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Molecular Endotypes for Sepsis and AKI

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

- Norvartis
- Astute Medical
- bioMérieux

Intellectual Property

- Astute Medical/bioMérieux
- Cytosorbents
- JƐRM
- Klotho

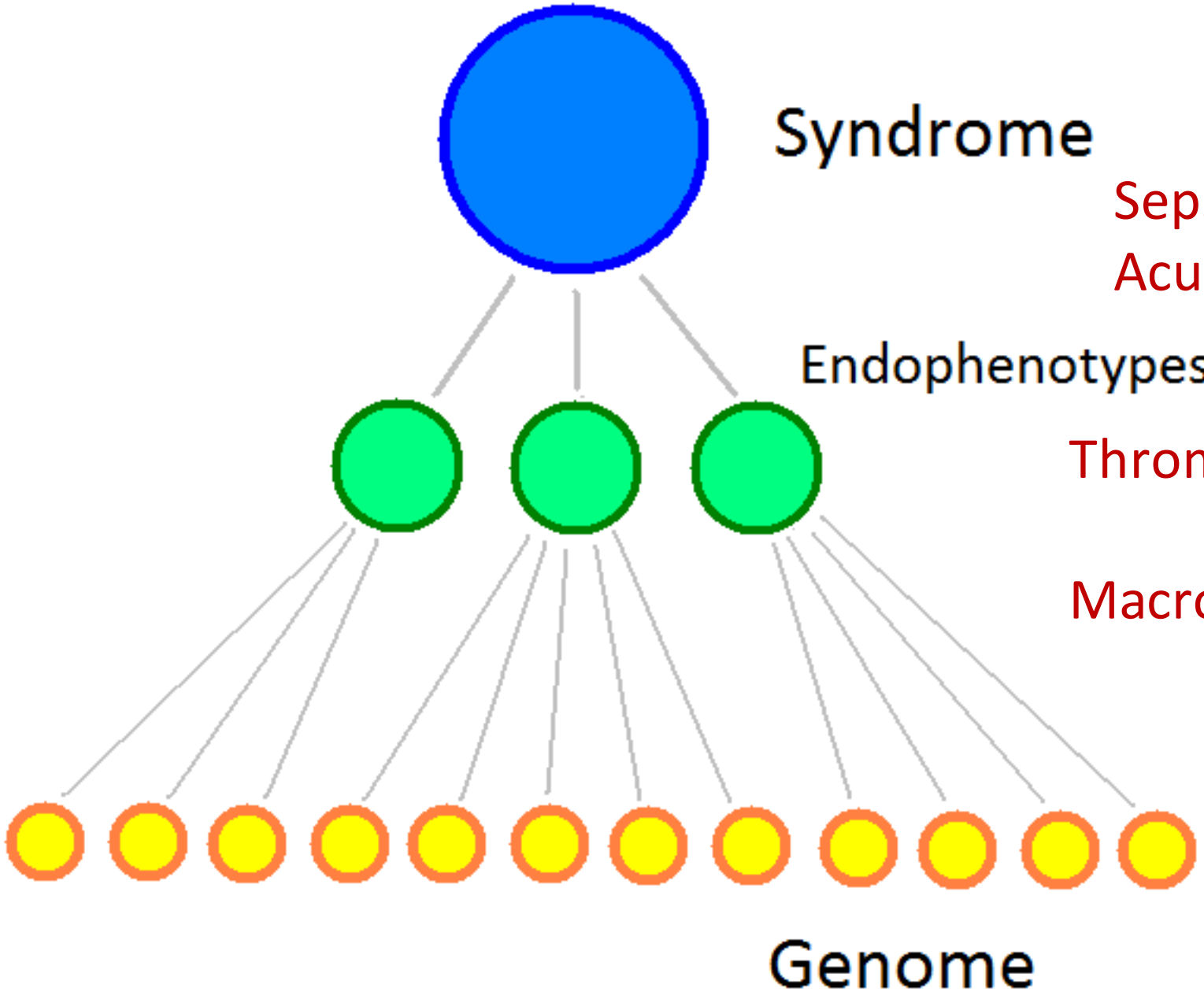
Endotype = Endophenotype

- … ability to differentiate between potential diagnoses that present with similar symptoms.

- Genetic epidemiology
  - Separate behavioral symptoms into more stable phenotypes with a clear genetic connection.
  - The concept to explain the geographic distribution of grasshoppers. 1966

- Psychiatric genetics
  - Bridge the gap between high-level symptom presentation and low-level genetic variability, such as single nucleotide polymorphisms.
  - Examples: bipolar disorder and schizophrenia

- Other conditions
  - ADHD, addiction, Alzheimer's disease, obesity and cystic fibrosis



