Sepsis

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Outline

- Sepsis Defined
- New mechanistic insights
- Sepsis subphenotypes

Sepsis

- Sepsis is a term derived from the ancient Greek for rotten flesh and putrefaction.
- 1680s: Leeuwenhoek's observed "animalcules" (bacteria)
- 200 years passed before bacteria were linked to infection (Koch, Pasteur, Semmelweis, and Lister).
- 1914: Schottmueller concluded that pathogenic germs in the bloodstream caused systemic symptoms and signs
- 1975: Systemic release of cytokines and activation of white blood cells and coagulation even in the absence of whole bacteria caused sepsis

Sepsis

- Third most common cause of death world wide
- Over 1 million cases of sepsis in the US with a mortality of 10 - 40%
- Major sites of infection leading to sepsis:
  - Lung
  - Abdomen
  - Urinary tract
  - Skin and Soft Tissues
  - Central nervous system
    (30% unknown source)

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPH; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

Literature review, Delphi, 3 Cohorts ~3.2 million pts

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkhorst, MD; Thomas D. Rea, MD, MPH; André Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

Assess predictive validity in ~1.3 million patients

JAMA February 23, 2016

SEPSIS-3, ICU Definition:

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

Organ dysfunction is measured by abnormal laboratory values, blood pressure, and mental status. The Sequential Organ Failure Assessment (SOFA) score is used to grade severity of organ dysfunction on a 0-4 point scale for each organ system

A 2 point change in total SOFA from infection is associated with a 10% mortality risk in a general hospital population.

Singer JAMA 2016

SOFA Score

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Sepsis Surveillance Using Adult Sepsis Events Simplified eSOFA Criteria Versus Sepsis-3 Sequential Organ Failure Assessment Criteria*

Chanu Rhee, MD, MPH[1,2]; Zilu Zhang, MS[1]; Sameer S. Kadri, MD, MS[3]; David J. Murphy, MD, PhD[4]; Greg S. Martin, MD, MSc[4]; Elizabeth Overton, MS[4]; Christopher W. Seymour, MD, MSc[5]; Derek C. Angus, MD, MPH[5]; Raymund Dantes, MD, MPH[6,7]; Lauren Epstein, MD, MS[6]; David Fram, BA[8]; Richard Schaaf, SM[8]; Rui Wang, PhD[1]; Michael Klompas, MD, MPH[1,2]; for the CDC Prevention Epicenters Program

TABLE 1. The Sequential Organ Failure Assessment Score and eSOFA Criteria

Organ System	Sequential Organ Failure Assessment Score	eSOFA
Cardiovascular[a]	1) Mean arterial pressure < 70 mm Hg	Vasopressor initiation
	2) Dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	
	3) Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1 µg/kg/min	
	4) Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1 µg/kg/min	
Pulmonary	1) Pao_2/Fio_2 300–399	Mechanical ventilation initiation (> 1 calendar day required between vent episodes)
	2) Pao_2/Fio_2 200–299	
	3) Pao_2/Fio_2 100–199 and ventilated	
	4) Pao_2/Fio_2 ratio < 100 and ventilated	
Renal[b]	1) Creatinine 1.2–1.9 mg/dL	2× Creatinine or ↓≥ 50% of eGFR relative to baseline (excluding patients with end-stage renal disease)
	2) Creatinine 2.0–3.4 mg/dL	
	3) Creatinine 3.5–4.9 mg/dL or UOP < 500 cc/d	
	4) Creatinine > 5.0 mg/dL or UOP < 200 cc/d	
Hepatic	1) Bilirubin 1.2–1.9 mg/dL	Bilirubin ≥ 2.0 mg/dL and ↑2× from baseline
	2) Bilirubin 2.0–5.9 mg/dL	
	3) Bilirubin 6.0–11.9 mg/dL	
	4) Bilirubin > 12.0 mg/dL	
Coagulation	1) Platelets 100–149 cells/µL	Platelet count < 100 cells/µL and ↓≥ 50% from baseline (baseline must be ≥ 100 cells/µL)
	2) Platelets 50–99 cells/µL	
	3) Platelets 20–49 cells/µL	
	4) Platelets < 20 cells/µL	
Neuro	1) Glasgow Coma Scale score 13–14	"None"
	2) Glasgow Coma Scale score 10–12	Perfusion dysfunction: lactate ≥ 2.0 mmol/L
	3) Glasgow Coma Scale score 6–9	
	4) Glasgow Coma Scale score < 6	

SEPSIS-3: Septic Shock

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality

Septic Shock Definition:

Persisting hypotension requiring vasopressors to maintain a mean arterial pressure of > 65 mmHg and having a serum lactate level > 2mmol/L despite "adequate" (NOS) volume resuscitation.

Hospital mortality > 40%.

Singer JAMA 2016

Outline

- Sepsis Defined
- New mechanistic insights
- Sepsis subphenotypes

Innate Immune Response Triggered by Interactions with Pattern Recognition Receptors:

Toll-like receptors

Receptor for advanced glycation end products

Nucleotide-binding oligomerization domain-like receptors

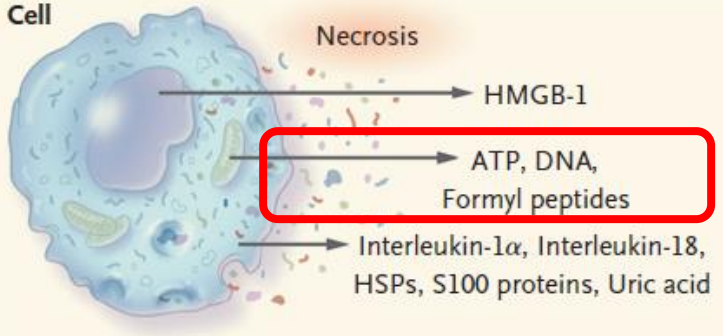
C-type lectin receptors

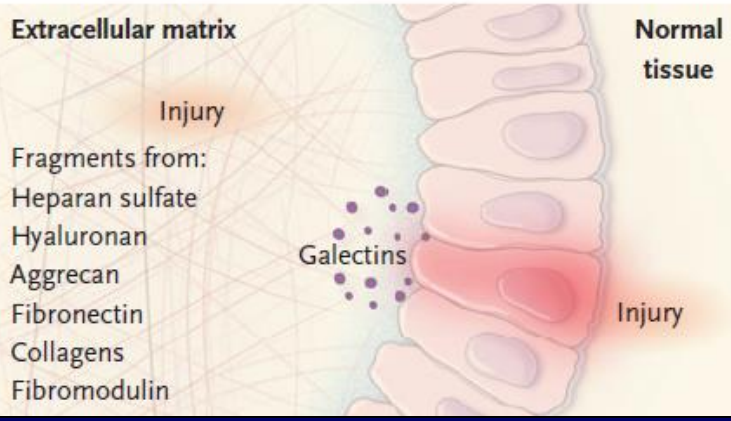
Retinoic acid–inducible gene-1-like receptors

