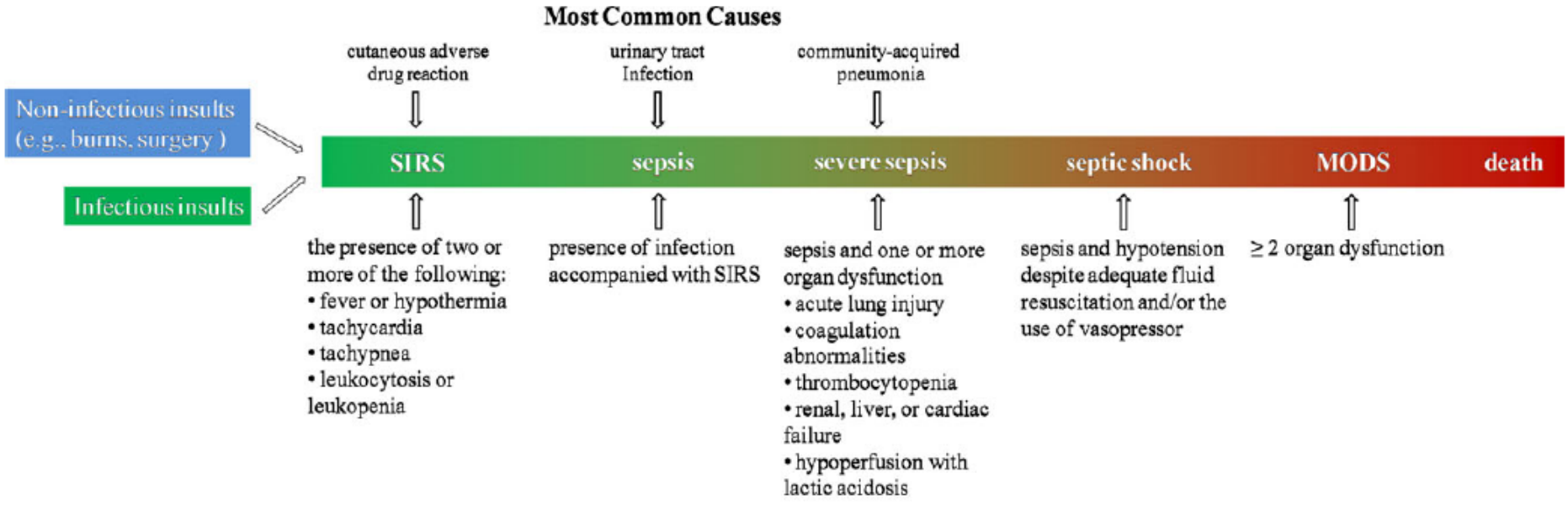
Současná patofyziologie sepse a MODS – 10 novinek, o kterých bych měl vědět

Jan Maláska
(Brno)

One of the great disappointments during the past 30 years has been the failure to convert advances in our understanding of the underlying biologic features of sepsis into effective new therapies.

Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.

N Engl J Med 2013;369:840-51.



Proteomics Clin. Appl. 2014, *8*, 35–52


STOP
KONTROLA
ZI VL 82

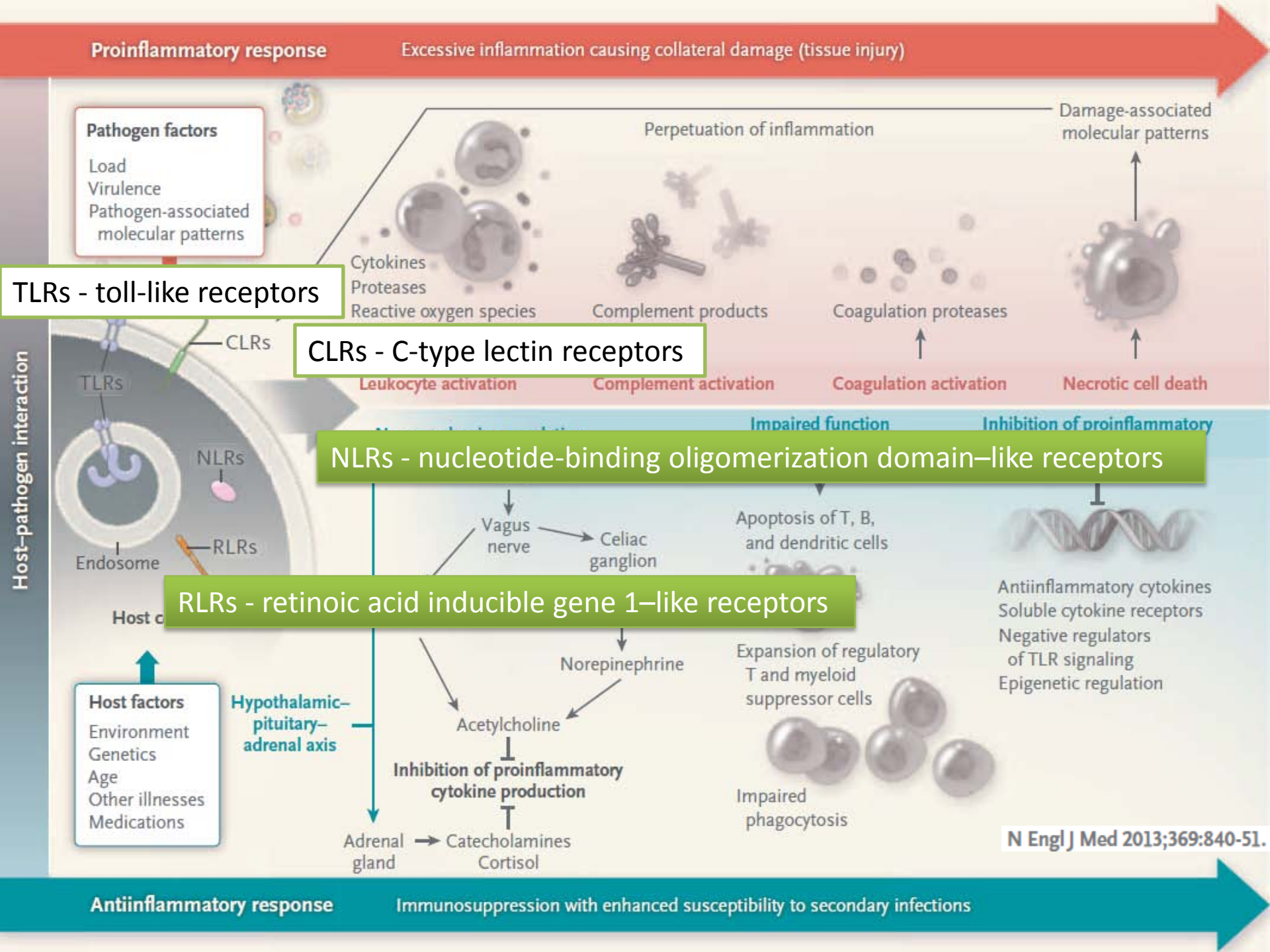
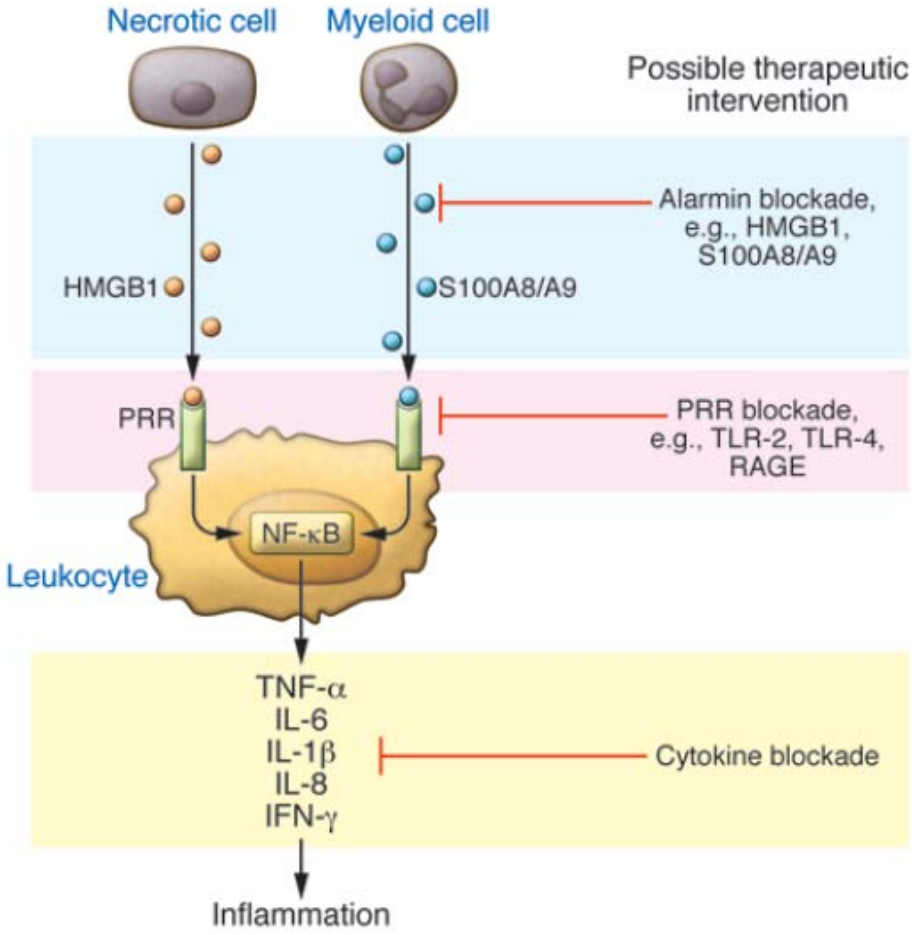

