

# ČO MA NAUČILA SEPSA ?

Prednáška venovaná pamiatke  
Roger C. Bone

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KAIM LF UK na Onkologickom ústave  
Svätej Alžbety v Bratislave

# Obsah a témy

## prednášky

- Úvod - vývoj pojmov septický syndróm, sepsa a SIRS
- Etiopatogenéza a imunopatogenéza
- Dynamika sepsy
- Význam epidemiológie sepsy  
Biomarkery sepsy a NLR
- Omics v sepse – metabolomika
- Späť k terapii septického šoku

**21. Colours of Sepsis , Ostrava 2019**

# Definície sepsy ,

R. Bone 1991, Th. Calandra 2001, ANGUS d. 2013, M. Singer 2016

- **Sepsa predstavuje klinický syndróm systémovej zápalovej odpovede na infekciu**  
*R. Bone, et al. 1991*
- Sepsa znamená klinickú manifestáciu **akútneho zlyhania vrodenej imunitnej reakcie na infekciu** , ktorá vedie k nadmernej a neprimeranej odpovedi orgánových systémov hostiteľa  
*Thierry Calandra 2001.*
- **Sepsa** znamená systémovú aktiváciu **imunitného, retikulo- endotelového a hemokoagulačného systému** , ktoré indukujú neurovegetatívnu, endokrinnú, metabolickú a orgánovú odpoveď.  
*Angus D., T. Poll, NEJM 2013.*
- **Sepsa** je definovaná ako **život- ohrozujúci stav orgánovej dysfunkcie zapríčinený dysregulovanou odpoveďou organizmu na infekciu**  
*Sepsis-3 definiton. M.Singer et al. /2016. ..*

# Roger Bone: Pathogenesis of Sepsis, 1989

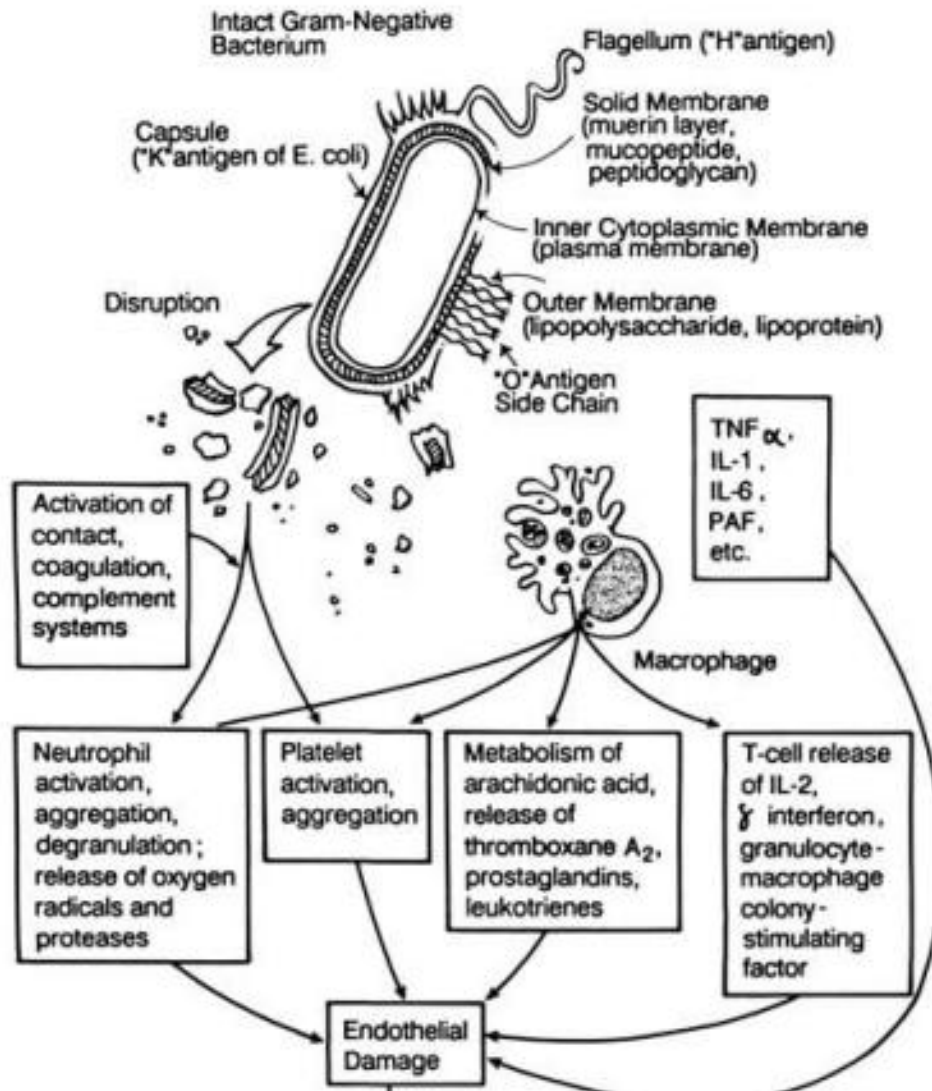


Figure 1.1 that although the pathogenesis of sepsis is not fully understood, the events that lead to endothelial damage are well defined.