Sepsis

Acute Kidney Injury

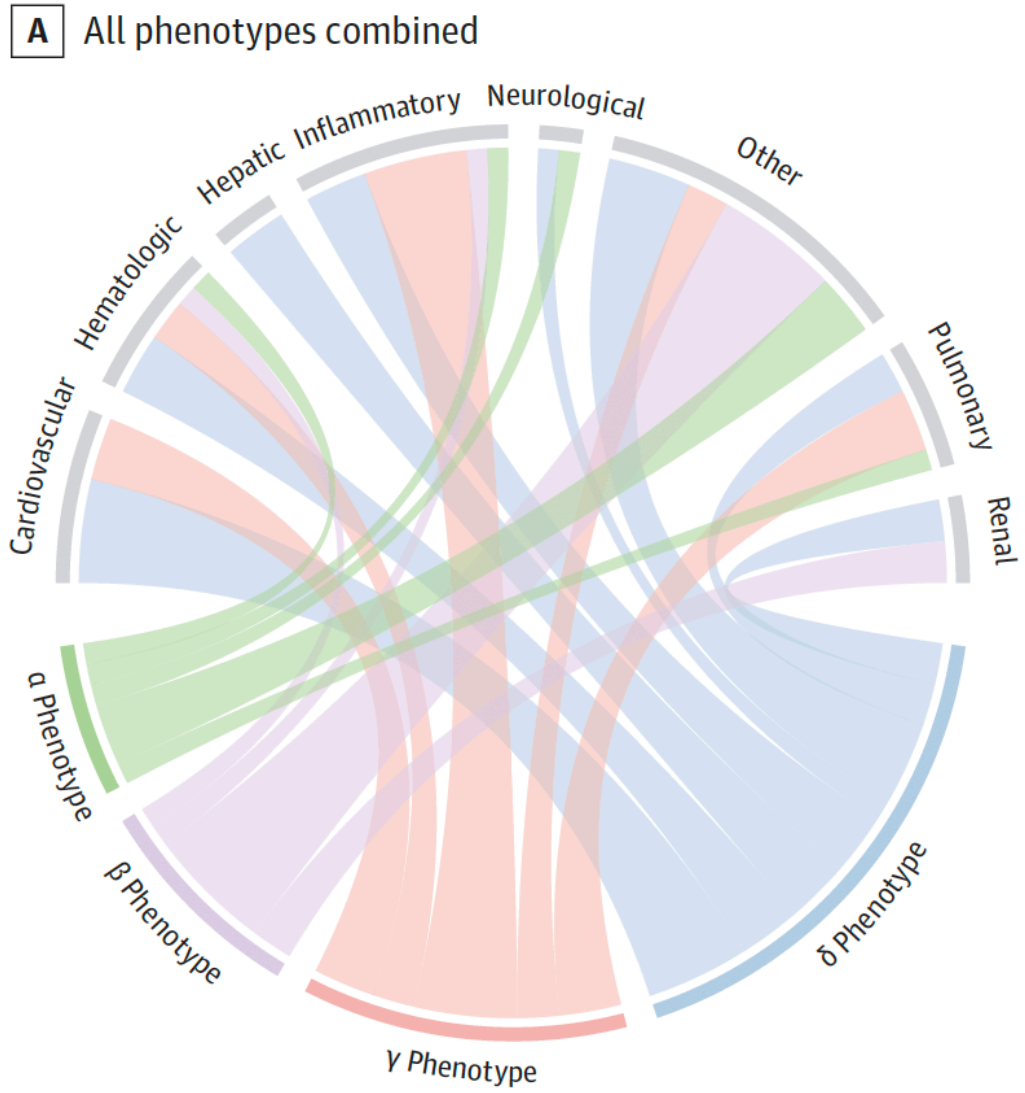
Thrombotic microangiopathy

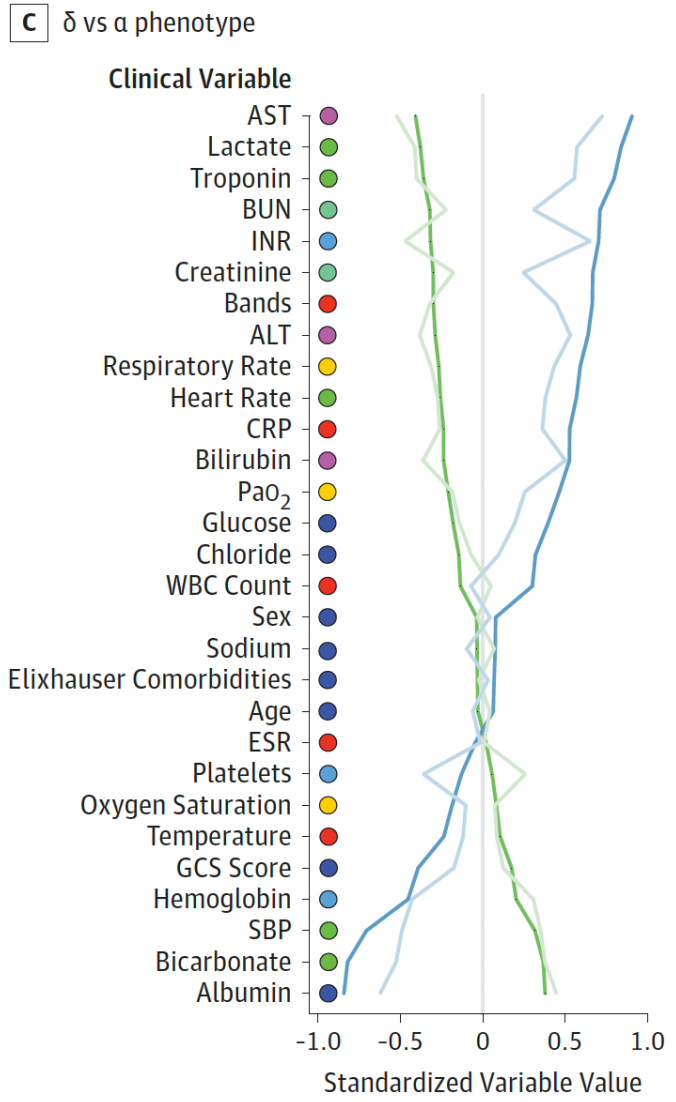
Macrophage activation

C3, CD46, CFHR5

UNC13D

Sub-phenotype vs Endotype





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

Sub-phenotypes by Machine Learning

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

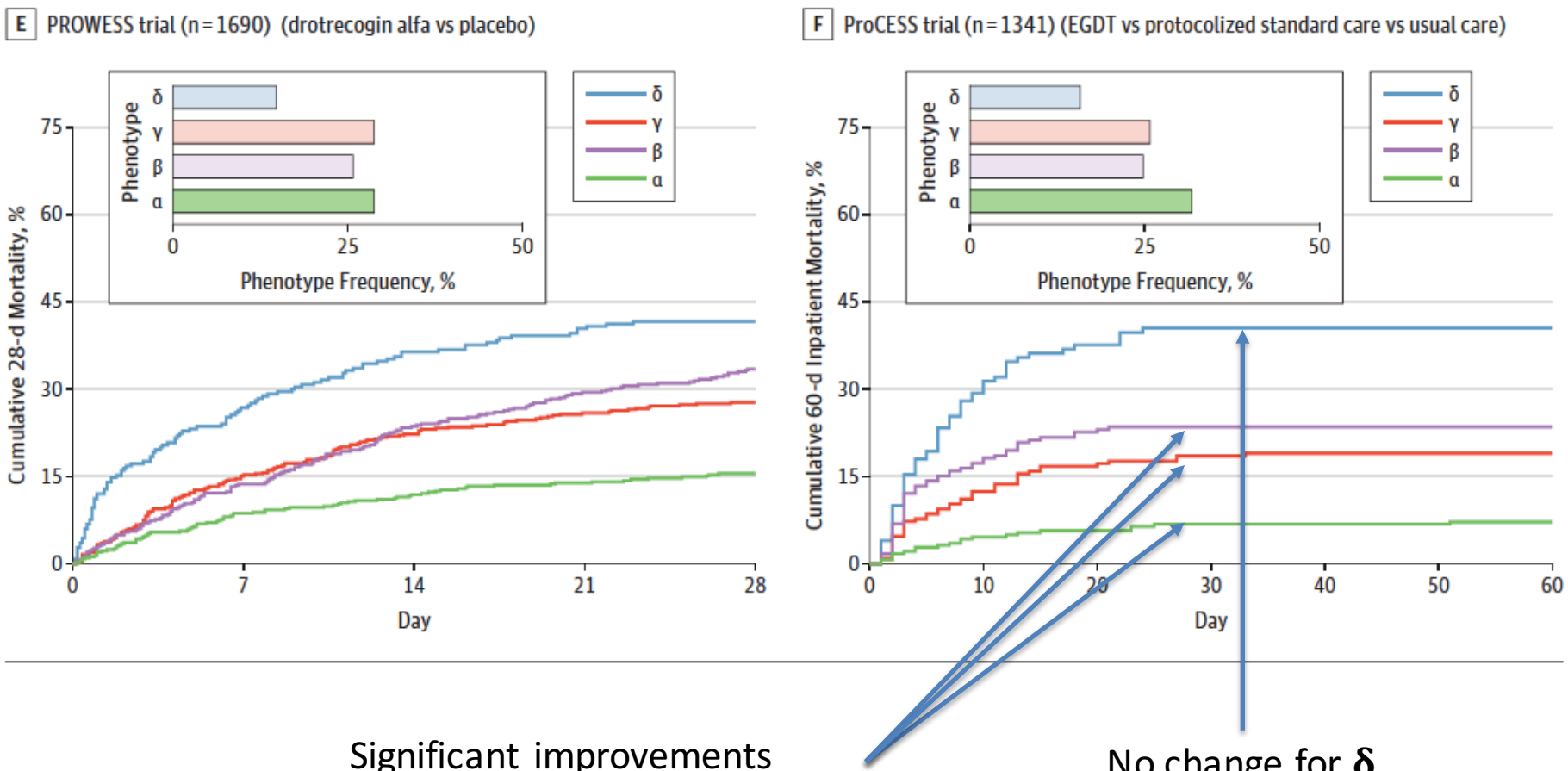
Acute Kidney Injury
Hepatic Dysfunction
Endothelial Dysfunction

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

Survival improving for most forms of sepsis . . .