Proinflammatory response
Excessive inflammation causing collateral damage (tissue injury)
Pathogen factors
Load
Virulence
Pathogen-associated molecular patterns
Perpetuation of inflammation
Damage-associated molecular patterns
Cytokines
Proteases
Reactive oxygen species
Complement products
Coagulation proteases
TLRs - toll-like receptors
CLRs - C-type lectin receptors
CLRs
TLRs
Leukocyte activation
Complement activation
Coagulation activation
Necrotic cell death
Host–pathogen interaction
NLRs - nucleotide-binding oligomerization domain–like receptors
NLRs
Impaired function
Inhibition of proinflammatory
Vagus nerve
Celiac ganglion
Apoptosis of T, B, and dendritic cells
Endosome
RLRs
RLRs - retinoic acid inducible gene 1–like receptors
Antiinflammatory cytokines
Soluble cytokine receptors
Negative regulators of TLR signaling
Epigenetic regulation
Norepinephrine
Expansion of regulatory T and myeloid suppressor cells
Host factors
Environment
Genetics
Age
Other illnesses
Medications
Hypothalamic–pituitary–adrenal axis
Acetylcholine
Inhibition of proinflammatory cytokine production
Impaired phagocytosis
Adrenal gland
Catecholamines
Cortisol
N Engl J Med 2013;369:840-51.
Antiinflammatory response
Immunosuppression with enhanced susceptibility to secondary infections

Table 1. PRRs and Their Ligands

PRRs	Localization	Ligand	Origin of the Ligand
TLR			
TLR1	Plasma membrane	Triacyl lipoprotein	Bacteria
TLR2	Plasma membrane	Lipoprotein	Bacteria, viruses, parasites, self
TLR3	Endolysosome	dsRNA	Virus
TLR4	Plasma membrane	LPS	Bacteria, viruses, self
TLR5	Plasma membrane	Flagellin	Bacteria
TLR6	Plasma membrane	Diacyl lipoprotein	Bacteria, viruses
TLR7 (human TLR8)	Endolysosome	ssRNA	Virus, bacteria, self
TLR9	Endolysosome	CpG-DNA	Virus, bacteria, protozoa, self
TLR10	Endolysosome	Unknown	Unknown
TLR11	Plasma membrane	Profilin-like molecule	Protozoa
RLR			
RIG-I	Cytoplasm	Short dsRNA, 5′triphosphate dsRNA	RNA viruses, DNA virus
MDA5	Cytoplasm	Long dsRNA	RNA viruses (Picornaviridae)
LGP2	Cytoplasm	Unknown	RNA viruses
NLR			
NOD1	Cytoplasm	iE-DAP	Bacteria
NOD2	Cytoplasm	MDP	Bacteria
CLR			
Dectin-1	Plasma membrane	β-Glucan	Fungi
Dectin-2	Plasma membrane	β-Glucan	Fungi
MINCLE	Plasma membrane	SAP130	Self, fungi


Neinfekční příčiny SIRS/MODS



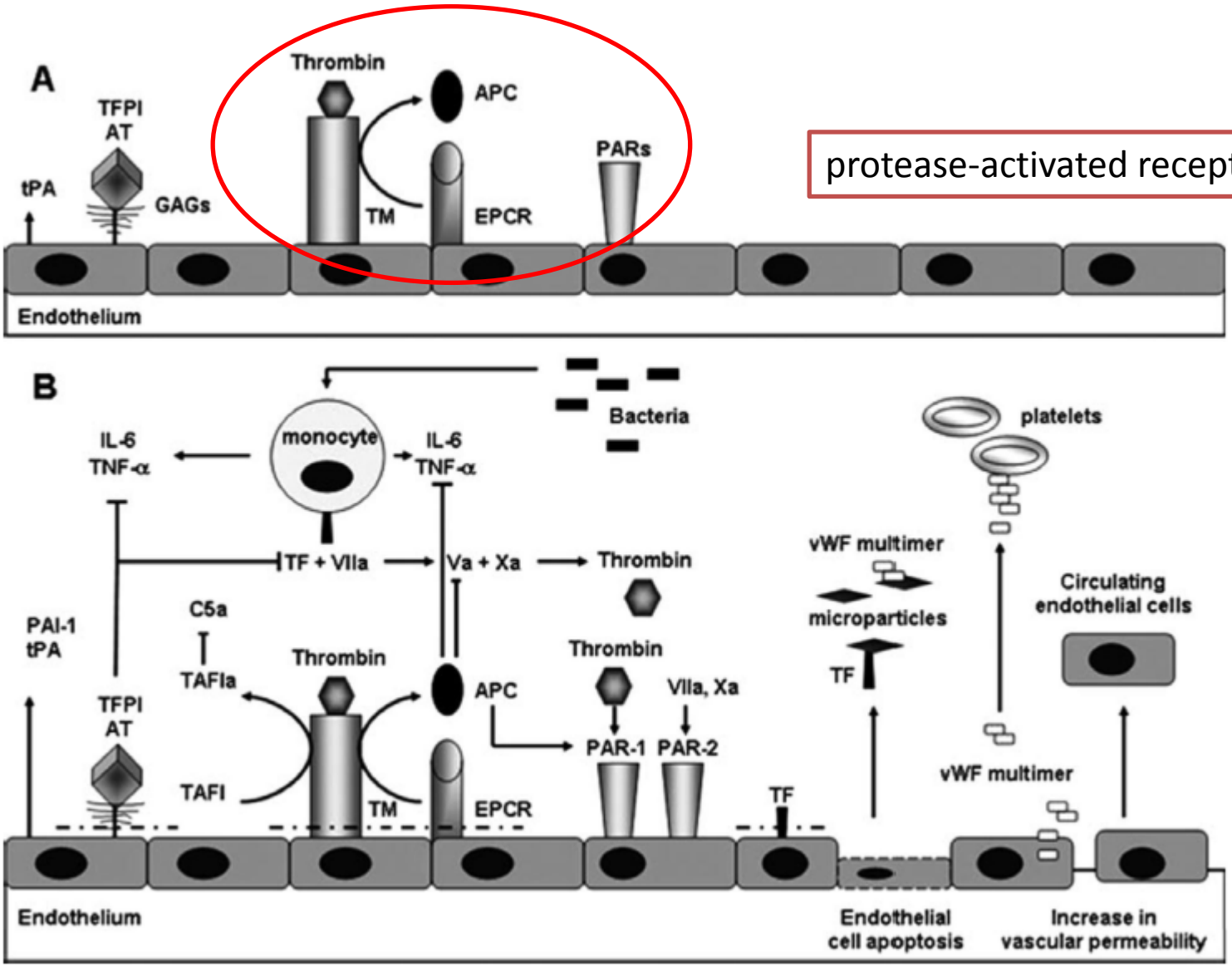
Alarminy

J Clin Invest. 2012;122(8):2711–2719.