Bone R.C, Fisher M... Balk R: **SEPSIS SYNDROME : A VALID CLINICAL ENTITY** . *Crit Care Med* 1989, 17:389 -

- **Definovanie problému sepsy a septického syndrómu**
- vytvorenie **novej klinickej entity SIRS**
- **Implementácia SIRS kritérii** pre rýchly skríning septických stavov .
- **Koncepcia neinfekčného SIRS** (neinfekčná etiopatogenéza , a **infekčného SIRS (sepsa – etiopatogenéza sepsy spustená infekciou ,**
- **Význam imunitného systému** v patogenéze sepsy a SIRS

## Gram-Negative Sepsis\*

### Background, Clinical Features, and Intervention

Roger C. Bone, M.D., F.C.C.P.

Table 2—Criteria for Sepsis Syndrome\*

Clinical evidence of infection

Rectal temperature  $>38.3^{\circ}\text{C}$  or  $<35.5^{\circ}\text{C}$

Tachycardia ( $>90$  beats/min)

Tachypnea ( $>20$  breaths/min while spontaneously breathing)

At least one of the following manifestations of inadequate organ function/perfusion:

Alteration in mental status

Hypoxemia ( $\text{PaO}_2 < 72$  mm Hg breathing room air) (w/vent pulmonary disease not direct cause of hypoxemia)

Elevated plasma lactate level

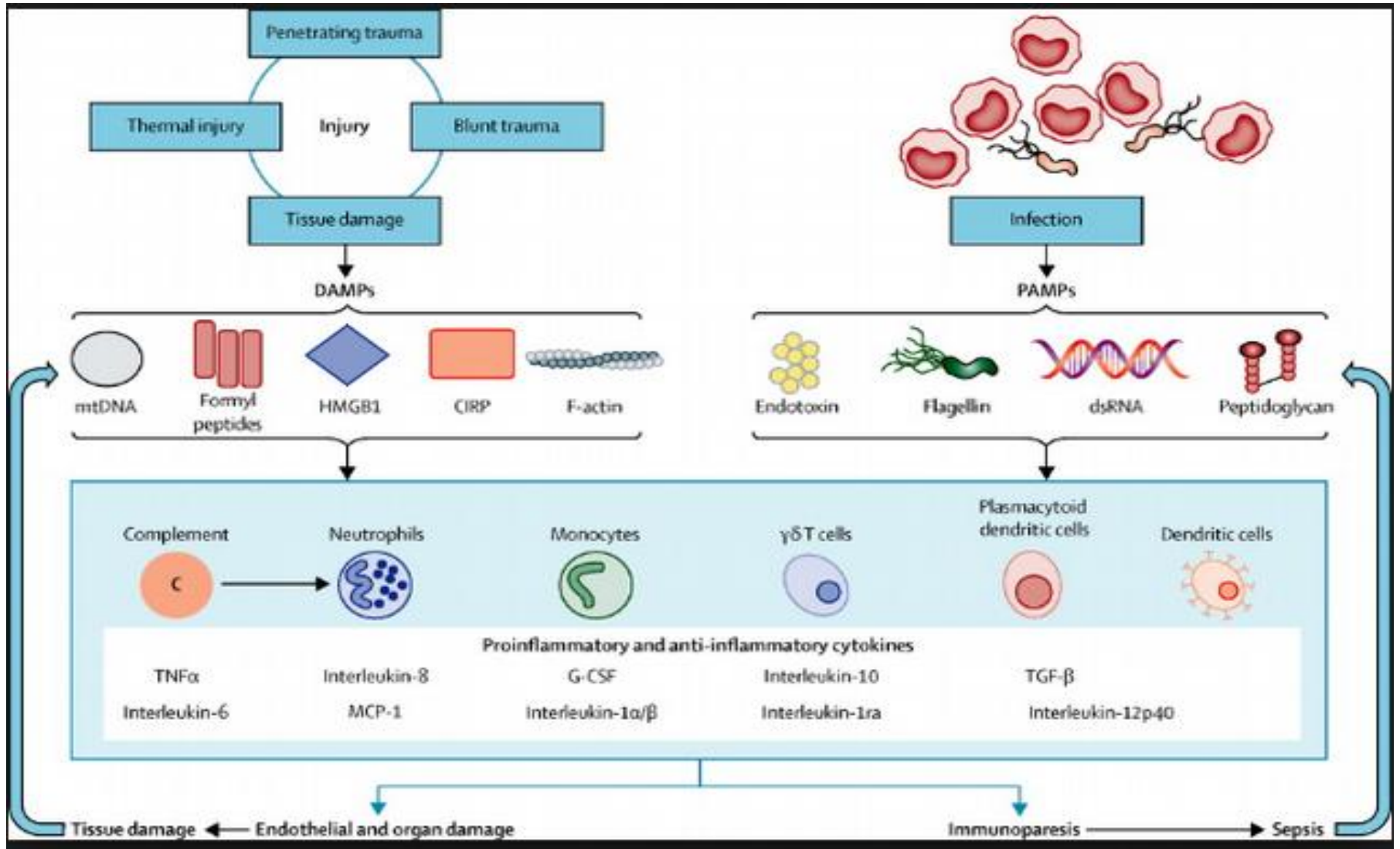
Oliguria (urine output  $<30$  ml or  $0.5$  ml/kg for at least 1 h)