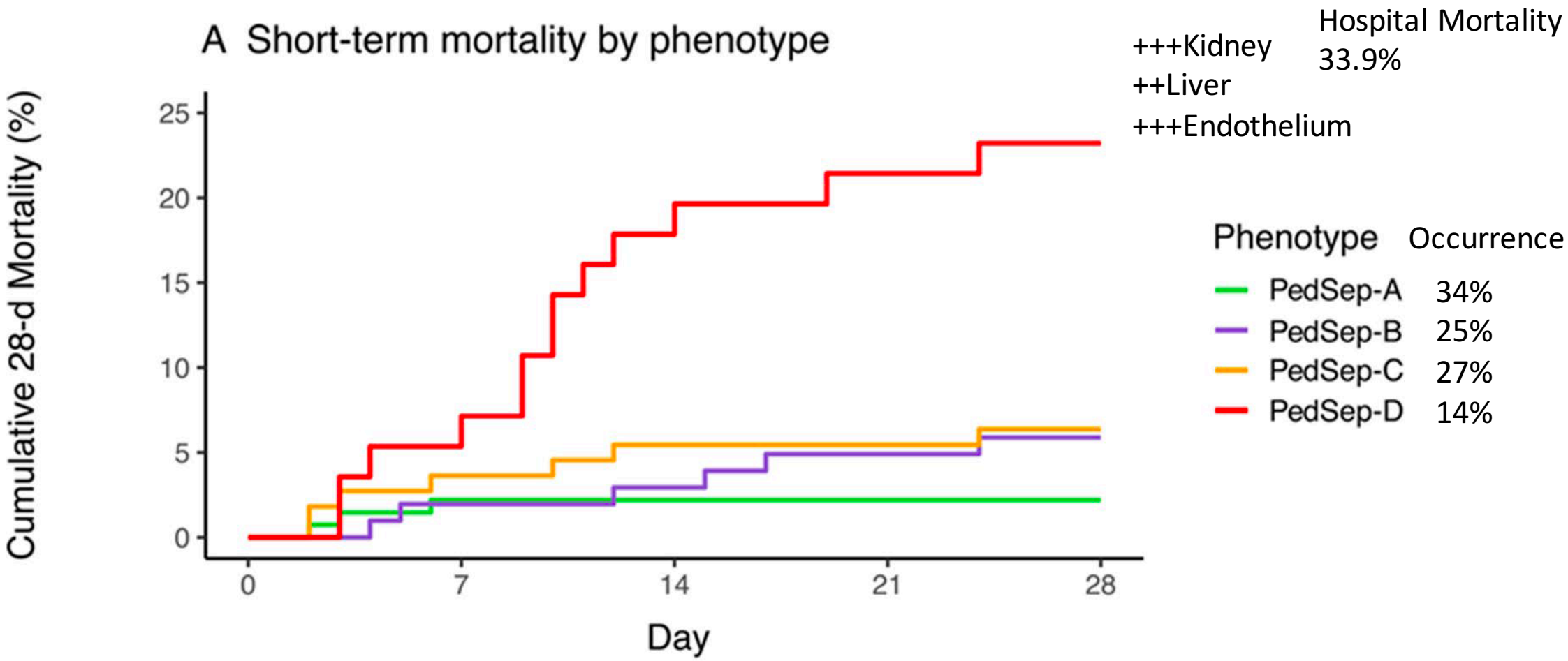
2001

2014

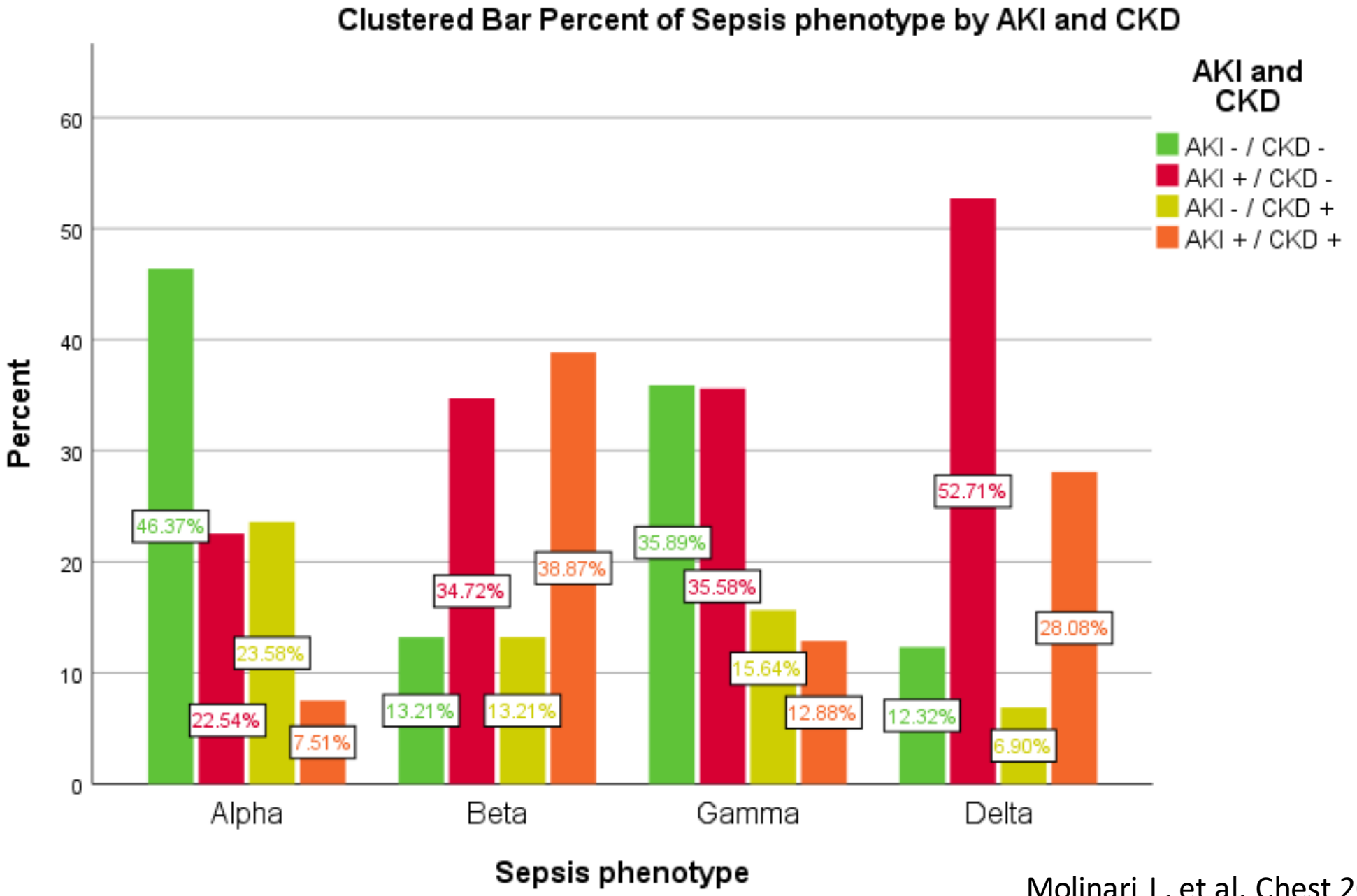


Seymour et al. JAMA. 2019;321(20):2003-2017.