Examples of Pathogen-Associated Molecular Patterns (PAMPs)

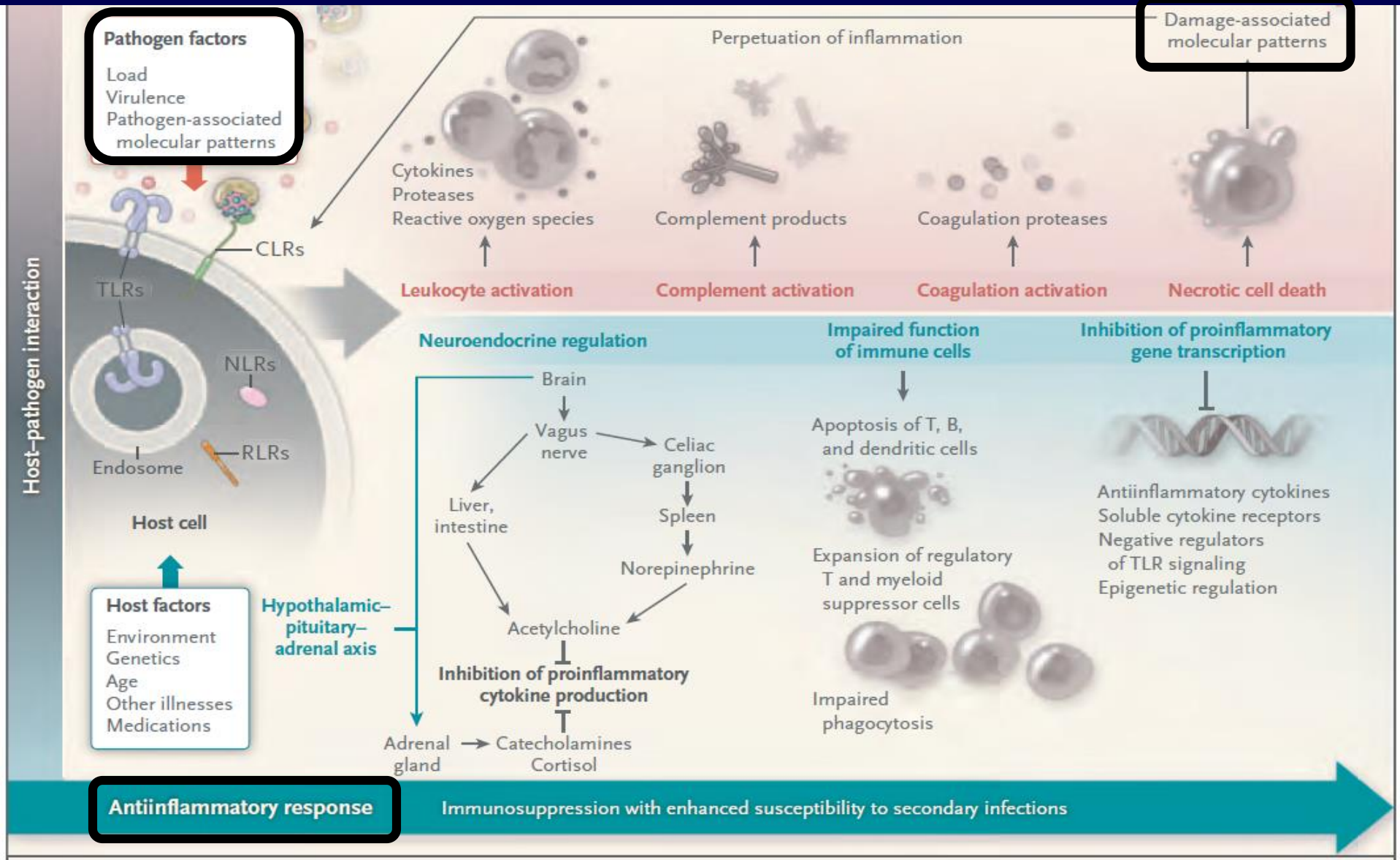
Bacteria		Flagellin, LPS, Peptidoglycans, Lipoteichoic acid, Formyl peptides, DNA, Unmethylated CpG motifs, Glycolipids, Lipoproteins
Virus		Envelope glycoprotein, ssRNA, dsRNA, Unmethylated CpG motifs
Fungus		β-glucans, Mannoproteins, Unmethylated CpG motifs, Phospholipomannan
Parasite		Profilin, Glycolipids, DNA

Examples of Damage-Associated Molecular Patterns (DAMPs)