\*Reprinted with permission.<sup>1</sup>

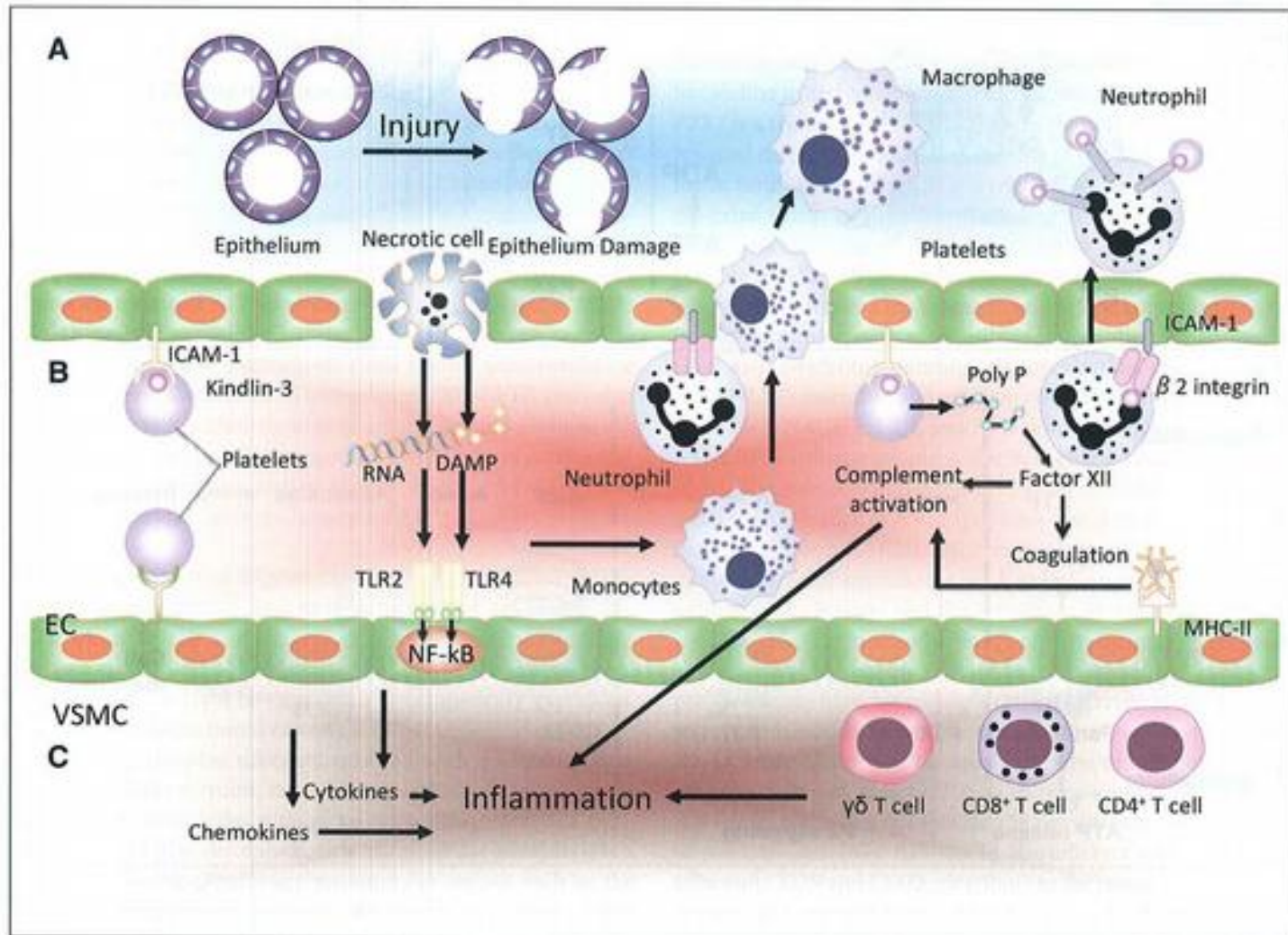


FIGURE 3. Agents or techniques that have been postulated to have a salutary effect on patient survival with sepsis syndrome. Solid lines = agents generally accepted (but not necessarily subjected to controlled clinical trials); hatched lines = agents subjected to controlled clinical trials that have shown efficacy in some patient populations; and dashed lines = agents postulated to improve outcome. Some have been subjected to human studies, others have been subjected only to *in vitro* or animal studies.