Alarmins as biomarkers

Alarmin	Condition type
S100A8, A9, A12	Sepsis, autoimmune (RA, JIA, psoriasis, etc.), respiratory (ARDS, cystic fibrosis), vascular (Kawasaki disease), gastrointestinal (IBD), neurological (MS)
S100B	Traumatic brain injury
HMGB1	Sepsis, trauma, acute coronary syndrome, solid organ transplantation


Spojení zánětu a koagulace

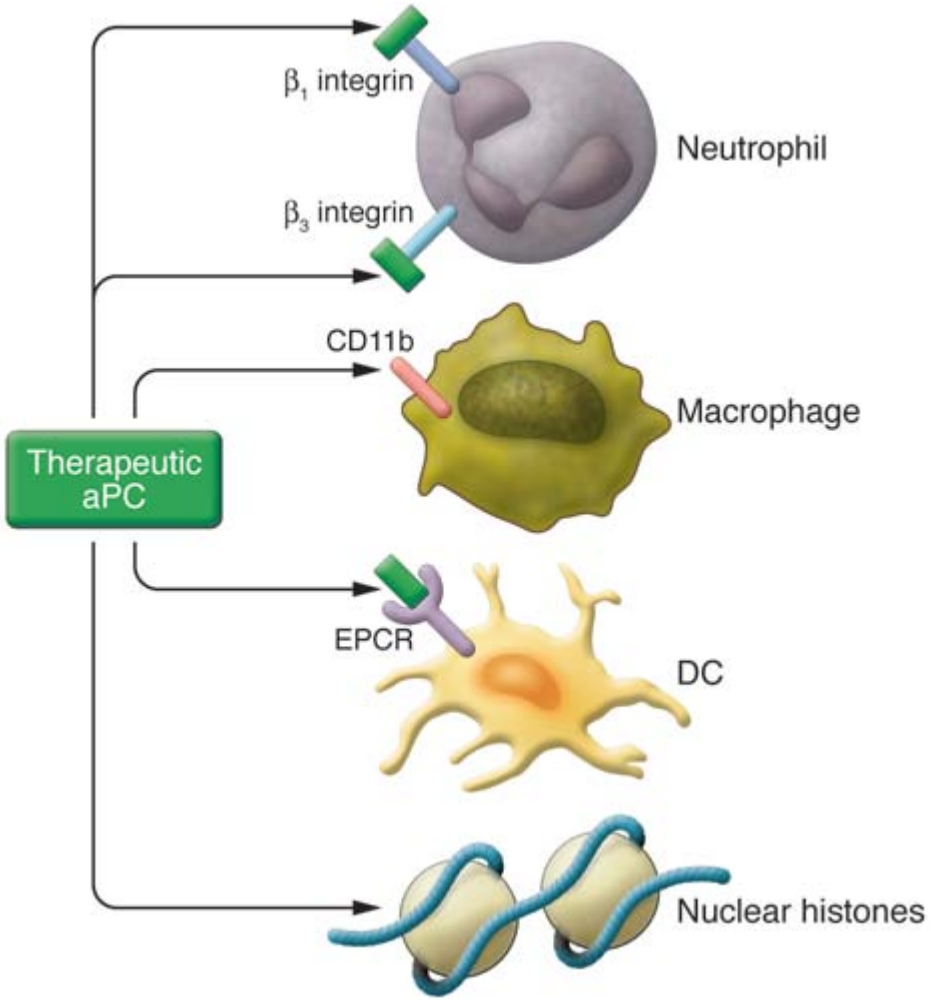


protease-activated receptors (PAR)

PARP – spojení mezi koagulací a inflamací
PAR1 – cytoprotektivní efekt po stimulaci APC nebo low-dose trombinem x vysoké dávky poškození endotelu

Crit Care Med 2010 Vol. 38, No. 2 (Suppl.)

Nově identifikované cíle vrozené imunity pro aPC v sepsi



regulace migrace a extravazace neutrofilů

suprese aktivace makrofágů

kontrola vyzrávání a aktivace dendritických bb.

neutralizuje pozdní mediátory zánětu degradací histonů z apoptotických bb.

J Clin Invest. 2010; 120(9):3084–3087

Alice G. Vassiliou
Nikolaos A. Maniatis
Anastasia Kotanidou
Marina Kallergi
Foteini S. Karystinaki
Eleftheria Letsiou
Constantinos Glynos
Petros Kopterides
Dimitra Vassiliadi
Nikitas Nikitas
Ioanna Dimopoulou
Apostolos Armaganidis
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Endothelial protein C receptor polymorphisms and risk of severe sepsis in critically ill patients

Intensive Care Med (2013) 39:1752–1759

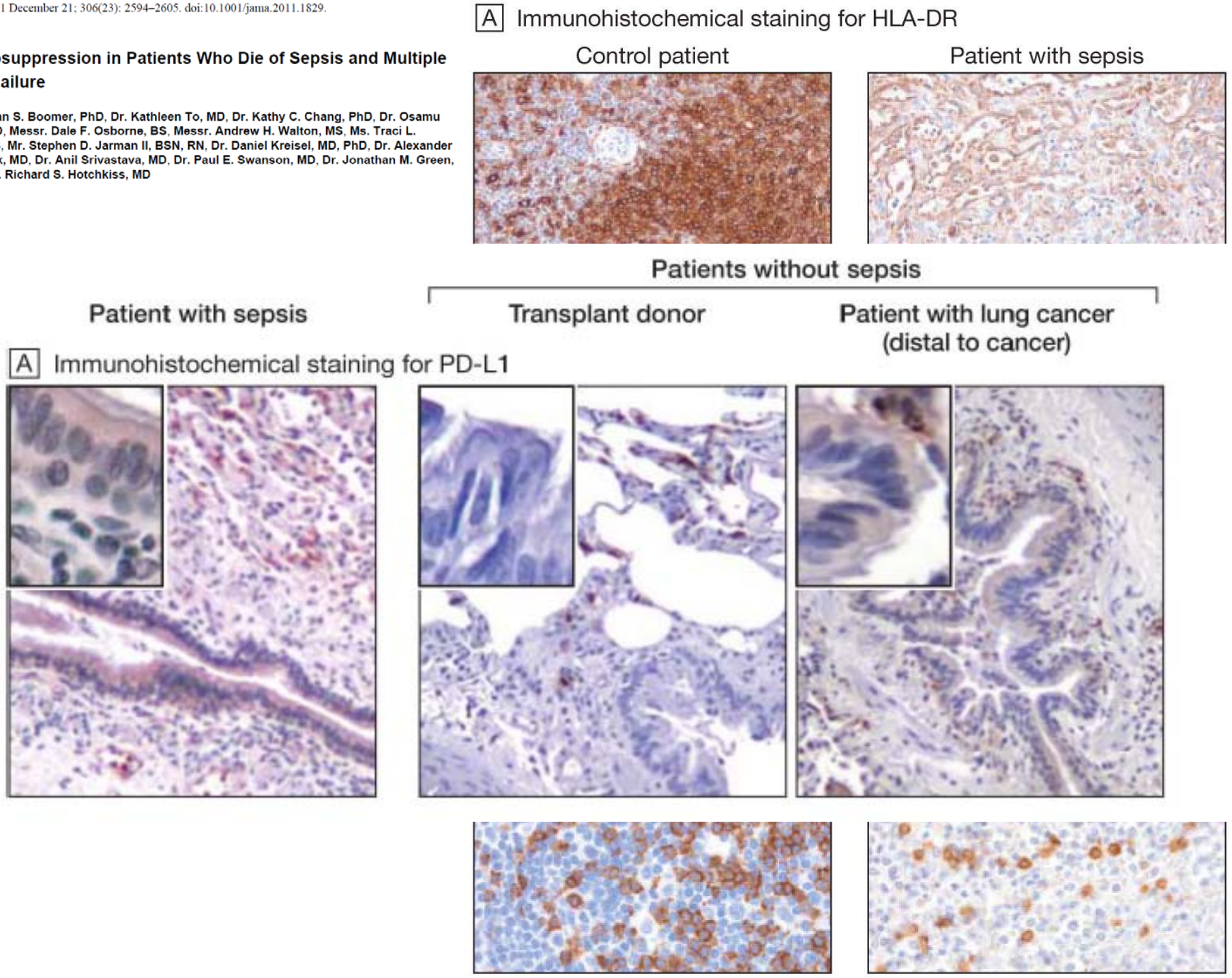
Genotype combination	Percentage of patients with SS/SS	Crude OR (95 % CI)	Adjusted OR (95 % CI)
H2 (no H1 no H3) 6333TT/1651CC/6936AA	65.20 %	Referent	Referent
H1 haplotype only 6333CT or 6333CC/ 1651CC/6936AA	58.0 %	0.74 (0.45–1.20) $p = 0.221$	0.65 (0.37–1.13) $p = 0.123$
H3 haplotype only 6333TT/ 1651GC or 1651GG/ 6936GA or 6936GG	64.30 %	0.96 (0.49–1.87) $p = 0.905$	0.82 (0.39–1.70) $p = 0.590$
Both H1 and H3 haplotypes present 6333CT or 6333CC/ 1651GC or 1651GG/ 6936GA or 6936GG	38.80 %	0.34 (0.17–0.67) $p = 0.002$	0.34 (0.16–0.76) $p = 0.008$


Imunosuprese a imunitní dysregulace

JAMA. 2011 December 21; 306(23): 2594–2605. doi:10.1001/jama.2011.1829.

Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

Dr. Jonathan S. Boomer, PhD, Dr. Kathleen To, MD, Dr. Kathy C. Chang, PhD, Dr. Osamu Takasu, MD, Messr. Dale F. Osborne, BS, Messr. Andrew H. Walton, MS, Ms. Traci L. Bricker, BS, Mr. Stephen D. Jarman II, BSN, RN, Dr. Daniel Kreisel, MD, PhD, Dr. Alexander S. Krupnick, MD, Dr. Anil Srivastava, MD, Dr. Paul E. Swanson, MD, Dr. Jonathan M. Green, MD, and Dr. Richard S. Hotchkiss, MD



JAMA. 2011 December 21; 306(23): 2594–2605. doi:10.1001/jama.2011.1829.

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Days in hospital, median (range)	11 (1–195)
Days in intensive care unit, median (range)	8 (1–195)
Days of sepsis, median (range)[b]	4 (1–>40)


Mikrocirkulace

- **↓densita kapilár vede ke zvětšení difůzní vzdálenosti pro O2**

- **neperfundované a perfundované kapiláry jsou v těsné blízkosti**

- **vede to k alteraci extrakci O2 a k zónám hypoxie i při celkově zachované perfuzi orgánu**

- **tato heterogenita mikrocirkulace je kruciální**

Virulence 5:1, 73–79; January 1, 2014

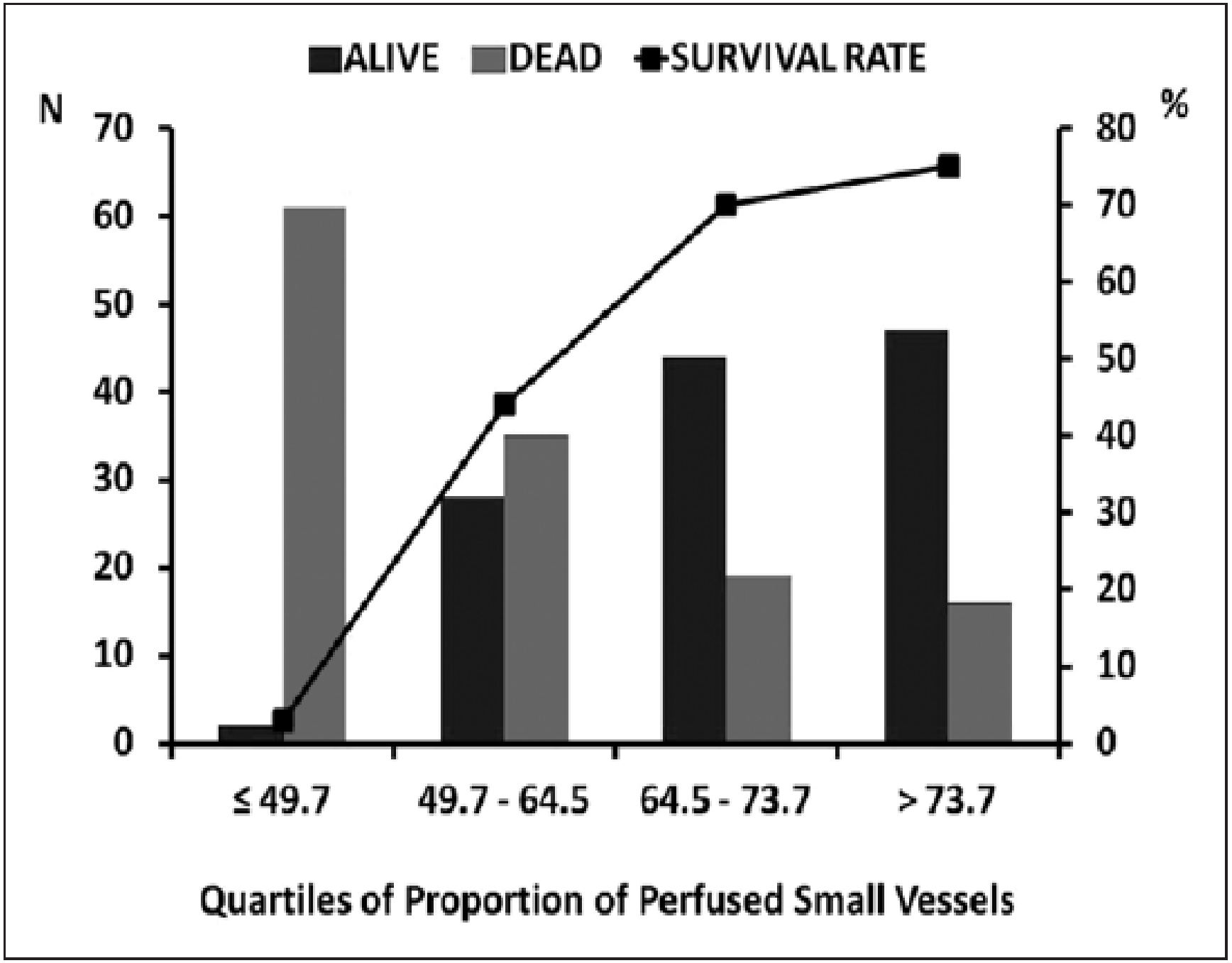
Microcirculatory Alterations in Patients With Severe Sepsis: Impact of Time of Assessment and Relationship With Outcome*

