannot use for blood

- Endotoxin Activity Assay (EAA)
  - Able to quantify endotoxin in whole blood
  - FDA approved for sepsis risk assessment in 2003

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.



Diagnostic and Prognostic Implications of Endotoxemia in Critical Illness: Results of the MEDIC Study

John C. Marshall,[1] Debra Foster,[4] Jean-Louis Vincent,[6] Deborah J. Cook,[5] Jonathan Cohen,[11] R. Phillip Dellinger,[9,a] Steven Opal,[7] Edward Abraham,[8] Stephen J. Brett,[10] Terry Smith,[2] Sangeeta Mehta,[3] Anastasia Derzko,[4] and Alex Romaschin[1,4]

[1]University Health Network, [2]Sunnybrook and Womens' Health Science Centre, and [3]Mt. Sinai Hospital, Ur Diagnostics, Toronto, and [5]St. Joseph's Hospital, McMaster University, Hamilton, Canada; [6]Erasme Universi Brussels, Belgium; [7]Memorial Hospital of Rhode Island, Brown University, Providence; [8]University of Colora [9]Rush Presbyterian University, Chicago, Illinois; [10]Hammersmith Hospital, London, and [11]Brighton and Susse of Brighton, Brighton, United Kingdom

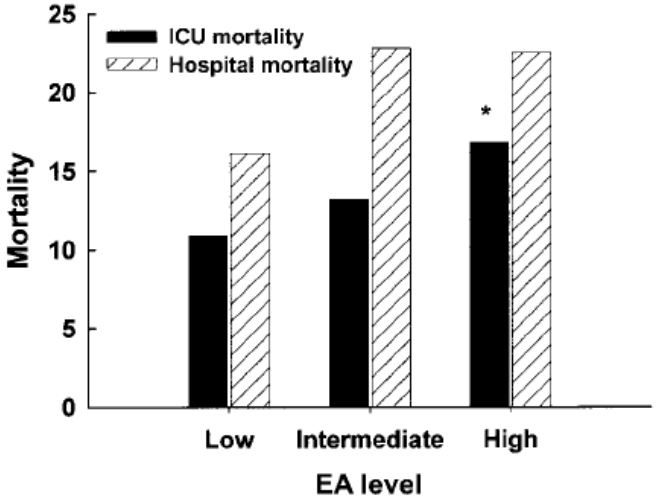


Table 4. Endotoxin activity (EA) level and risk of severe sepsis.

EA level	Risk of severe sepsis in first 24 h of ICU admission, % (no./total)	OR (95% CI)[a]	*P*
Low (<0.40)	4.9 (18/367)	…	…
Intermediate (0.40–0.60)	9.2 (21/228)	2.0 (1.0–3.8)	<.05
High (>0.60)	13.4 (35/262)	3.0 (1.7–0.5)	<.001

NOTE. CI, confidence interval; ICU, intensive-care unit; OR, odds ratio.

[a] Mantel-Haenzel $\chi^2 = 13.962$, $P = .0002$.

J Infect Dis (2004):190, 527–534.