# SIRS a SEPSA immunopatogenezája

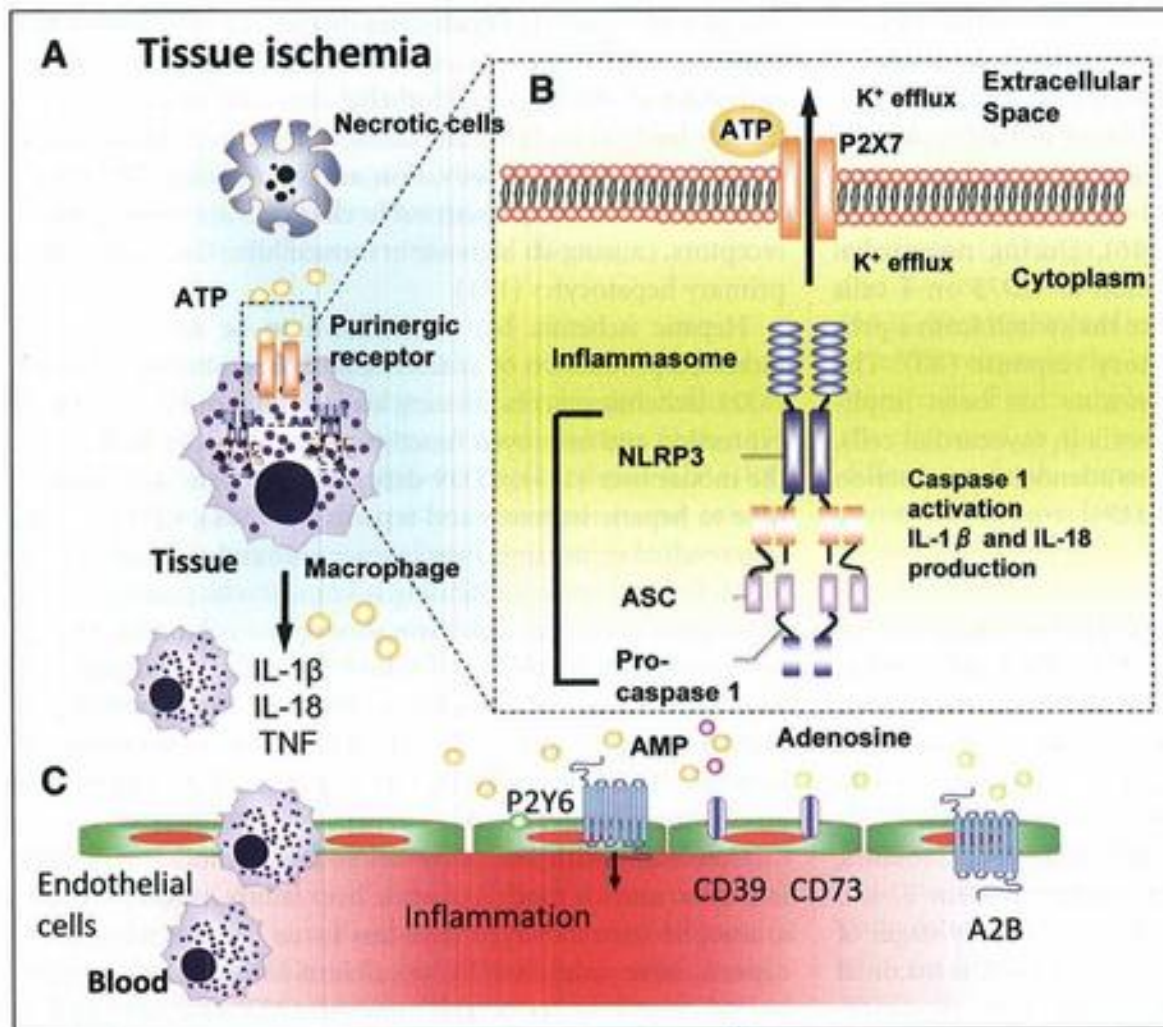


# SIRS vyvolaný traumou, nekrózou, chirurgickým výkonom





**SIRS vyvolaný ischemií**, resp. ischemicko-reperfúznym poškodením makrofágy, IL-1, -18, TNF, a CD39, CD73.

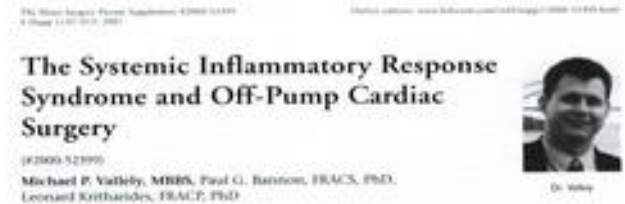


# Klinický syndróm SIRS ako nozologická entita – heterogénna skupina p. etiopatogenézy a patofyziológie

- **Negovsky V.A: The second step in resuscitation--the treatment of the 'post-resuscitation disease'. Resuscitation 1972 , 1 (1): 1-7**
- **„ SIRS po resuscitácii „ , ischemicko reperfúzny a metabolický syndróm**  
Kirklin J.K : **Complement and the damaging effects after cardio-pulmonary bypass . J Thor Cardiovasc Surgery 1983. ... The whole body inflammation .. SIRS po mimotelovom obehu krvi.**

## „Traumatický“ SIRS po traume.

- SIRS po traume je spojený so signif. Lymfocytopéniou < 1000 /ul
- **„Post-šokový „ SIRS , po cirkulačnom šoku hemoragickom, kardiogénnom.**
- **„Cancer SIRS“ , resp. „SIRS z malignity“ – syndróm systémovej zápalovej odpovede vyvolaný pokročilou rakovinou s nekrózami a metastázami .**  
(Záhorec 2018)