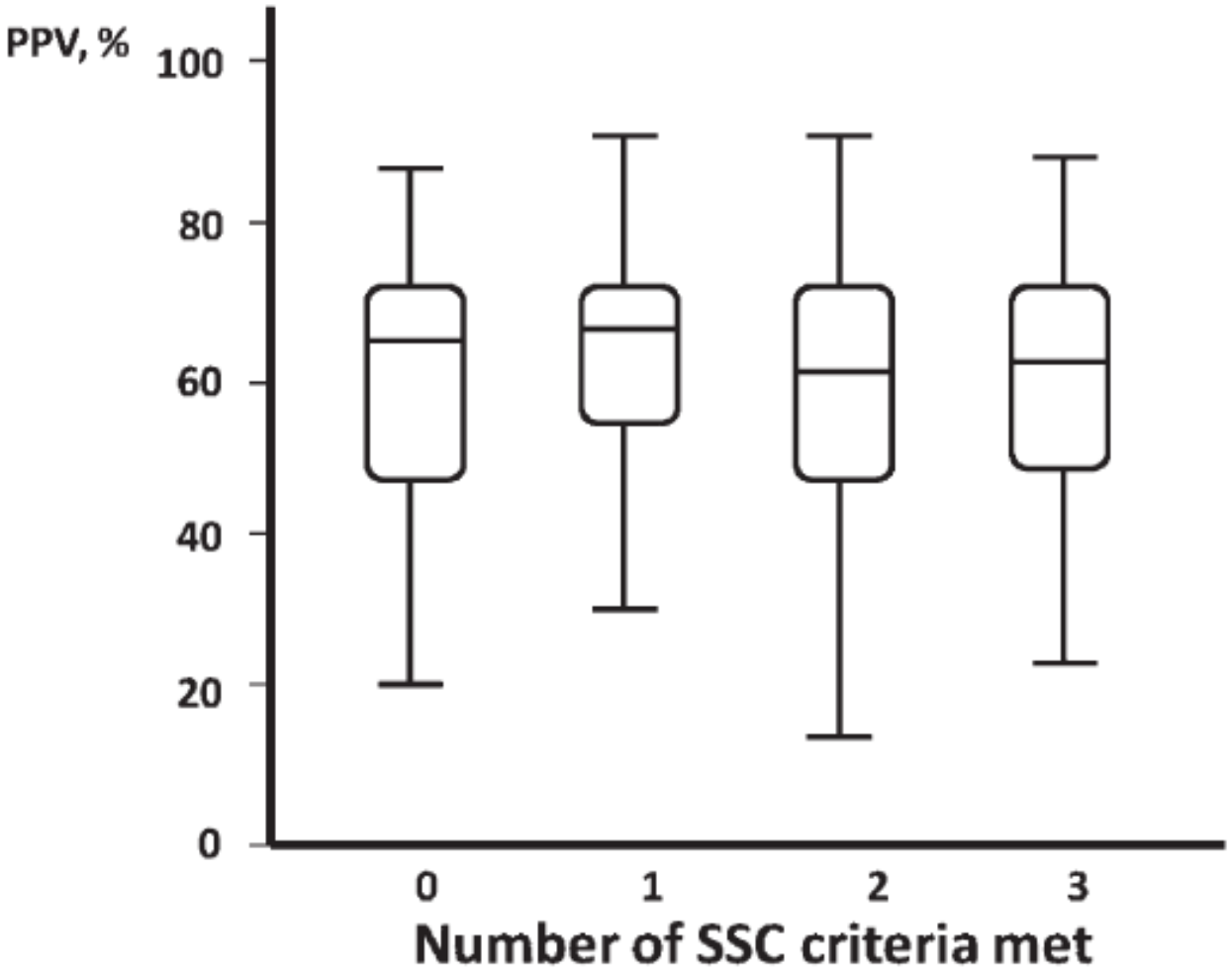
March 2013 • Volume 41 • Number 3

Daniel De Backer, MD, PhD; Katia Donadello, MD; Yasser Sakr, MD, PhD; Gustavo Ospina-Tascon, MD; Diamantino Salgado, MD; Sabino Scolletta, MD; Jean-Louis Vincent, MD, PhD, FCCM

TABLE 3. Main Hemodynamic and Microcirculatory Variables in ICU Survivors and Nonsurvivors

	ICU Survivor ($n = 122$)	ICU Nonsurvivor ($n = 130$)	p
Heart rate (bpm)	102 [88–117]	105 [94–116]	0.54
Mean arterial pressure (mm Hg)	71 [66–78]	69 [64–75]	0.11
Cardiac index (L/min.m^2)	3.5 [2.8–4.3]	3.2 [2.6–3.8]	0.036
Central venous pressure (mm Hg)	12 [9–14]	13 [10–16]	0.013
Svo_2 (%)	70.0 [64.4–76.7]	67.0 [62.0–72.0]	0.005
Lactate (mEq/L)	1.9 [1.2–2.8]	2.4 [1.4–4.0]	0.004
pH	7.37 [7.32–7.44]	7.35 [7.27–7.40]	0.19
Total vessel density (n/mm)	7.5 [6.2–8.9]	6.8 [5.1–8.3]	0.08
Density of perfused small vessels (n/mm)	3.4 [2.7–4.6]	2.2 [1.6–3. 2]	0.001
Proportion of perfused small vessels (PPV, %)	71 [65–78]	50 [40–66]	0.001
Microvascular flow index	2.35 [1.90–2.52]	1.95 [1.65–2.60]	0.036
Heterogeneity PPV (%)	27 [17–47]	41 [23–60]	0.08
Acute Physiology and Chronic Health Evaluation II score	20 [17–27]	23 [18–28]	0.07
Sequential organ failure assessment score	10 [8–11]	11 [9–14]	0.002
Vasopressor use, n (%)	61 (50)	86 (66)	0.016
Vasopressor dose[a] (mcg/kg.min)	0.20 [0.11–0.40]	0.19 [0.11–0.39]	0.18


ALIVE
DEAD
SURVIVAL RATE
N
%
70
60
50
40
30
20
10
0
80
70
60
50
40
30
20
10
0
≤ 49.7
49.7 - 64.5
64.5 - 73.7
> 73.7
Quartiles of Proportion of Perfused Small Vessels