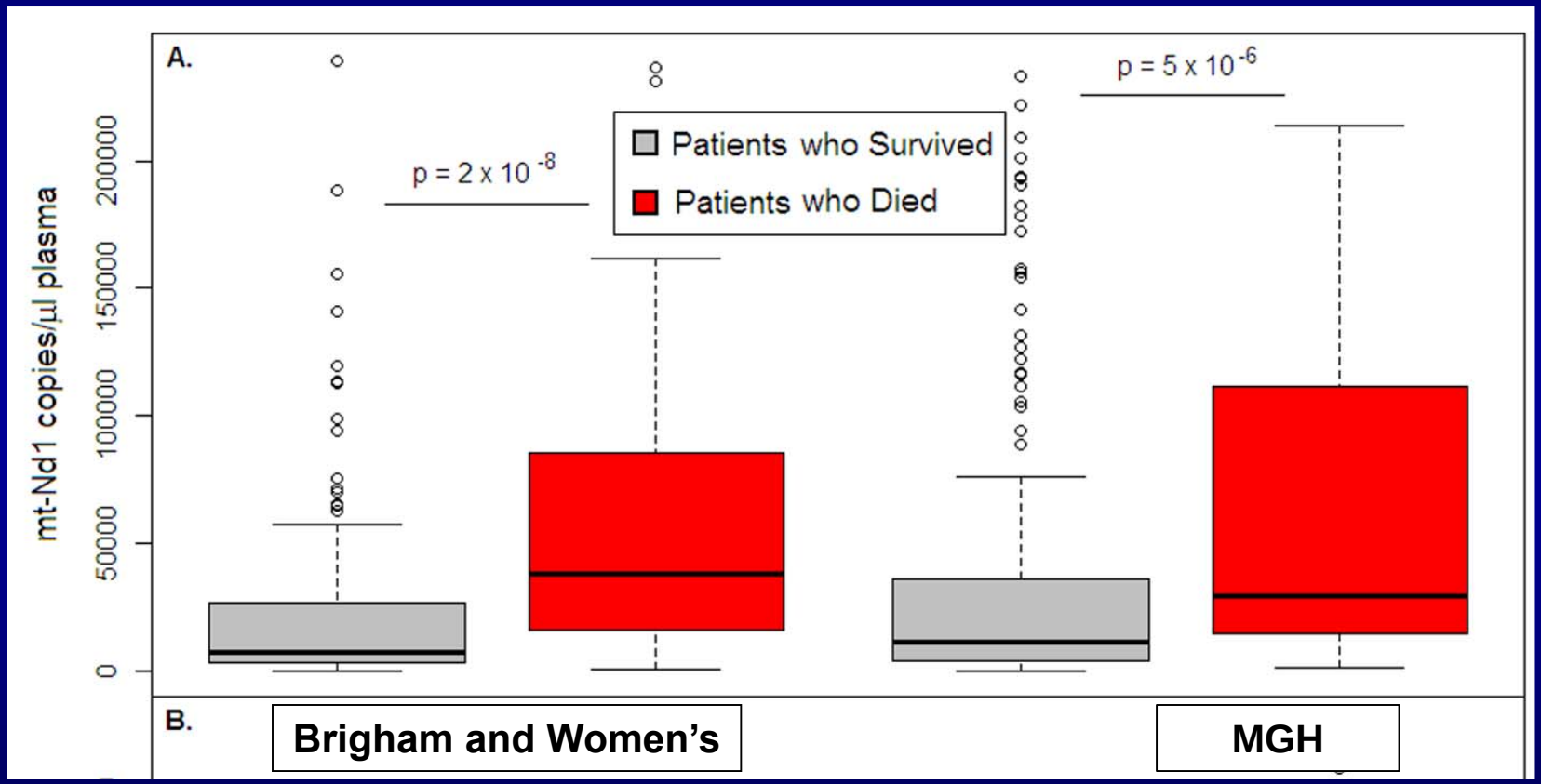




Klempner NEJM 2010


Host–pathogen interaction
Pathogen factors
Load
Virulence
Pathogen-associated molecular patterns
CLRs
TLRs
NLRs
RLRs
Endosome
Host cell
Host factors
Environment
Genetics
Age
Other illnesses
Medications
Hypothalamic–pituitary–adrenal axis
Perpetuation of inflammation
Damage-associated molecular patterns
Cytokines
Proteases
Reactive oxygen species
Complement products
Coagulation proteases
Leukocyte activation
Complement activation
Coagulation activation
Necrotic cell death
Neuroendocrine regulation
Brain
Vagus nerve
Celiac ganglion
Liver, intestine
Spleen
Norepinephrine
Acetylcholine
Inhibition of proinflammatory cytokine production
Adrenal gland
Catecholamines
Cortisol
Impaired function of immune cells
Apoptosis of T, B, and dendritic cells
Expansion of regulatory T and myeloid suppressor cells
Impaired phagocytosis
Inhibition of proinflammatory gene transcription
Antiinflammatory cytokines
Soluble cytokine receptors
Negative regulators of TLR signaling
Epigenetic regulation
Antiinflammatory response
Immunosuppression with enhanced susceptibility to secondary infections

Higher Circulating Mitochondrial DNA in Fatal Sepsis



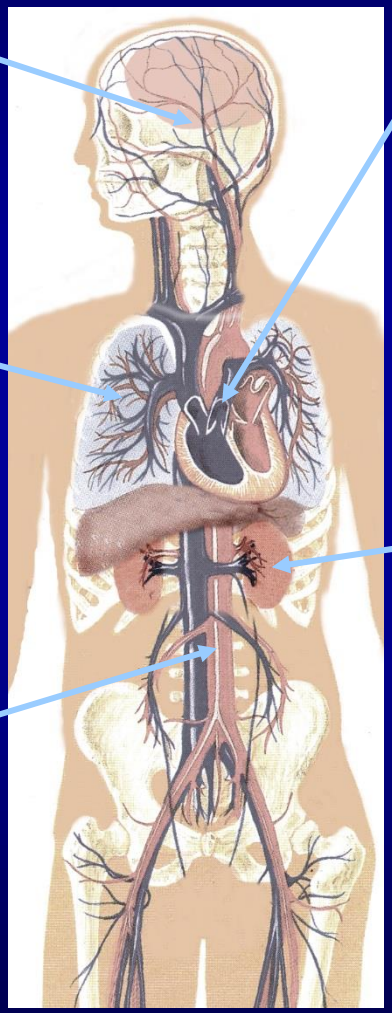
Nakihira PLOS Med 2013

Sepsis and Organ Dysfuntion

Coma or Encephalopathy
- Altered consciousness, confusion, psychosis
- EEG shows diffuse slowing
- Brain structurally normal

ARDS
- Inflammation, vascular leak, intravascular coagulation

Shock
- Vascular smooth muscle cells become hyper-polarized due to changes in potassium conductance
- Increased endogenous vasodilators