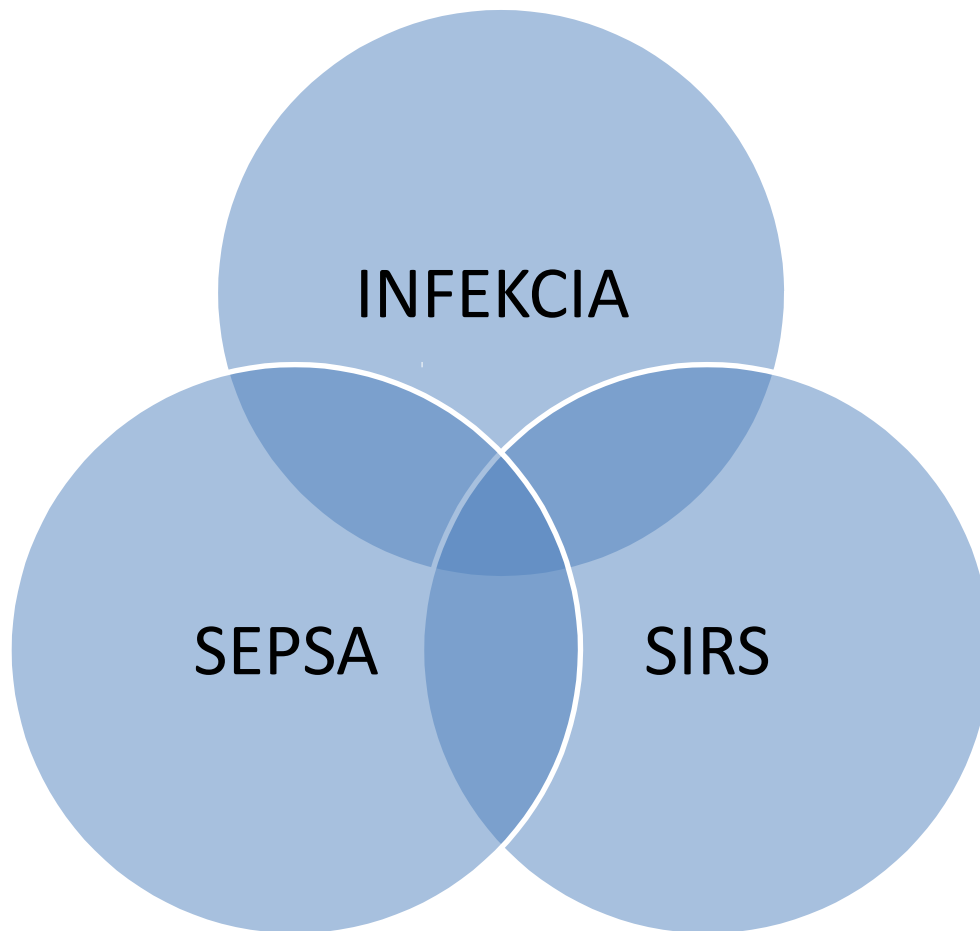


Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern

Darsh S. Heffernan<sup>1\*</sup>, Sean P. Monaghan<sup>1</sup>, Rajan K. Thakkar<sup>1</sup>, Jason T. Macham<sup>2</sup>, William G. Coffey<sup>3</sup> and Alfred Ayala<sup>1</sup>

# Dynamické vzťahy infekcie, syndrómu sepsy a SIRS u kritických stavov

R. Zahorec, 2018



# Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients

## A prospective observational study

Domonkos Trásy, MD <sup>1,\*</sup>, Krisztián Tánzos, MD <sup>2</sup>, Márton Németh, MD <sup>2</sup>, Péter Hankovszky, MD <sup>2</sup>, András Lovas, MD <sup>2</sup>, András Mikor, MD <sup>2</sup>, Ildikó László, MD <sup>2</sup>, Edit Hajdú, MD <sup>1b</sup>, Angelika Osztróluczki <sup>2</sup>, János Fazakas, MD <sup>3</sup>, Zsolt Molnár, MD <sup>2</sup> The EProK study group

<sup>1</sup> University of Szeged, Faculty of Medicine, Department of Anaesthesiology and Intensive Therapy, Szeged, Hungary

<sup>2</sup> University of Szeged, Faculty of Medicine, Division of Infectious Diseases, First Department of Internal Medicine, Szeged, Hungary

<sup>3</sup> Semmelweis University, Faculty of Medicine, Department of Transplantation and Surgery, Budapest, Hungary