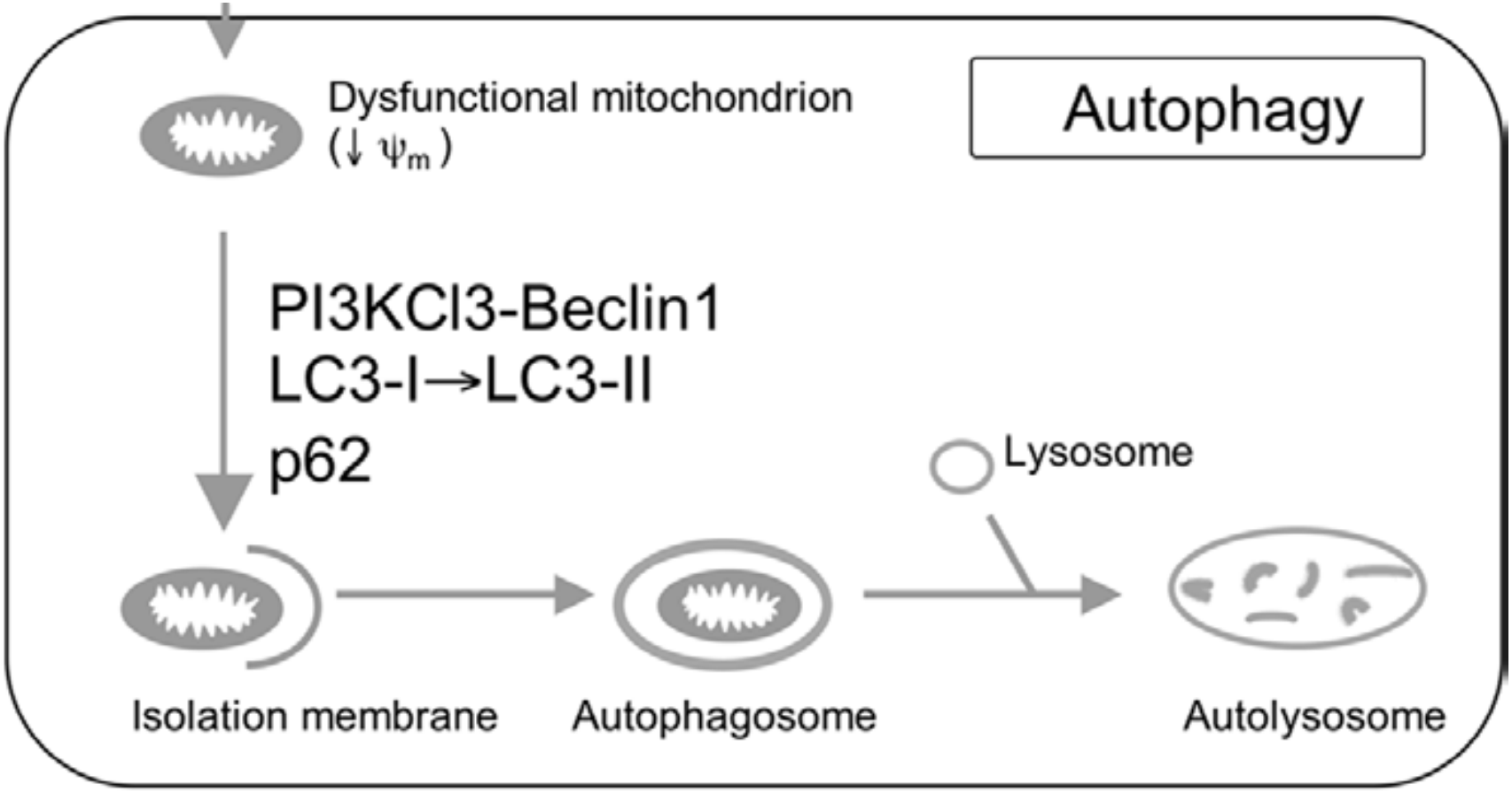


1. MAP > 65 mm Hg
2. Svo2 or Scvo2 above 65 or 70%
3. CVP between 8 and 12 mm Hg


Mitochondrie a MODS

Dysfunkce mitochondrií v sepsi

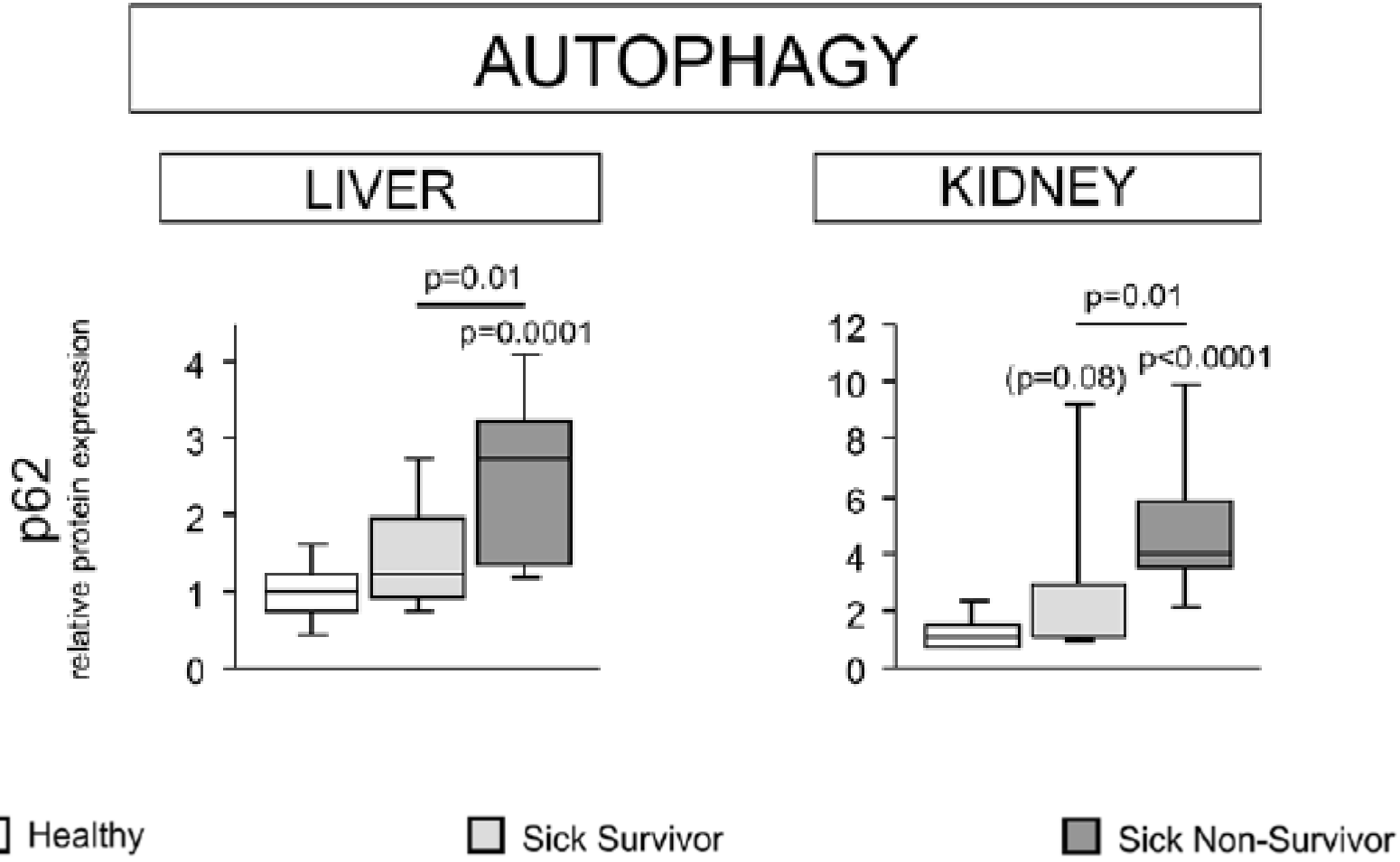
Preklinické i klinická data poukazují na asociaci tíže mitochondriální dysfunkce s klinickým průběhem onemocnění, s orgánovou dysfunkcí a mortalitou



Mitofágie, mitoptóza, mitochondriální biogeneze

Insufficient Autophagy Contributes to Mitochondrial Dysfunction, Organ Failure, and Adverse Outcome in an Animal Model of Critical Illness*

Jan Gunst, MD, PhD; Inge Derese, BSc; Annelies Aertgeerts, BSc; Eric-Jan Ververs, BSc; Andy Wauters, BSc; Greet Van den Berghe, MD, PhD; Ilse Vanhorebeek, PhD



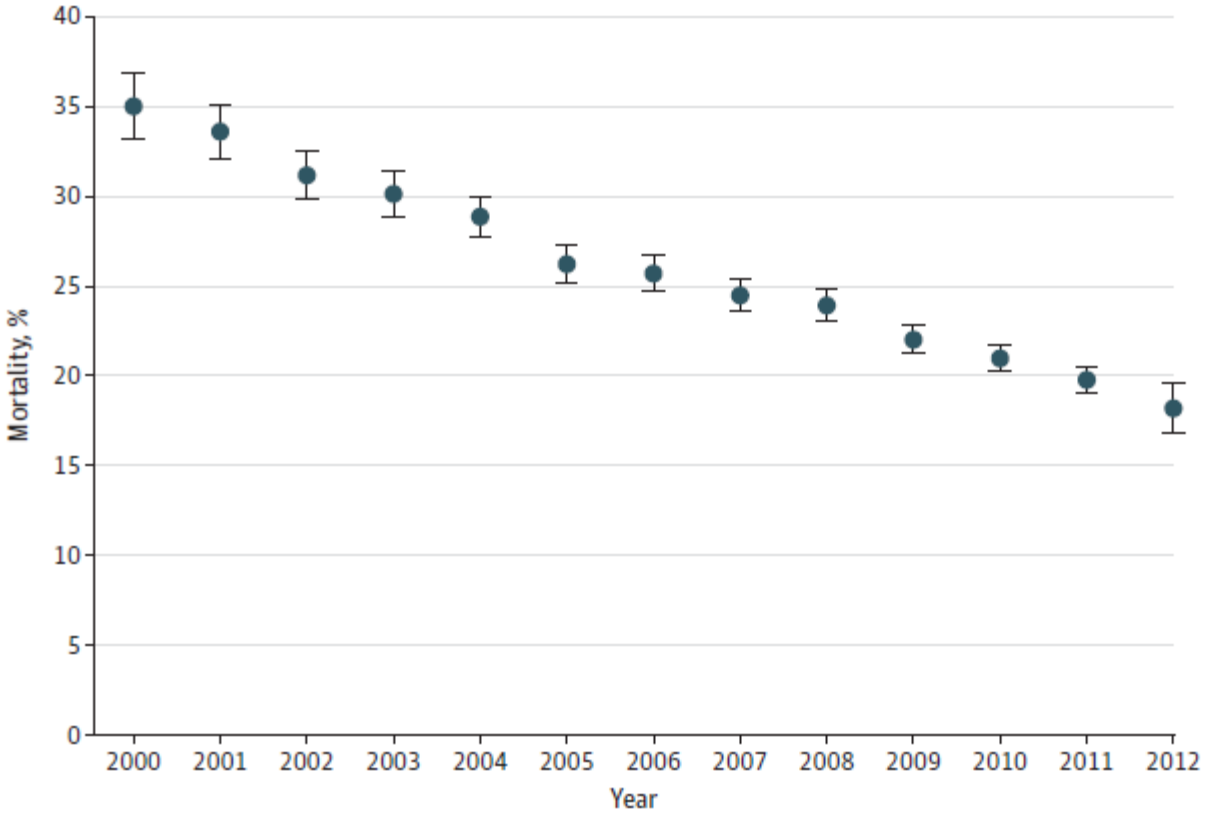

Význam znalostí patofyziologie sepse pro klinickou praxi?

- Proč vlastně potřebujeme znát patofyziologii sepse a MODS?
- Zlepší to moji klinickou praxi?
- Má to význam pokud neprovádím základní výzkum?

Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

Figure 1. Mean Annual Mortality in Patients With Severe Sepsis



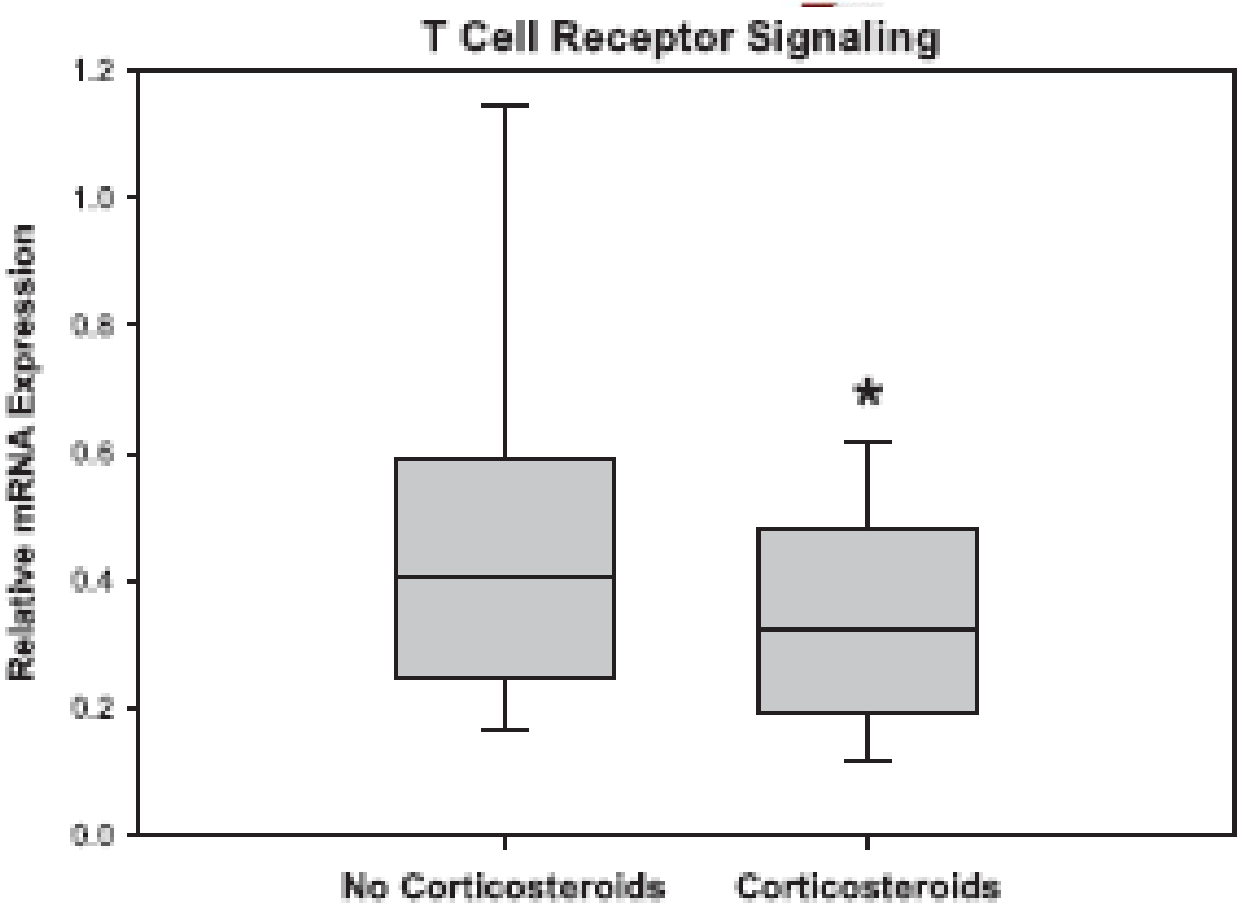
Error bars indicate 95% CI.


Kortikoidy a patofyziologie sepse

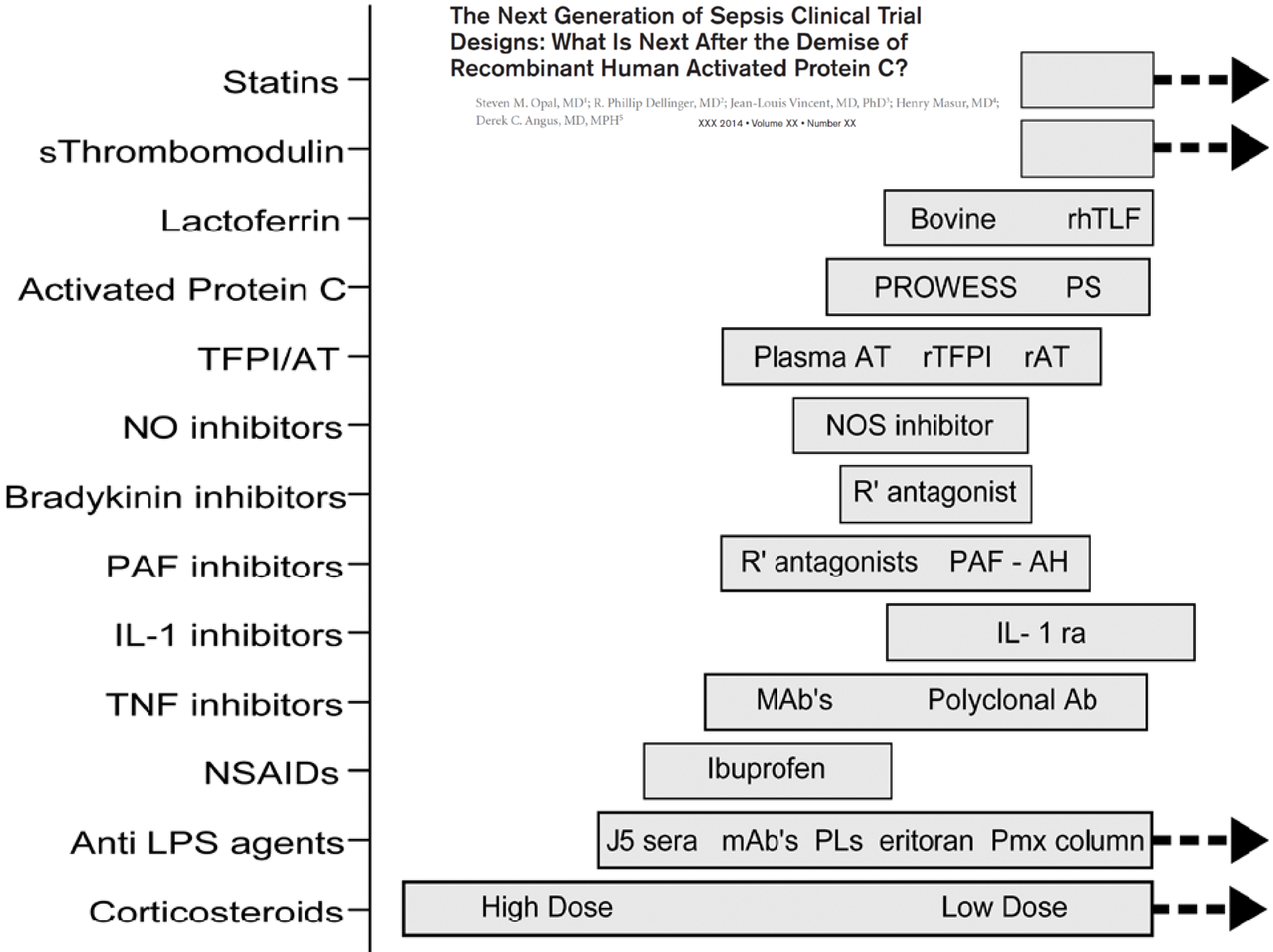
Corticosteroids Are Associated with Repression of Adaptive Immunity Gene Programs in Pediatric Septic Shock

Hector R. Wong[1], Natalie Z. Cvijanovich[2], Geoffrey L. Allen[3], Neal J. Thomas[4], Robert J. Freishtat[5], Nick Anas[6], Keith Meyer[7], Paul A. Checchia[8], Scott L. Weiss[9], Thomas P. Shanley[10], Michael T. Bigham[11], Sharon Banschbach[1], Eileen Beckman[1], Kelli Harmon[1], and Jerry J. Zimmerman[12]

American Journal of Respiratory and Critical Care Medicine Volume 189 Number 8 | April 15 2014