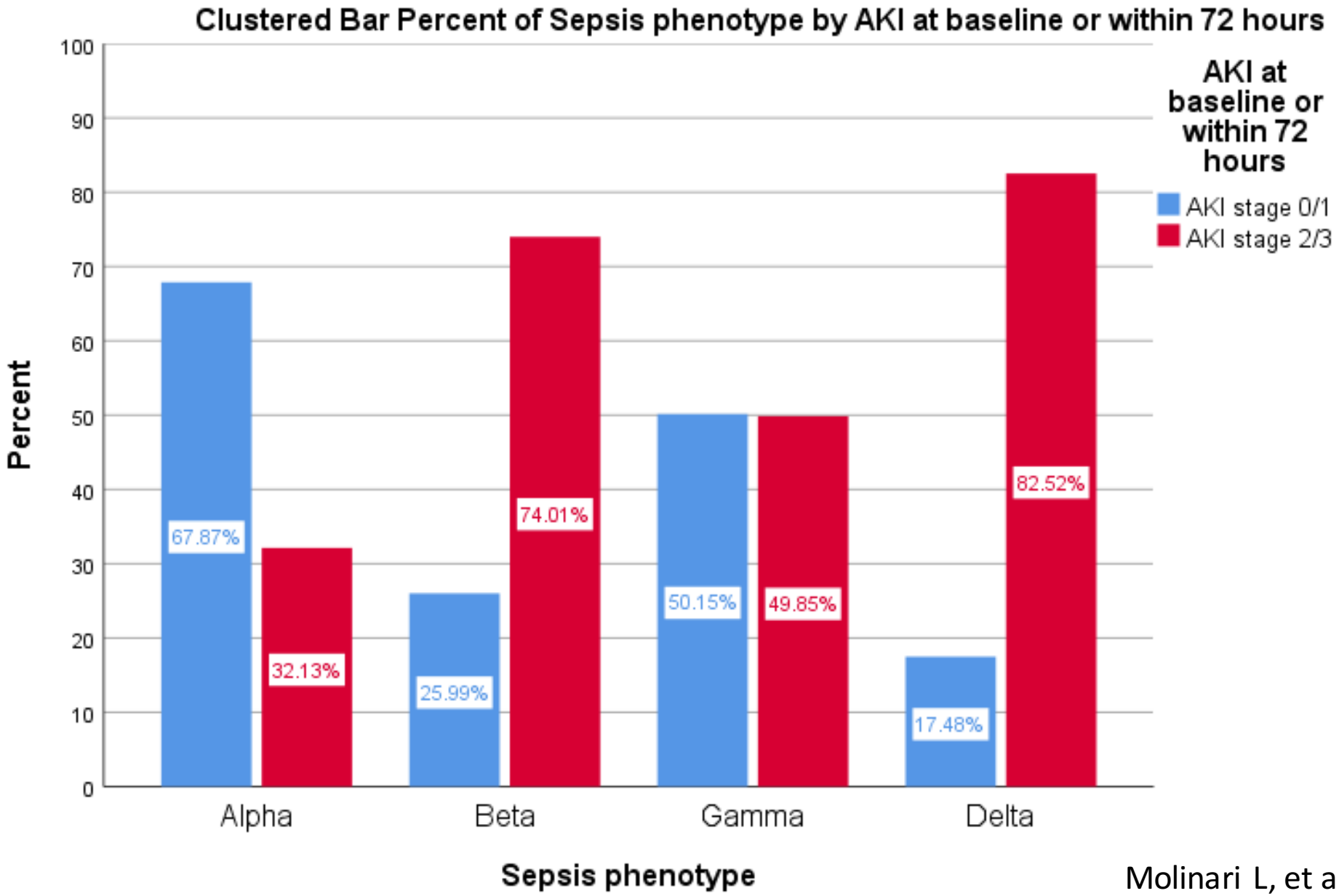
Pediatrics



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

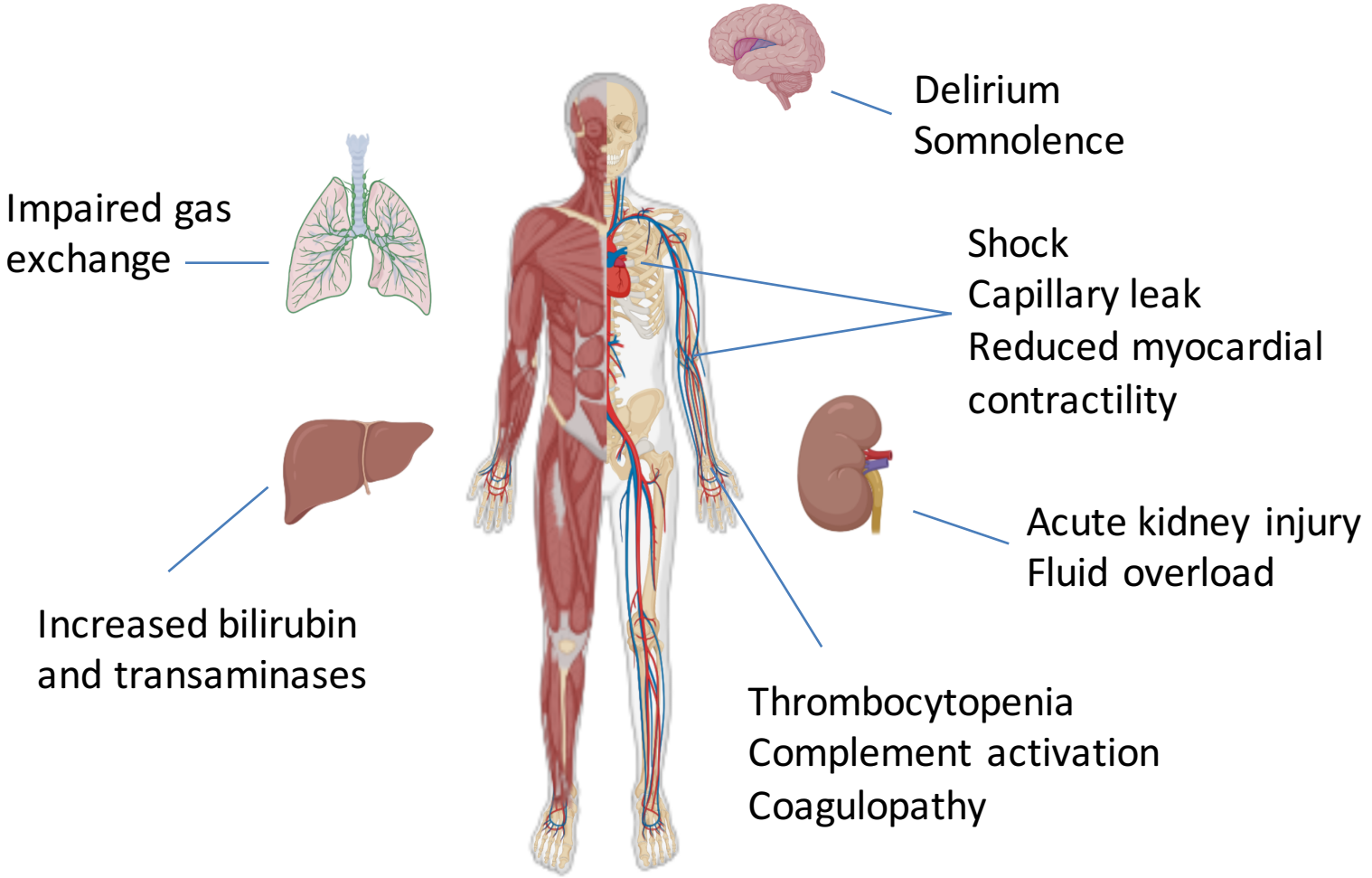


Molinari L, et al. Chest 2024 In Press



Molinari L, et al. Chest 2024 In Press

Sepsis-induced Organ Dysfunction



While patients can develop dysfunction in all organs, a typical patient has some but not all organs affected

Why do we see different Phenotypes?