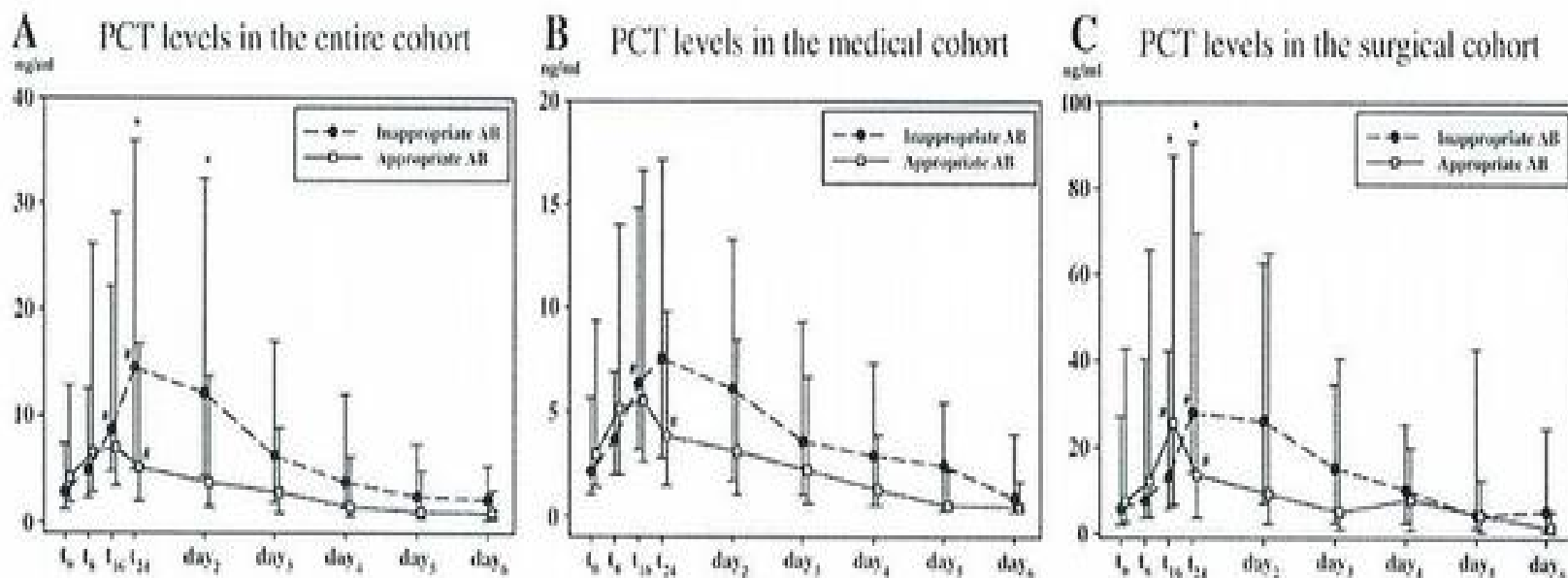


Fig. 2. PCT absolute values in the entire cohort and in the medical and surgical cohort. Data are presented as median and interquartile range. AB indicates antimicrobial therapy. #P<.05 within groups; \* P<.05 between groups.

# Dynamika sepsy a SIRS



## Sepsis: A New Hypothesis for Pathogenesis of the Disease Process\*

Roger C. Bone, MD, PhD (honorary), Master FCCP;<sup>†</sup> Charles J. Grodzin, MD; and Robert A. Balk, MD, FCCP

(CHEST 1997; 112:235-43)

sepsis and its sequelae, innovative the

Immunologic Dissonance: A Continuing Evolution in Our Understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MOOS)