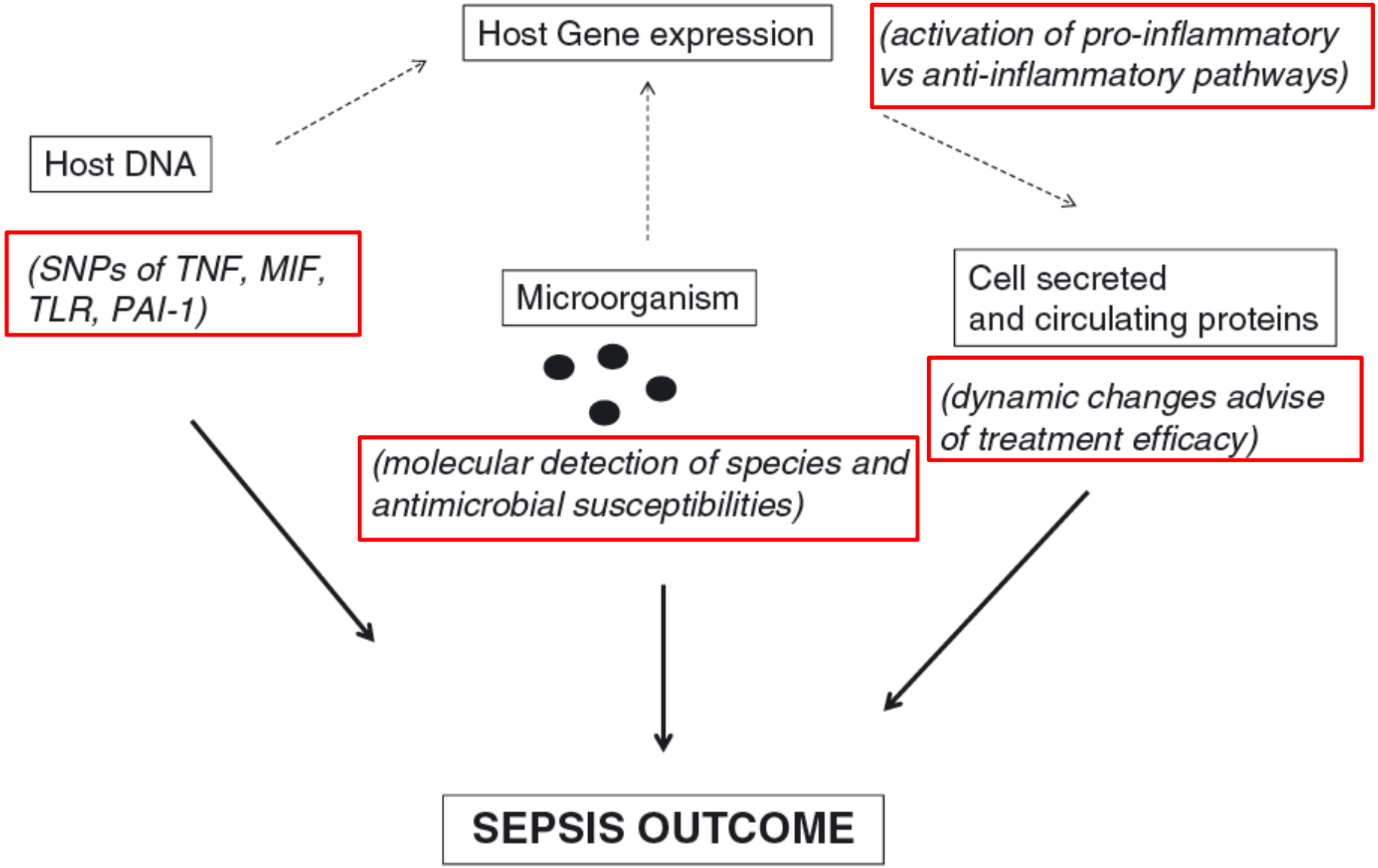

Výzkum patofyziologie se mění



The Next Generation of Sepsis Clinical Trial Designs: What Is Next After the Demise of Recombinant Human Activated Protein C?
Steven M. Opal, MD[1]; R. Phillip Dellinger, MD[2]; Jean-Louis Vincent, MD, PhD[3]; Henry Masur, MD[4]; Derek C. Angus, MD, MPH[5]
XXX 2014 • Volume XX • Number XX
Statins
sThrombomodulin
Lactoferrin
Bovine
rhTLF
Activated Protein C
PROWESS
PS
TFPI/AT
Plasma AT
rTFPI
rAT
NO inhibitors
NOS inhibitor
Bradykinin inhibitors
R' antagonist
PAF inhibitors
R' antagonists
PAF - AH
IL-1 inhibitors
IL- 1 ra
TNF inhibitors
MAb's
Polyclonal Ab
NSAIDs
Ibuprofen
Anti LPS agents
J5 sera
mAb's
PLs
eritoran
Pmx column
Corticosteroids
High Dose
Low Dose

The beginning of personalized medicine in sepsis: small steps to a bright future

Clin Genet 2014: 86: 56–61




Currently no anti-sepsis trial!!

1	Preclinical animal studies are limited in value and need to be more realistic	Study aged animals using a salvage model after the septic insult has occurred
2	Develop biomarkers or response indicators to guide patient selection early in development	Biomarkers should fit the mechanism of action of the drug or device to select responsive patients and improve success
3	Phase II trials need several hundred patients with detailed mechanism of action studies, biomarker surveys, and dose finding	Phase II trial data should be large enough to assess accurately the chance for success in phase III studies
4	Biomarkers or surrogate endpoint measures are greatly needed to define optimal patient cohorts, and biomarkers or response indicators should guide patient selection	Biomarkers should fit the mechanism of action of the drug or device to select responsive patients, and rapid methods are needed to immunophenotype patients before using immune modulators
5	Large phase III trials need to be adequately powered to find clinically meaningful improvements in outcome	Use conservative effect size calculations and low predicted mortality rates in control group (< 25%), consider investigator-driven, parallel trials as a comparator to industry sponsored studies
6	Consider study endpoints other than 28 d, all-cause mortality rates such as 60 or 90 d follow-up	Other patient-centered outcomes (e.g., ventilator-free days), or survival time analyses over longer periods (90 d) worth considering
7	Combinations of novel agents might be needed to show significant survival benefits	Combinations need to be mechanistically additive and safety needs to be assured
8	Adaptive trial design methodologies should be attempted in sepsis research	Early validation of a proposed intervention, supported by biomarkers, can identify a dose that affects the proposed target
9	Centers of excellence are optimal in phase II; but phase III study sites with variable expertise in sepsis should assess the "real-life" safety/efficacy of the experimental drug	Clinical coordinating centers can assist in phase III trials to limit variability and assure comparability across study centers
10	Study protocol entry criteria need to define a patient population at real risk for the study endpoint (e.g., death from sepsis) and some likelihood of responding to the study agent	Attributable risk for sepsis-related mortality is critical; patients at high risk of death should not be excluded, they are most likely to benefit
11	Two large clinical trials, demonstrating reproducible efficacy in sepsis trials, will likely be necessary for drug or device registration	Costs are already prohibitive; an improved set of biomarkers, study design, or additional financial incentives (extended patent life) may be needed
12	A central electronic repository of sepsis trial clinical information with standardized data collection needs to be established	Patient information derived from the past clinical trials, and a dedicated patient biobank of plasma and cells for genomic studies and biomarker studies are needed

Závěr I

- **Znalost patofyziologie sepse je nesmírně důležitá pro komplexní klinickou práci**
- **Sepse je iniciována rozpoznáním patogenu pomocí PPR systému (PAMP‘s)**
- **Alarminy (DAMP‘s) spouštějí SIRS/MODS obdobnými mechanismy**
- **V rozvoji MODS hraje významnou roli interakce inflamace/koagulace**
- **Imunosuprese v pozdních fázích sepse je zodpovědná za signifikantní mortalitu/morbiditu pacientů**

Závěr II

- **Dysfunkce mikrocirkulace je primární v rozvoji MODS nicméně v úzké interakci s ostatními mechanismy**
- **Cíle iniciální resuscitace u pacientů se sepsí?**
- **Podávání tzv. substituční dávky kortikoidů u předpokládaného CIRCI (Critical illness-related corticosteroid insufficiency) pravděpodobně není bez imunosupresivního vlivu**
- **Zásah do nesmírně komplexního procesu sepse/MODS není možný bez individualizace a šití terapie na míru konkrétnímu pacientovi**
- **Význam polymorfismu genů zapojených v patofyziologii sepse**
- **Nutnost změny přístupu při hodnocení účinnosti nových léků a strategií**