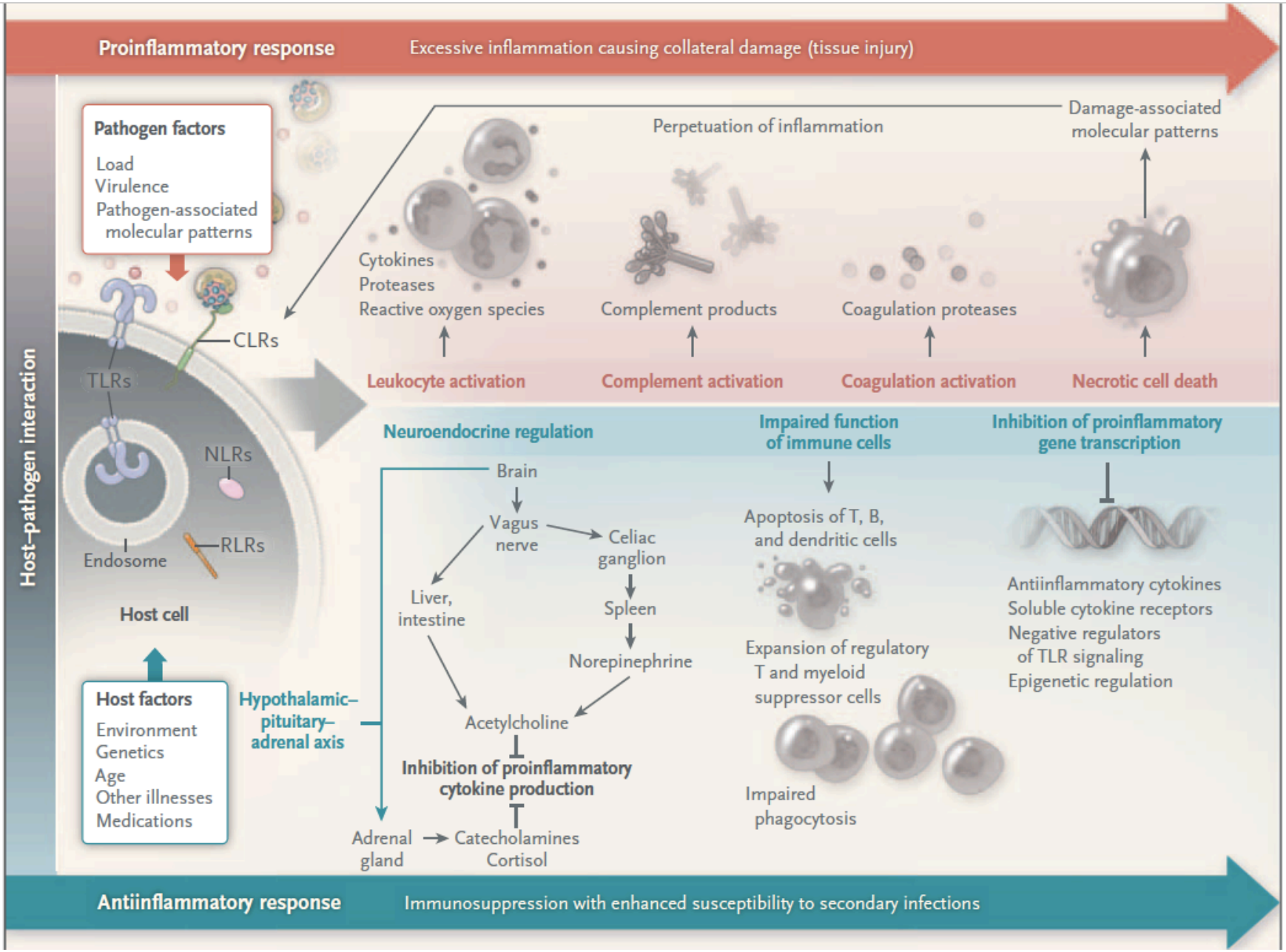
Genetics

Phenotype

Environment

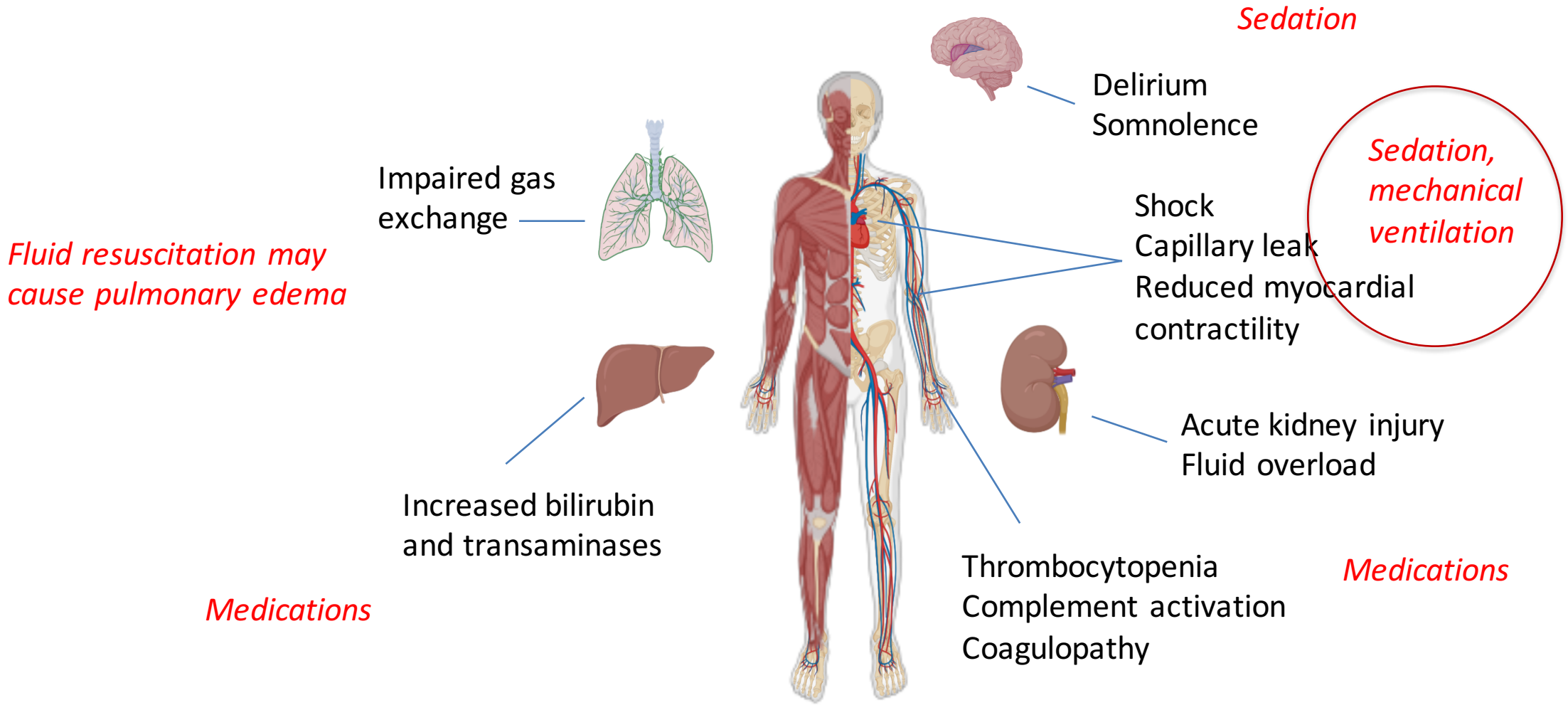
Why do we see different Phenotypes?

Environment



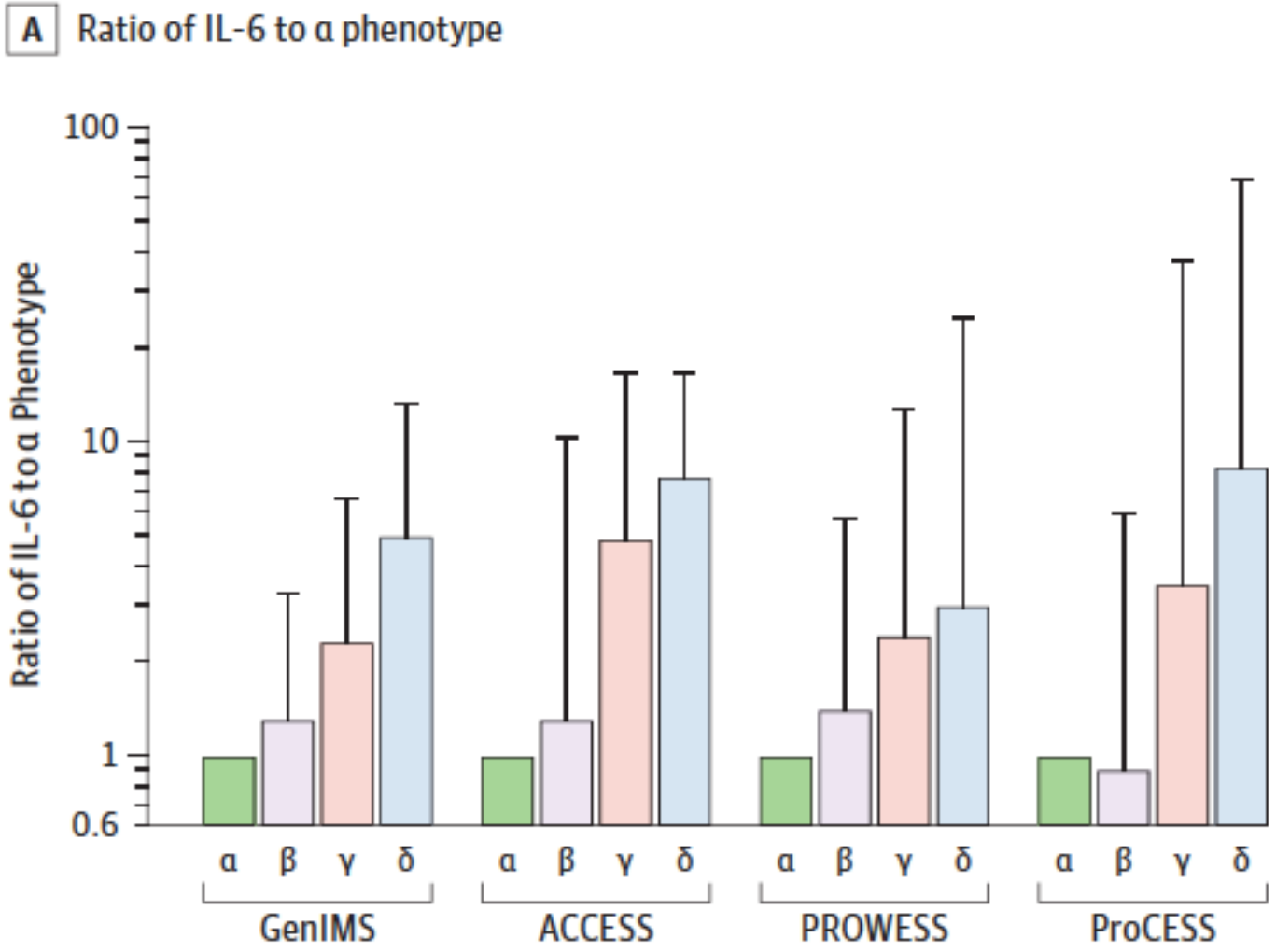
Angus and van der Poll. NEJM 2013;369:840-51.