Roger C. Bone, MD

Ann Intern Med 1998

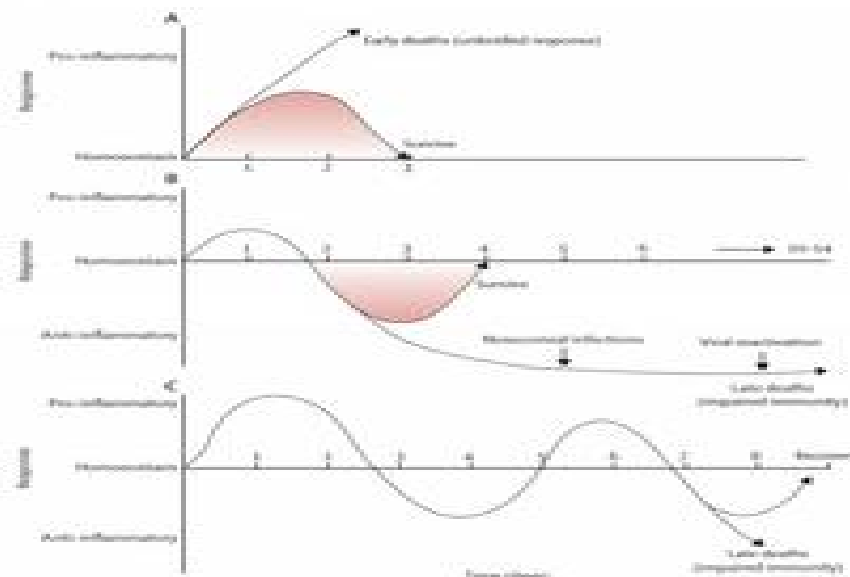
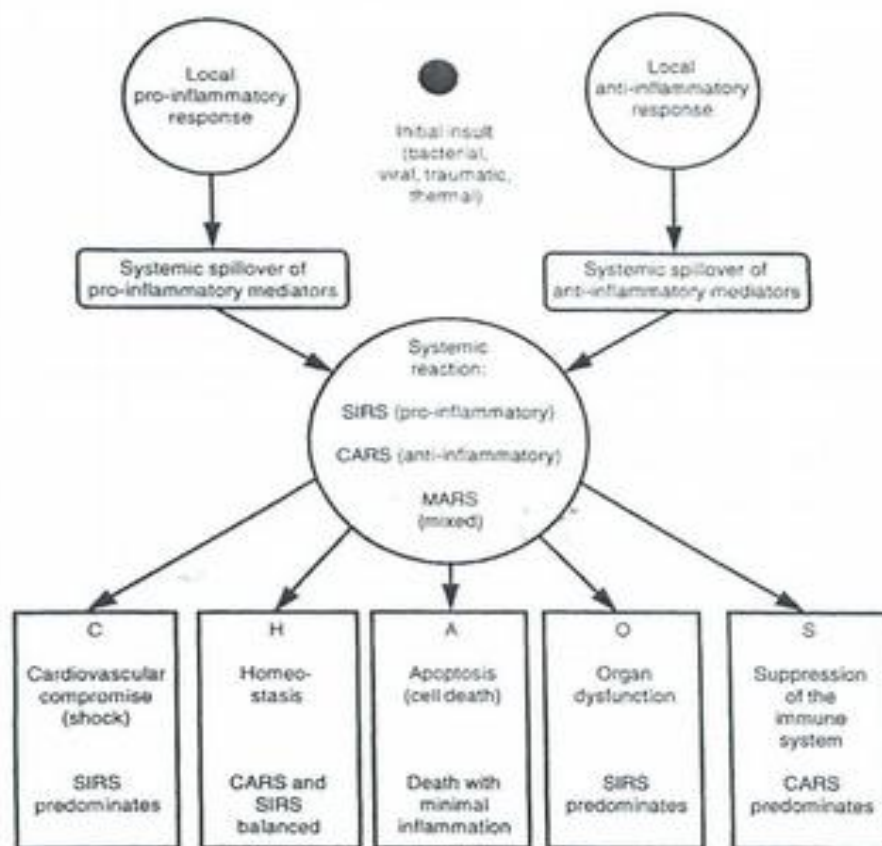
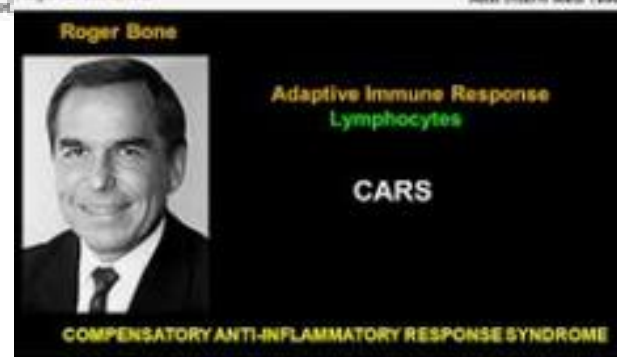
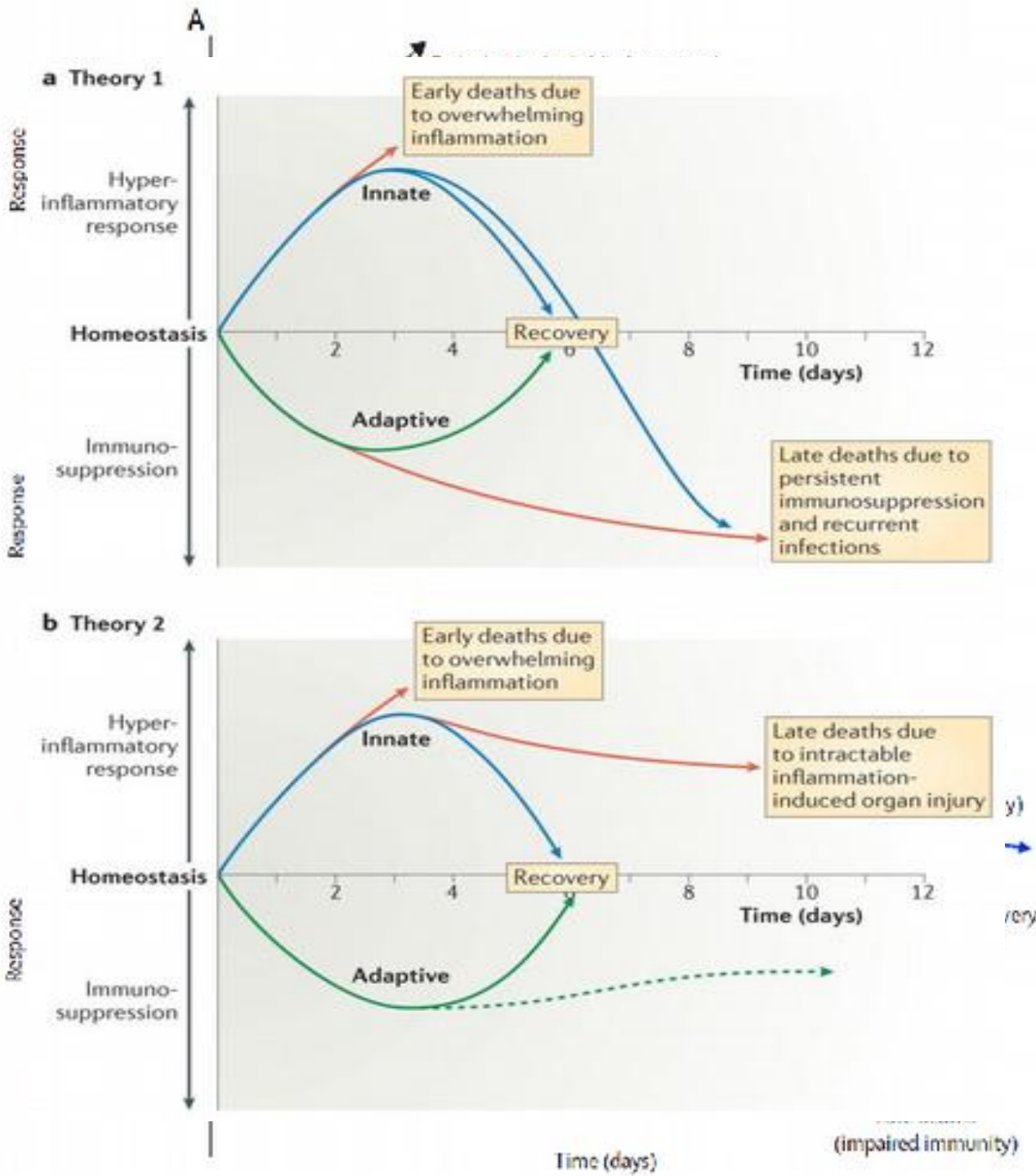