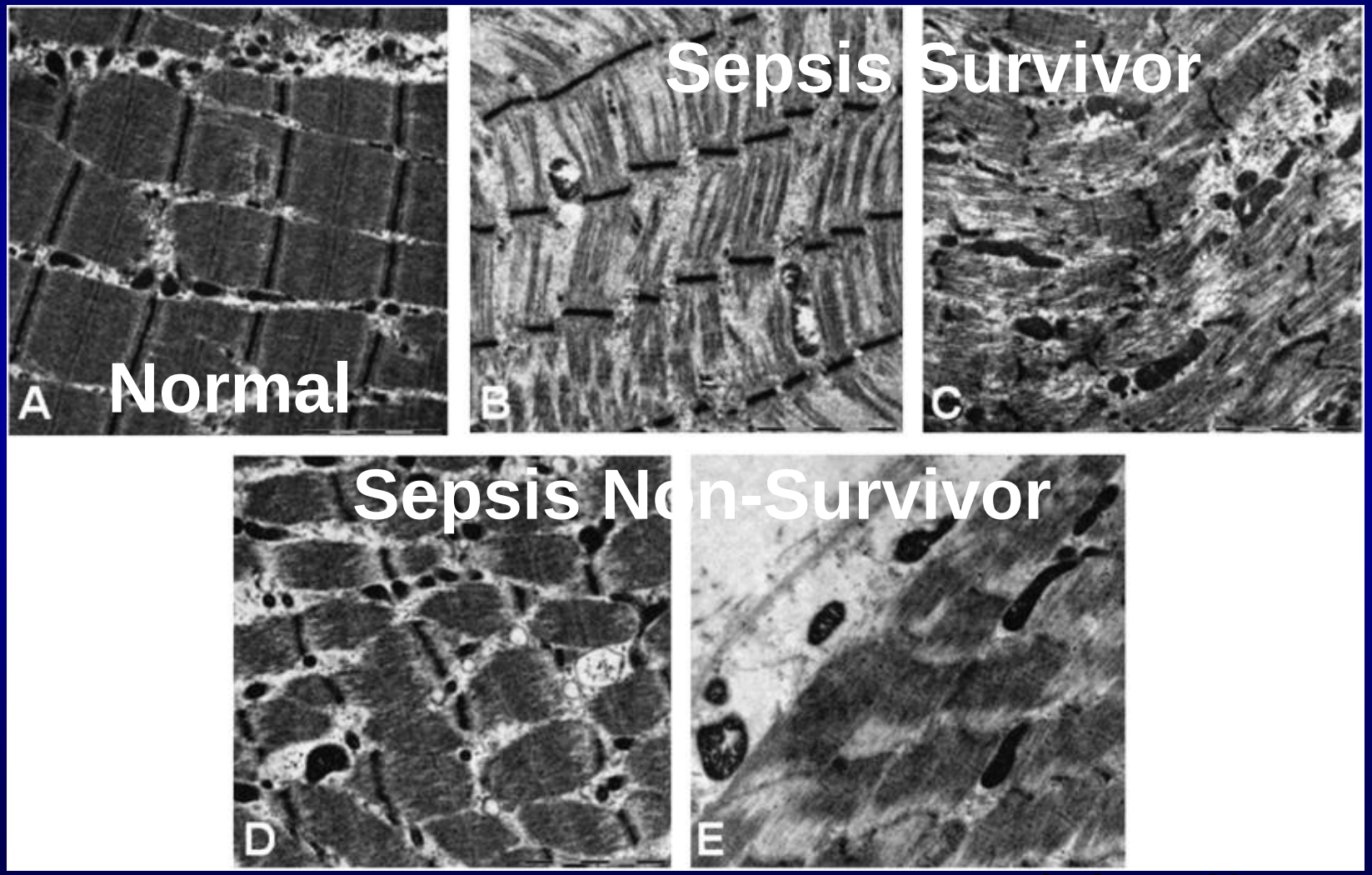


Heart Failure
- Heart weakens and dilates due to circulating factors
- Markers of heart muscle death circulate in the blood but the heart muscles largely appear to be normal histologically

Kidney Failure
- Urine flow is reduced and medicines to increase flow (diuretics) no longer work
- Epithelial cells are present in the urine suggesting injury though renal histology is largely normal
- Vast majority with failed kidneys requiring dialysis recover

Survival in Critical Illness Is Associated with Early Activation of Mitochondrial Biogenesis

Jane E. Carré[1], Jean-Christophe Orban[1,2], Lorenza Re[1,3], Karen Felsmann[4], Wiebke Iffert[4], Michael Bauer[5], Hagir B. Suliman[6], Claude A. Piantadosi[6], Terry M. Mayhew[7], Patrick Breen[1], Martin Stotz[1], and Mervyn Singer[1]