Infection-*associated* Organ Dysfunction



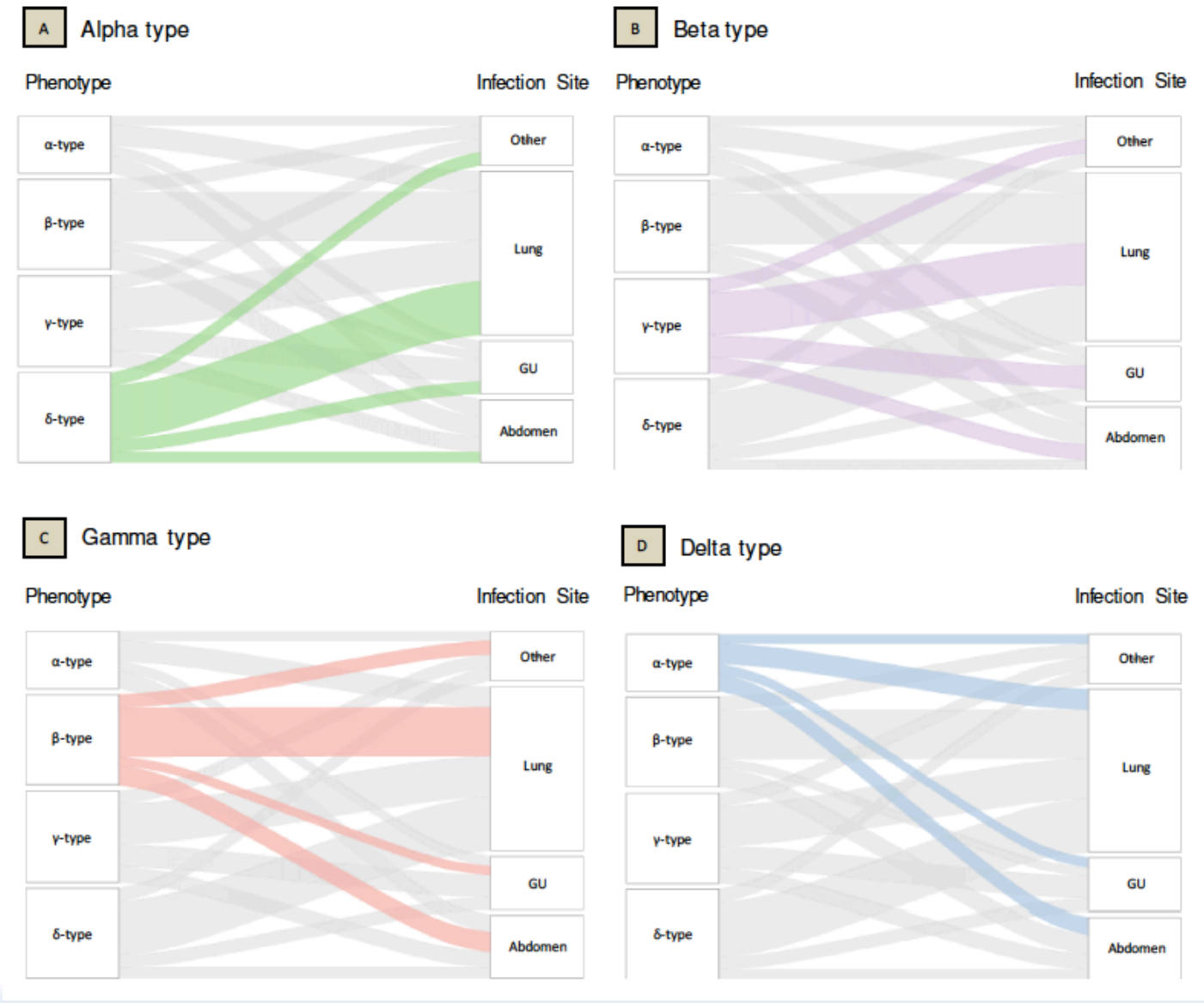
Various treatments for serous infection may be the cause organ dysfunction rather than sepsis.

Phenotype is related to inflammatory mediator expression

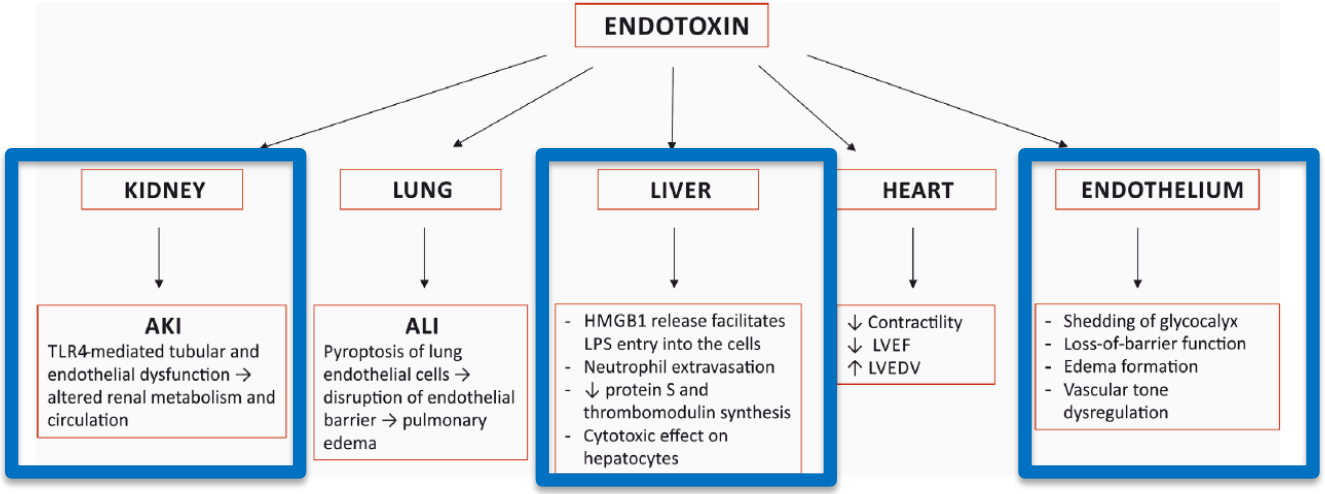


… on average

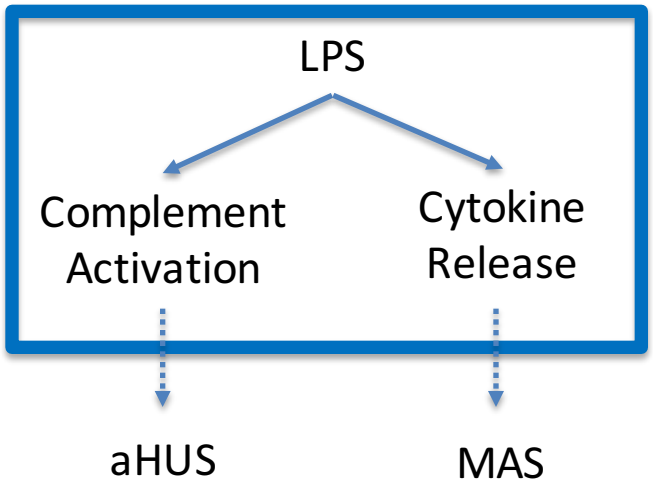
Environment: Phenotype is not related to site of infection



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



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

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§

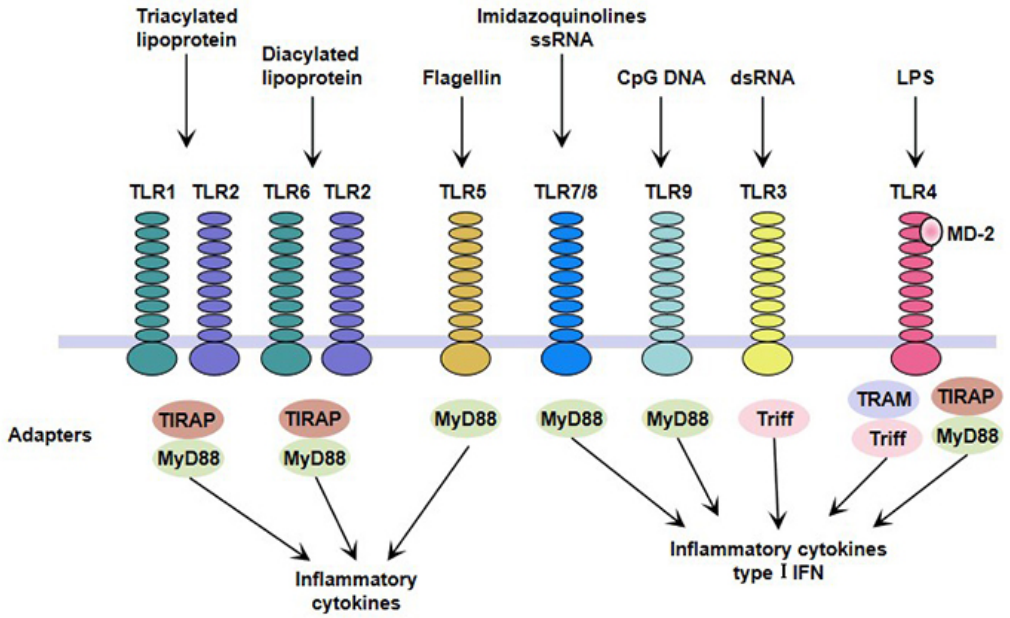
Mutations of the gene *Lps* selectively impede lipopolysaccharide (LPS) signal transduction in C3H/HeJ and C57BL/10ScCr mice, rendering them resistant to endotoxin yet highly susceptible to Gram-negative infection. The codominant Lps^d allele of C3H/HeJ mice was shown to correspond to a missense mutation 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

Nobel Prize, 2011
Together with
Jules Hoffman

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

Why do we see different Phenotypes?