Endotoxin adsorption

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

Overall no effect on survival

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

Table 3. Per-Protocol (Each Group Received 2 Treatments) 28-Day Mortality

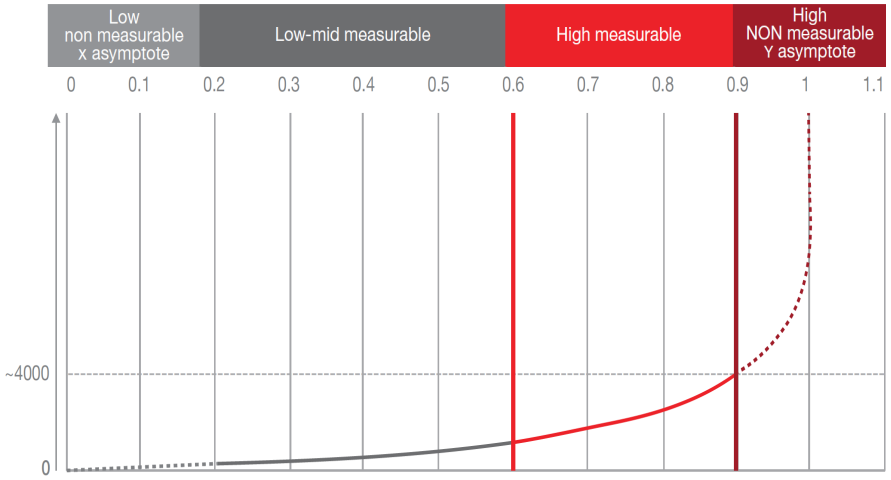
	No./Total (%)			
Population	Polymyxin-B Hemoperfusion	Sham	Difference, % (95% CI)	*P* Value[a]
All participants	50/173 (28.9)	59/202 (29.2)	−0.3 (−9.5 to 8.9)	.94
>9 MODS	38/115 (33.0)	47/129 (36.4)	−3.1 (−15.2 to 9.0)	.58

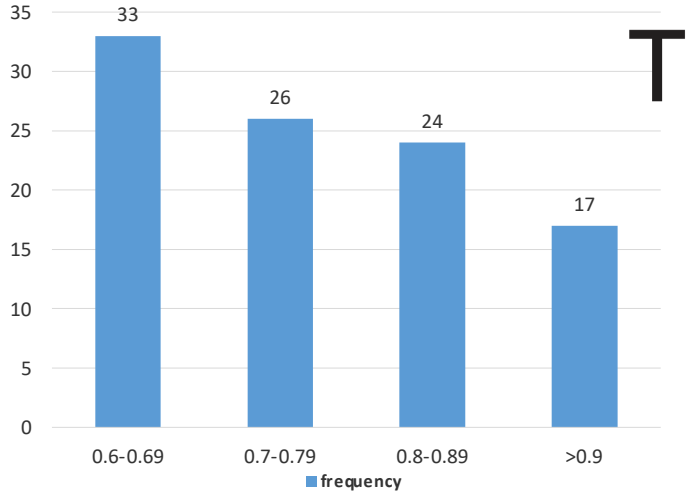
JAMA. 2018;320(14):1455-1463

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]

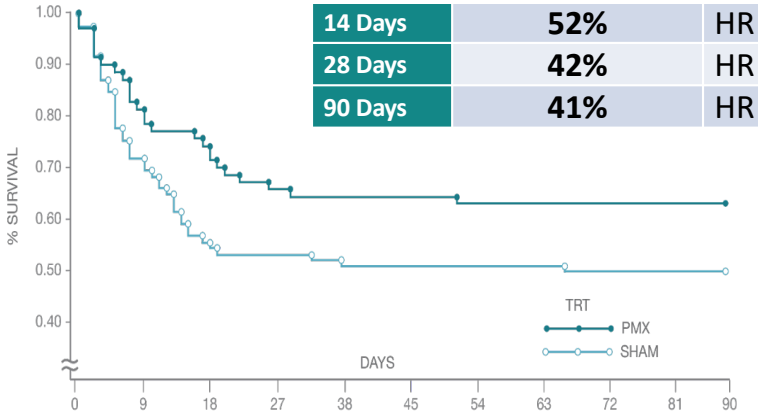




Tigris

a clinical trial for septic shock with endotoxemia

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

Conclusions

- Sepsis is not a single disease
- A "malignant" subgroup accounts for 15-20% of patient with sepsis who:
  - Have significant acute organ failure (especially kidney, liver and endothelial)
  - Mortality exceeding 40% at 28 days with no improvement in recent years
  - *Nearly identical subgroup in pediatrics*
- A genetic predisposition seems likely
- Endotoxin may the missing link in the pathophysiology of this high severity subgroup
  - EAA is an FDA-approved test to identify these patients
- Endotoxin removal has been safely practiced in many countries for decades