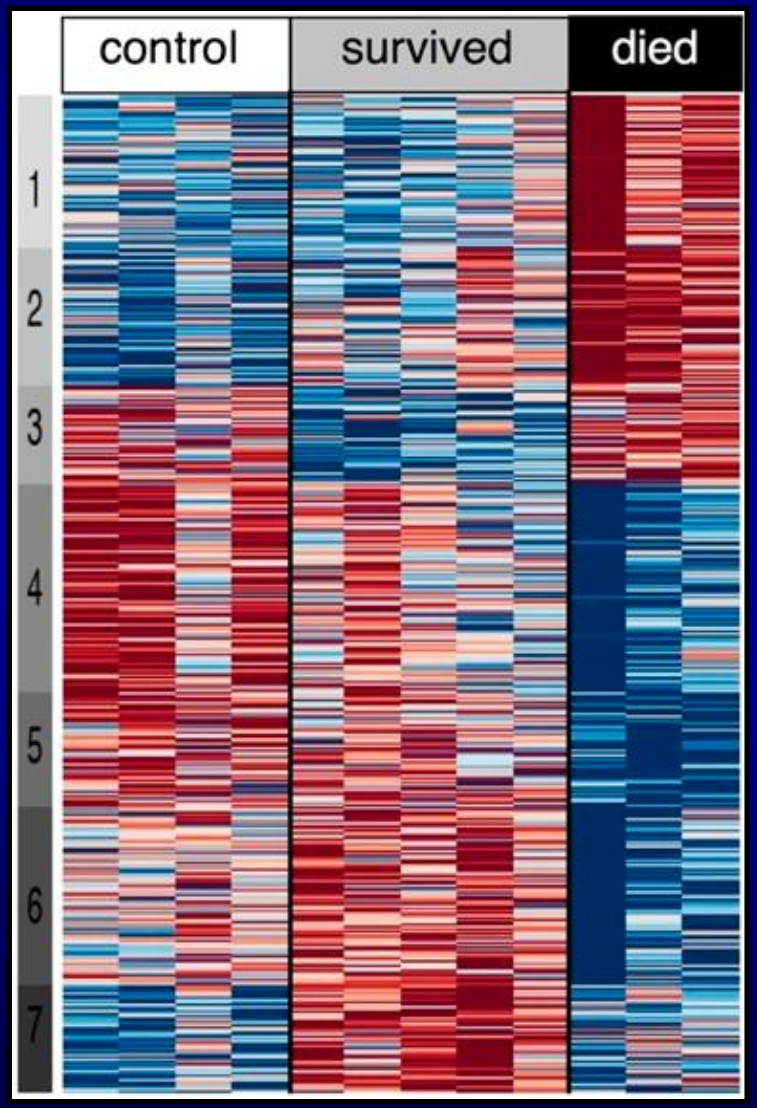


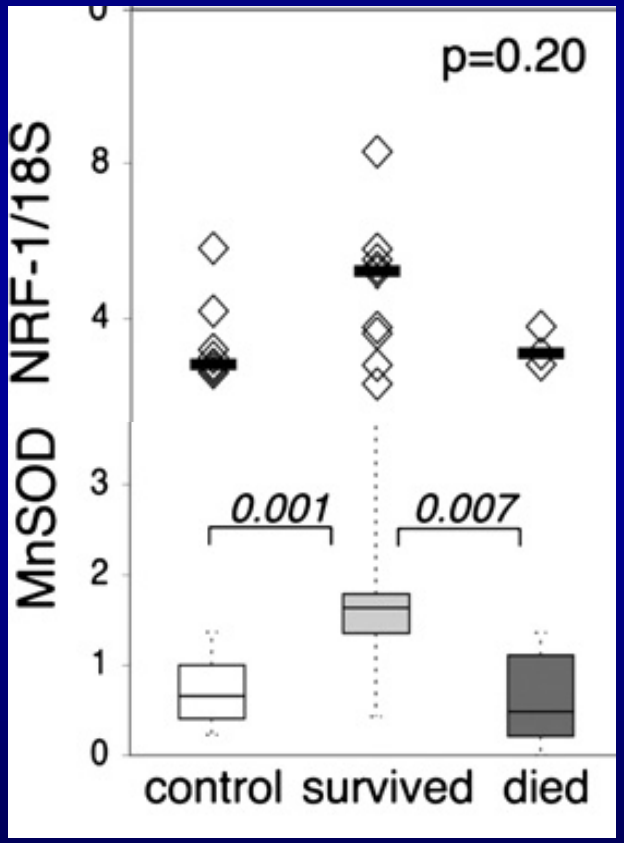
Kumar *Virulence* 2014

Survival in Critical Illness Is Associated with Early Activation of Mitochondrial Biogenesis

2010

Jane E. Carré[1], Jean-Christophe Orban[1,2], Lorenza Re[1,3], Karen Felsmann[4], Wiebke Iffert[4], Michael Bauer[5], Hagir B. Suliman[6], Claude A. Piantadosi[6], Terry M. Mayhew[7], Patrick Breen[1], Martin Stotz[1], and Mervyn Singer[1]





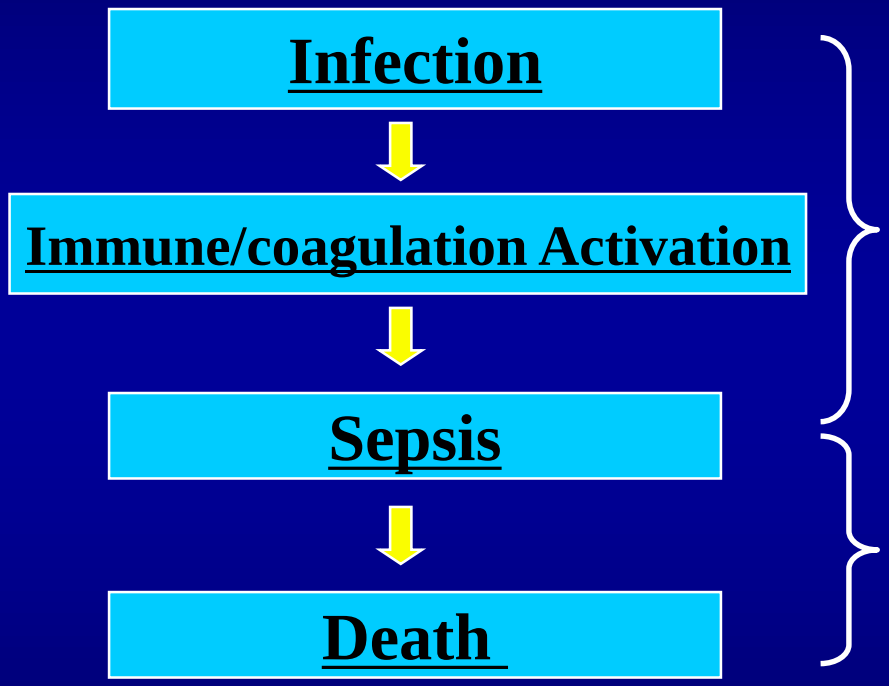
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2005 VOL. 352 NO. 6

Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress

Patient No.	Age	Sex	Race or Ethnic Origin	Coronary Risk Factors	Emotional Stressor	Time after Symptom Onset†
	yr					*hr*
1	62	F	B	HTN, smoking	Mother's death	12
2	63	F	AA	HTN, Chol	Car accident	1
3	48	F	W	HTN, Chol, smoking	Surprise reunion	4
4	60	F	W	HTN	Surprise party	2
5	66	F	W	HTN, FH	Father's death	5
6	77	F	W	HTN, FH	Husband's death	6
7	52	F	W	Smoking	Friend's death	2

Antibiotics and Sepsis; necessary but not sufficient for survival



Appropriate antibiotics decrease evolution to severe sepsis by ~50%[+]

Appropriate antibiotics reduce mortality by 10-15% ; mortality remains 10-40%*

[+] Kreger AJM 1980; Simon Crit Care Clin 2000

* Pittet AJRCCM 1996; Opal CCM 1997

Immune Modulation for Severe Sepsis has Largely Failed

No Benefit or Harm in >100 studies

- Anti-LPS (Polyclonal Ab, HA-1A, E5)
- Anti-TNF or IL-1 strategies
- IVIG, Interferon gamma, GCSF
- Growth hormone
- Soluble PLA_2, elastase, and PAF Inhibitors
- Heparin, antithrombin
- Ibuprofen
- APC for lower risk severe sepsis
- Tissue factor pathway inhibitor (Opal ESICEM 2009)
- Phospholipid emulsion (Dellinger CCM 2009)
- TLR-4 antagonist (Tidswell CCM 2010, Opal, 2012)
- APC for persistent septic shock (Ranieri & Thompson, 2012)