Genetics

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

Subject	Gene	Variant	Amino acid change	Disease	MAF
1	*C3*	c.1407G>C [52] NM_000064.2	p.Glu469Asp	aHUS	0.00394
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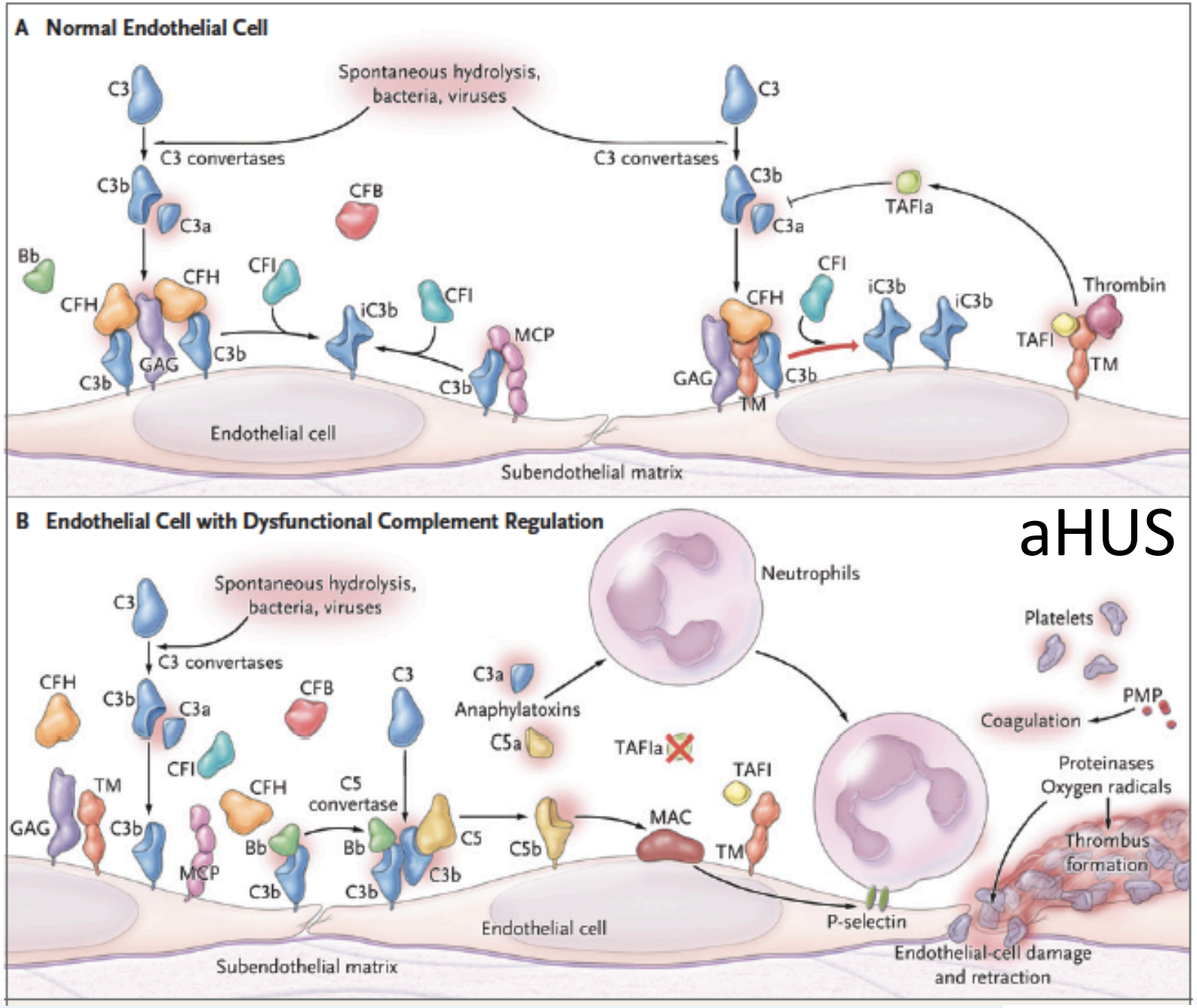


aHUS

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.*

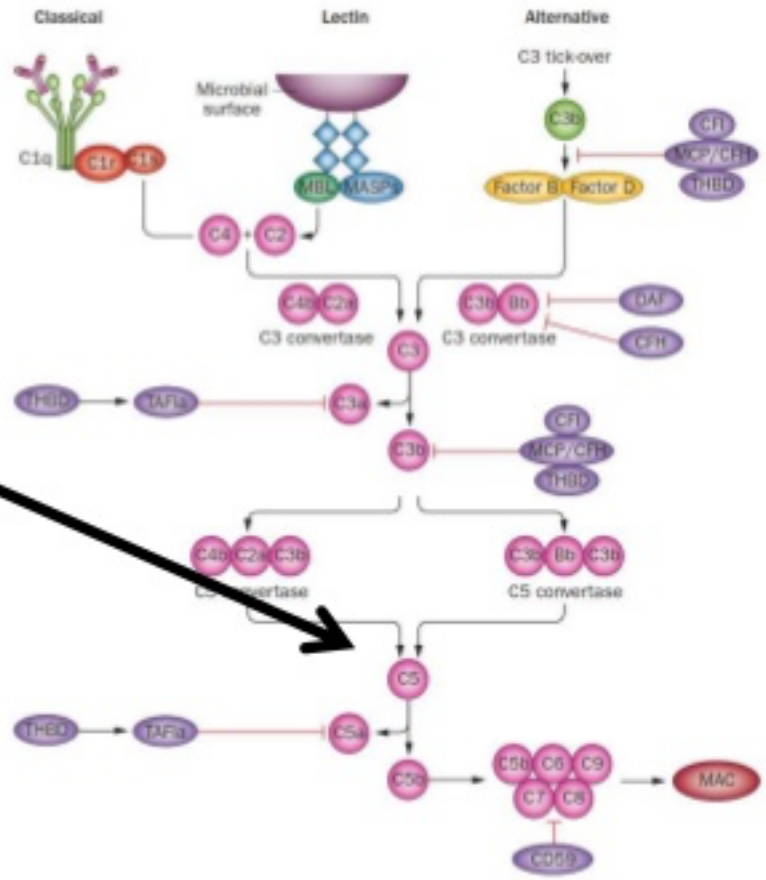
Gene	Protein Affected	Main Effect	Frequency	Response to Short-Term Plasma Therapy†	Long-Term Outcome‡	Outcome of Kidney Transplantation
			%			
CFH	Factor H	No binding to endothelium	20–30	Rate of remission: 60% (dose and timing dependent)	Rate of death or ESRD: 70–80%	Rate of recurrence: 80–90%§
CFHR1/3	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.