For sepsis, the drugs don't work

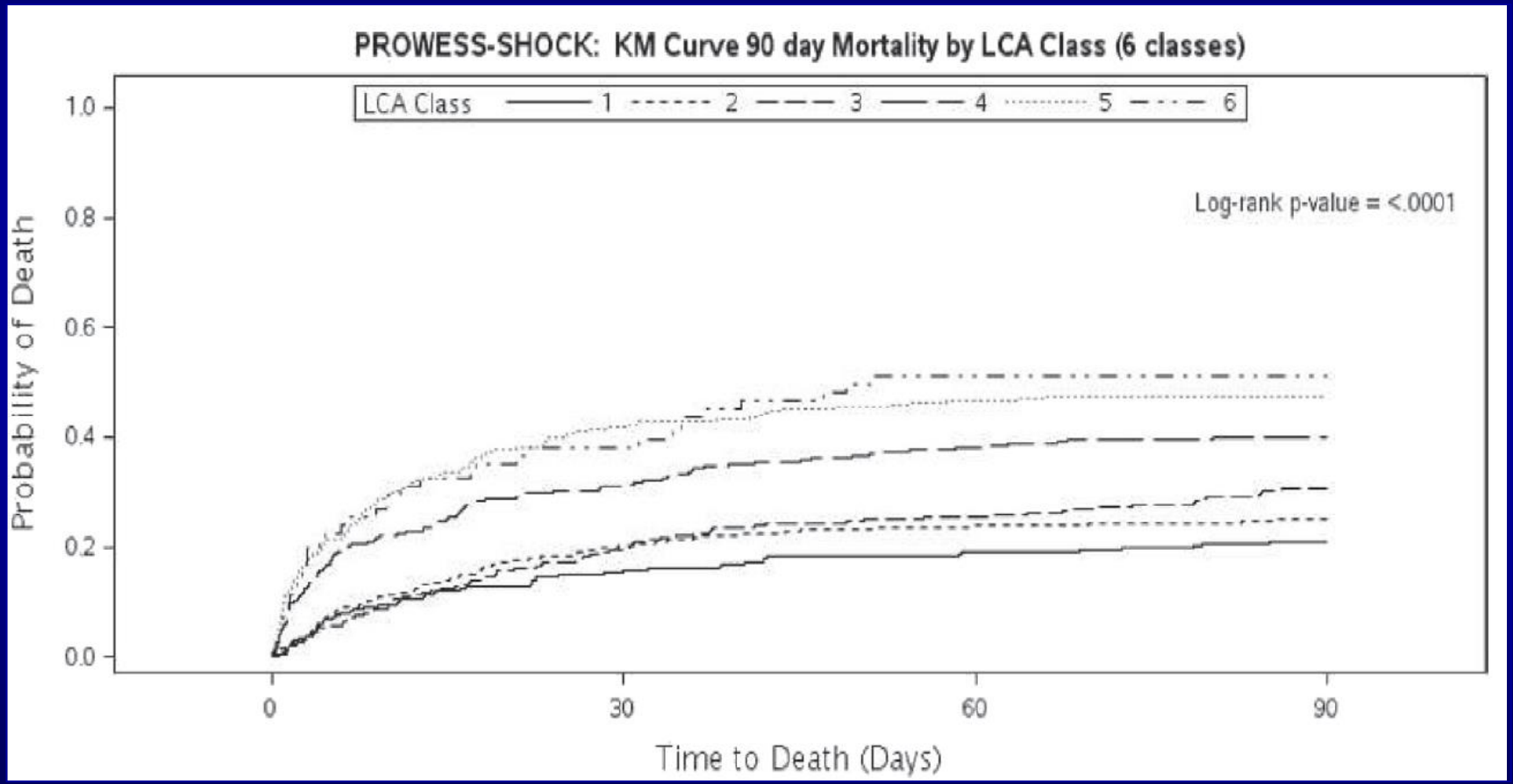
"A deeper understanding of the processes leading to sepsis is necessary before we can design an effective suite of interventions."

The Lancet Infectious Disease; Feb 2012

The response to infection differs between individuals. Up to 6 different sepsis responses (or sepsis subtypes) to infection have been reported

Six subphenotypes in septic shock: Latent class analysis of the PROWESS Shock study

Bengt Gårdlund [a,*], Natalia O. Dmitrieva [b], Carl F. Pieper [c], Simon Finfer [d], John C. Marshall [e], B. Taylor Thompson [f]

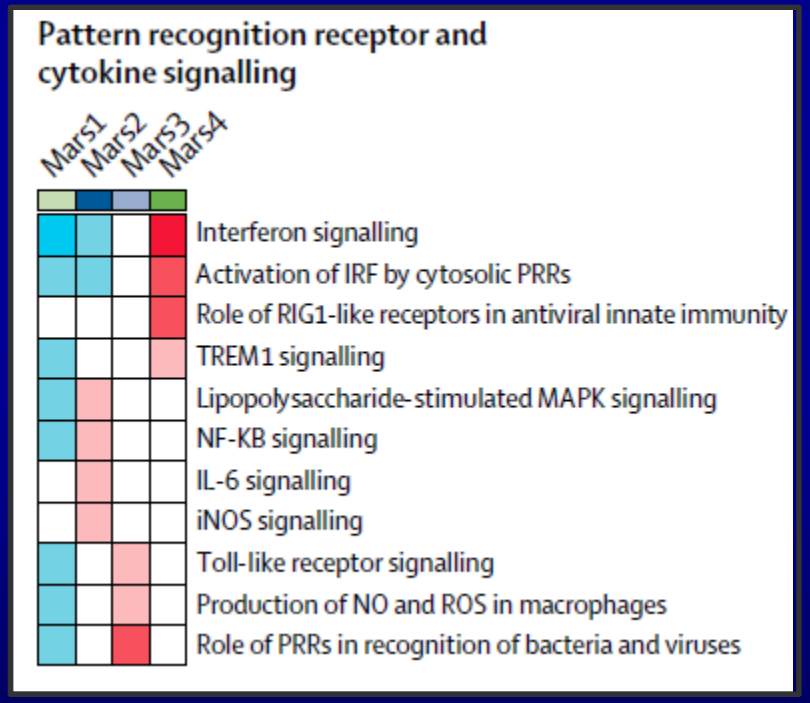


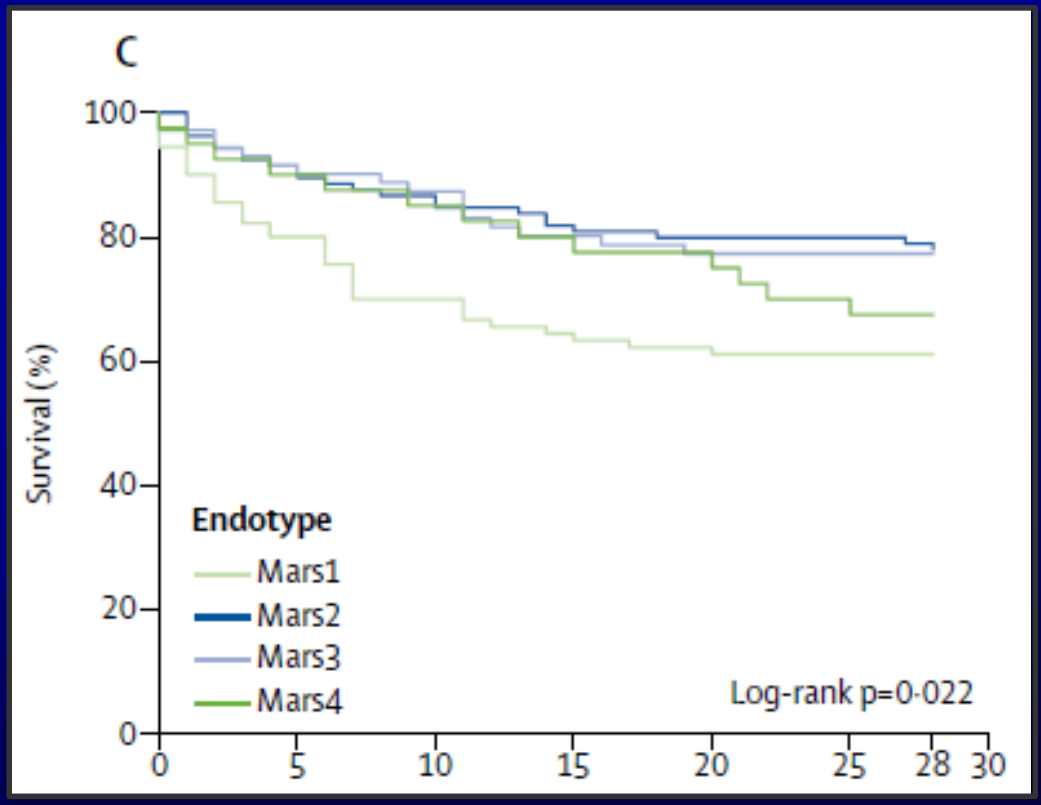
Journal of Critical Care 47 (2018) 70–79

Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

*Brendon P Scicluna, Lonneke A van Vught, Aeilko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium**

Unsupervised consensus clustering and machine learning of the blood transcriptome in patients with sepsis from severe CAP





Lancet Respir Med 2017

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

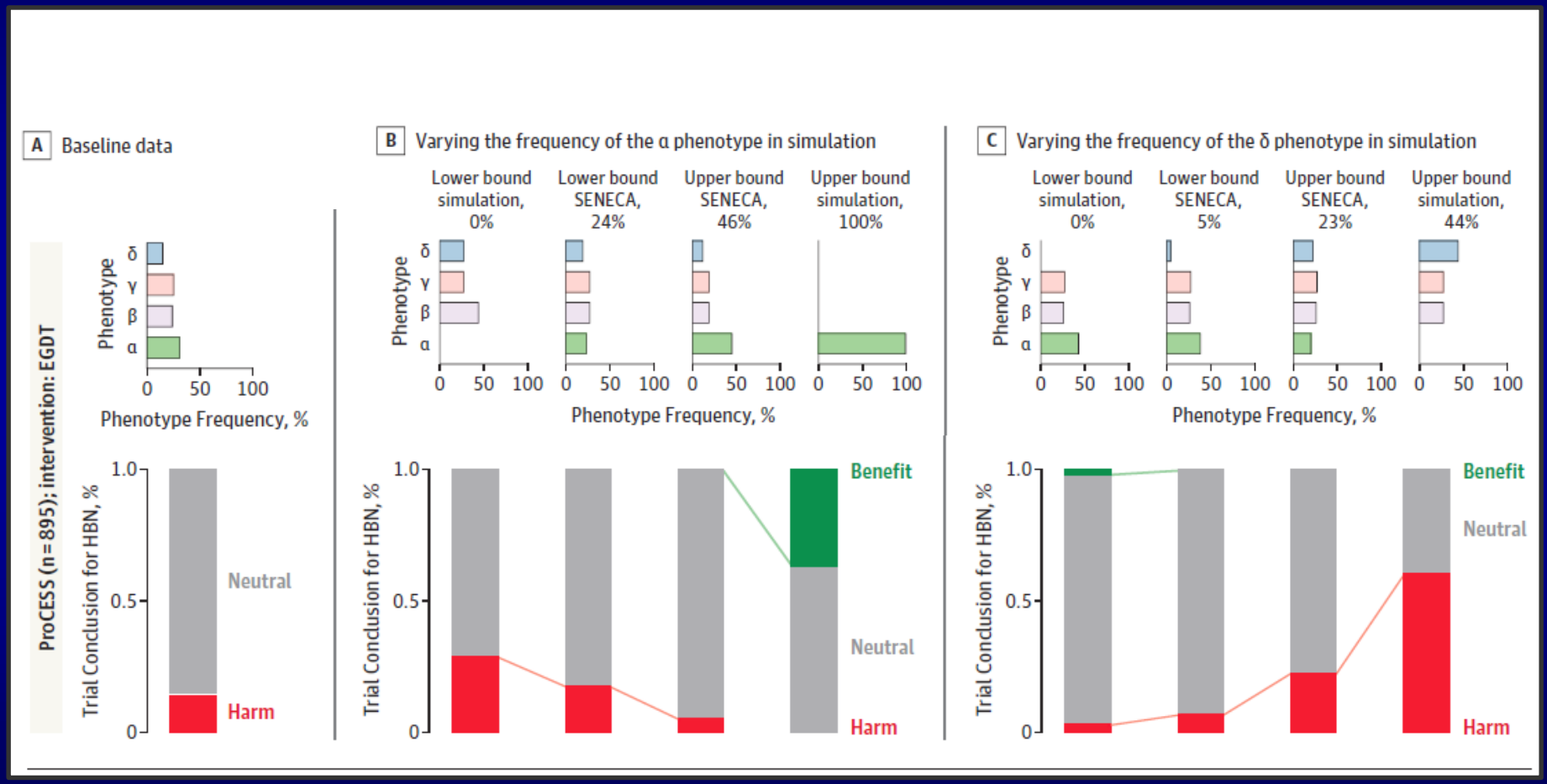
Retrospective analysis of four large datasets (n=16-43k) and 4 RCTs (n=)4737

Machine learning and unsupervised clustering methods using clinical data

Four subgroups of sepsis = best fit	Mortality
α (33%): most common, lowest vasopressors	5%
β (27%): older, more chronic illness and renal dysfunction	13%
γ (27%): more inflammation and pulmonary dysfunction	24%
δ (13%: more liver dysfunction and septic shock	40%

JAMA. 2019

Results of 10,000 simulated trials with different subtype distributions (more α or δ)



Patients with the immunocompetent Sepsis Response Type 2 subtype who were treated with corticosteroids had poorer survival than those given placebo

- **OR for death = 7.9 (1.6-39.9); interaction p = 0.02**

Sepsis Subtypes

As for Type 1 and Type 2 diabetics, we will have a different understanding of and will be making different treatment decisions for patients with “Type 1 sepsis, Type 2 sepsis, etc. etc. etc.”

Summary and Conclusion

- Sepsis is a common and potentially lethal response to infection
- The release if molecules from the initial tissue injury amplify the response
- Dysregulated innate immune response has both hyper and hypo-inflammatory responses that appear to differing degrees in different subtypes
- A Systems Biology approach to understanding sepsis and multiple organ failure will need to embrace this heterogeneity and perhaps explain it

Summary and Conclusion

- Future treatments will likely be guided by a better understanding of the subtypes of immune and coagulation system dysregulation and seek to restore homeostasis (and perhaps cellular energetics)

Thank you

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Extra Slides

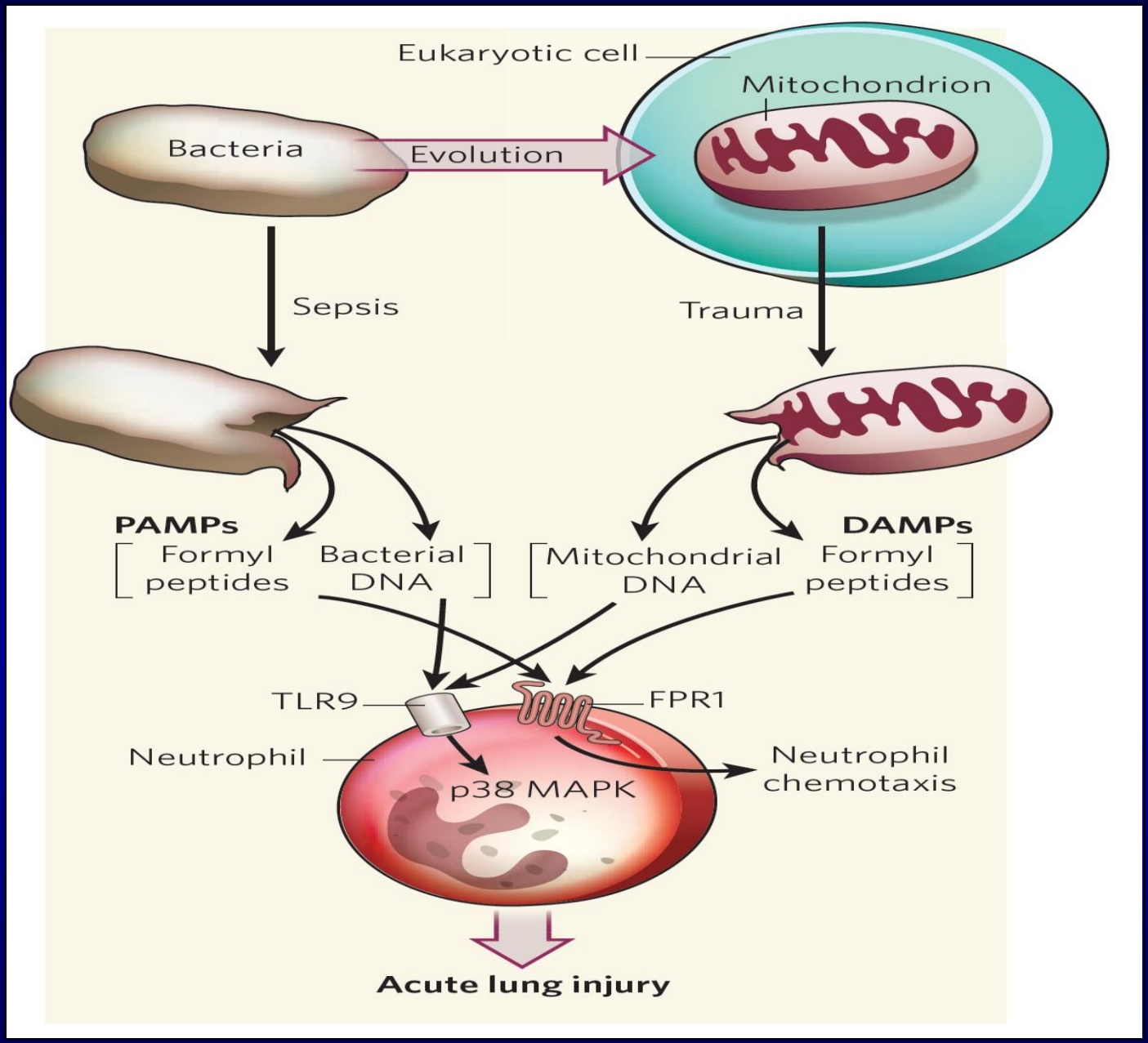
Hager *et al. Trials* (2019) 20:197
https://doi.org/10.1186/s13063-019-3254-2

Trials

STUDY PROTOCOL Open Access

The Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) Protocol: a prospective, multi-center, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial

David N. Hager[1*], Michael H. Hooper[2], Gordon R. Bernard[3], Laurence W. Busse[4], E. Wesley Ely[5,6,7], Alpha A. Fowler[8], David F. Gaieski[9], Alex Hall[10,11], Jeremiah S. Hinson[12], James C. Jackson[5,6,7,13], Gabor D. Kelen[12], Mark Levine[14], Christopher J. Lindsell[15], Richard E. Malone[16], Anna McGlothlin[17], Richard E. Rothman[12], Kert Viele[17], David W. Wright[10,11], Jonathan E. Sevransky[4] and Greg S. Martin[4,11]



Calfee and Matthay Nature 2010

SEPSIS-3 Definition of Shock
Why Vasopressors and Lactate > 2?

Variable	Hypotension after fluids	Vasopressor	Raised Lactate >2 mmol/L
Group 1	Yes	Yes	Yes
Group 2	Yes	Yes	No
Group 3	Yes	No	Yes
Group 4	No	No	Yes
Group 5	No hypotension before fluids	No	Yes
Group 6	Yes	No	No

Variables	**N**	**Hospital mortality, N (%)**
Group		
1 (referent)	8,520	3,602 (42.3)
2	3,985	1,198 (30.1)
3	223	64 (28.7)
4	3,266	839 (25.7)
5	2,696	802 (29.7)
6	150	28 (18.7)

Shankar-Hari JAMA eSuppl 2016

Sepsis Surveillance Using Adult Sepsis Events Simplified eSOFA Criteria Versus Sepsis-3 Sequential Organ Failure Assessment Criteria*

Chanu Rhee, MD, MPH[1,2]; Zilu Zhang, MS[1]; Sameer S. Kadri, MD, MS[3]; David J. Murphy, MD, PhD[4]; Greg S. Martin, MD, MSc[4]; Elizabeth Overton, MS[4]; Christopher W. Seymour, MD, MSc[5]; Derek C. Angus, MD, MPH[5]; Raymund Dantes, MD, MPH[6,7]; Lauren Epstein, MD, MS[6]; David Fram, BA[8]; Richard Schaaf, SM[8]; Rui Wang, PhD[1]; Michael Klompas, MD, MPH[1,2]; for the CDC Prevention Epicenters Program

Critical Care Medicine 2019