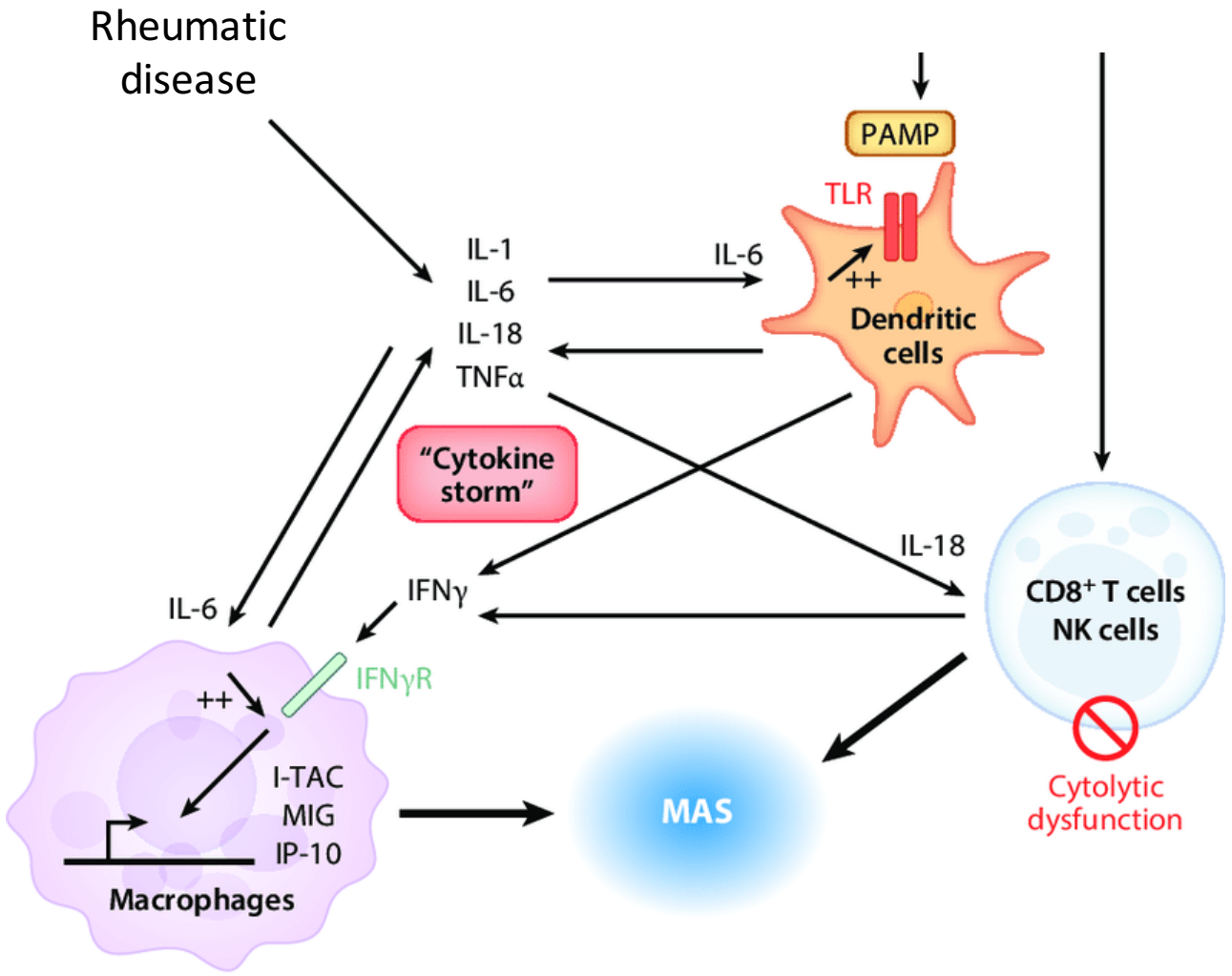
Treatment

Eculizumab

- C5 Inhibitor



MAS/HLH



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

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

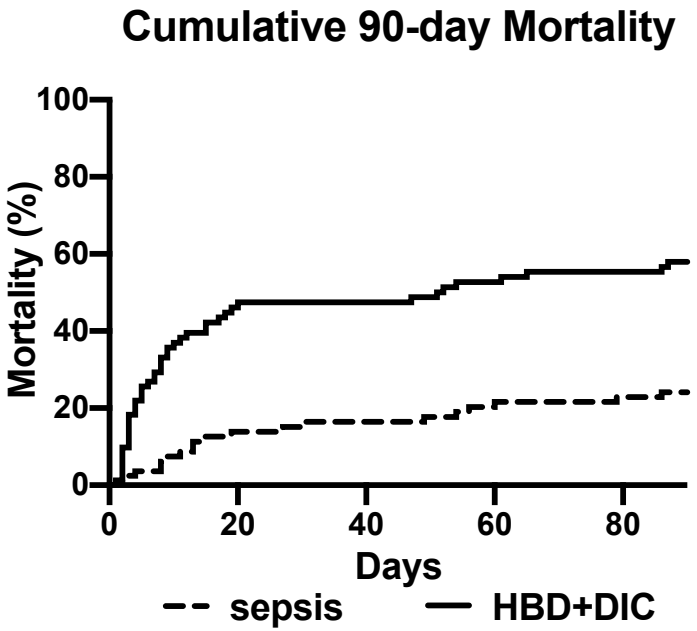
Histopathologic features

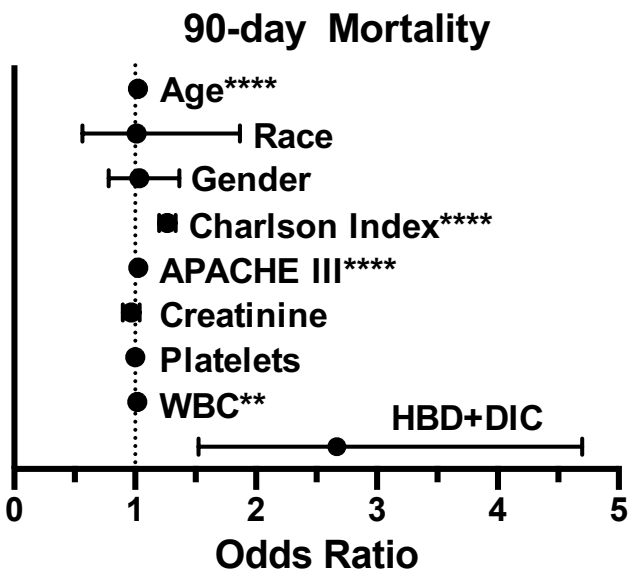
Bone marrow: Macrophage hemophagocytosis
Increased CD163 staining

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%)

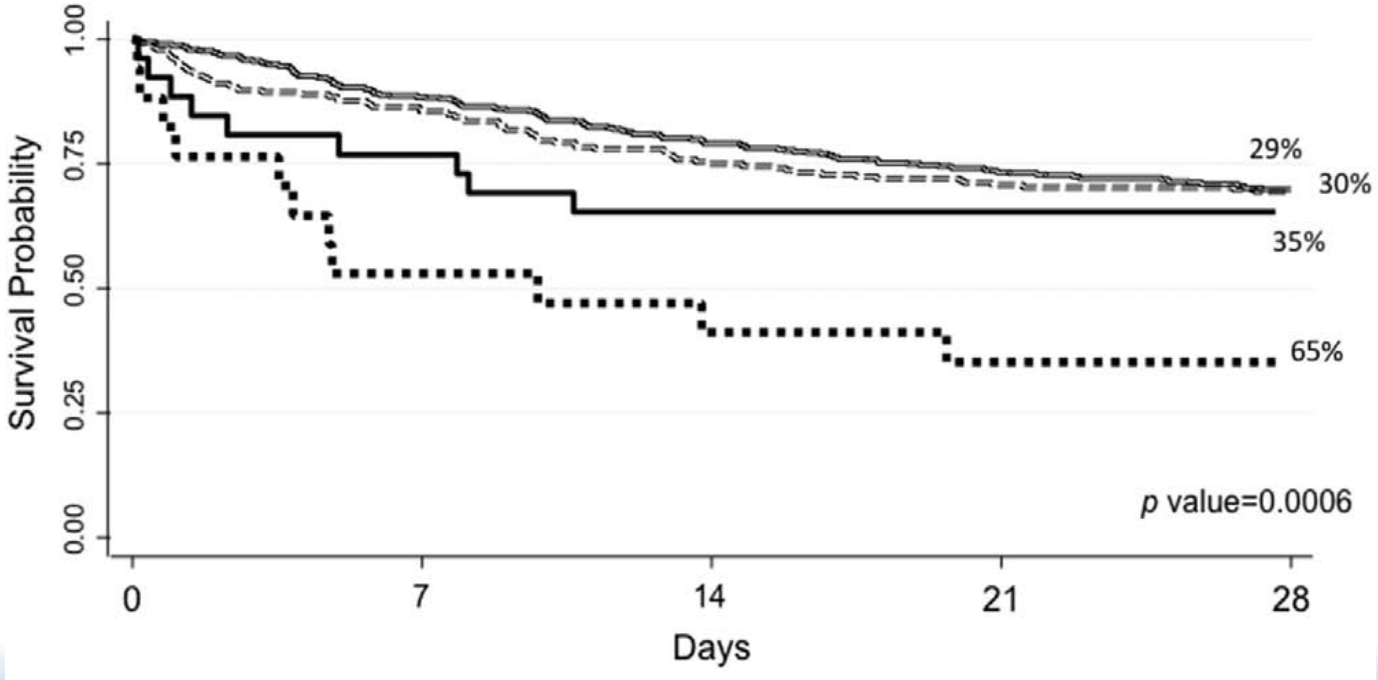




Anderko et al. ICMx. 2022;10(1):6.

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%

Conclusions

- Sepsis is not a single disease
- AKI in not a single disease (even in sepsis)
  - Sepsis associated AKI vs sepsis induced AKI
  - aHUS and MAS are underdiagnosed
- A "malignant" subgroup accounts for 15-20% of patients 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*
- Multiple molecular targets exist
  - Environmental: e.g. DAMPs and PAMPs
  - Host derived (~Genetic): e.g. complement, IL-1
- New diseases may be discovered for sepsis and AKI but existing conditions may help explain much of the observed variation.