FIGURE 4. New concepts for the clinical sequelae of sepsis, SIRS, CARS, and MARS. (This figure is an adaptation of Figure 1 by Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 1998; 24:1125-28.)

# Pro- and Anti-Inflammation in Sepsis

Hotchkiss RS et al. Lancet Infect Dis 2013; 13: 260–68



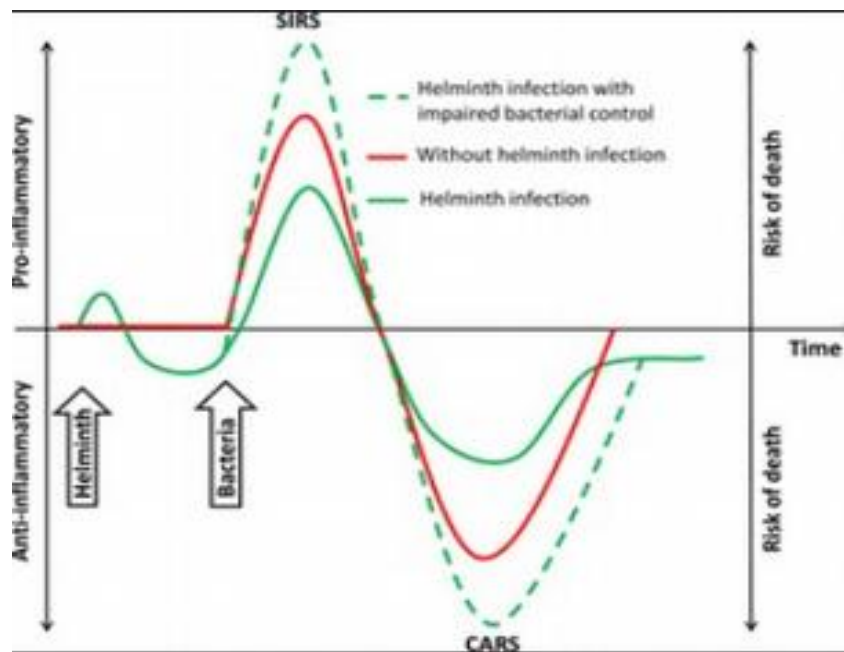
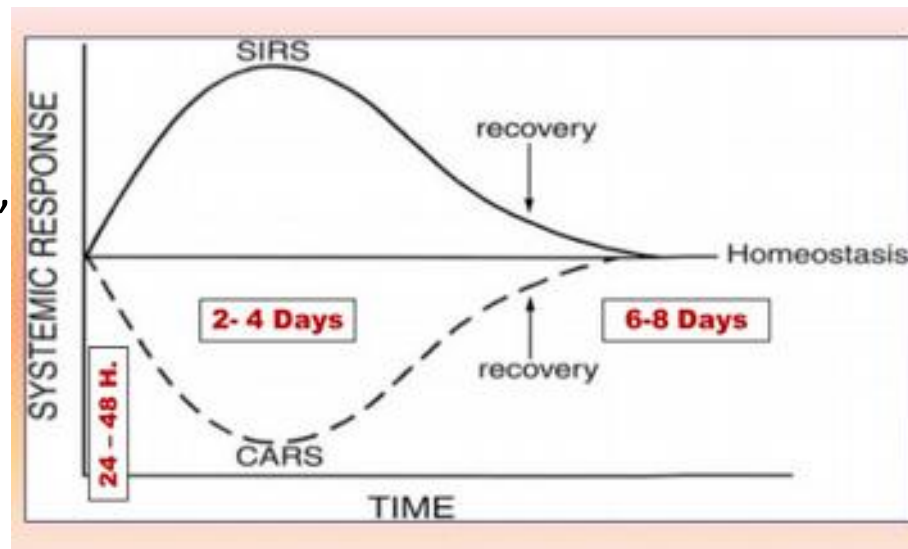
Dynamics of Sepsis /SIRS:

Acute (0-3 d.)  
Subacute (4-10)  
Chronic (> 10 d.)

With courtesy to A Nierhaus and Zs Molnár

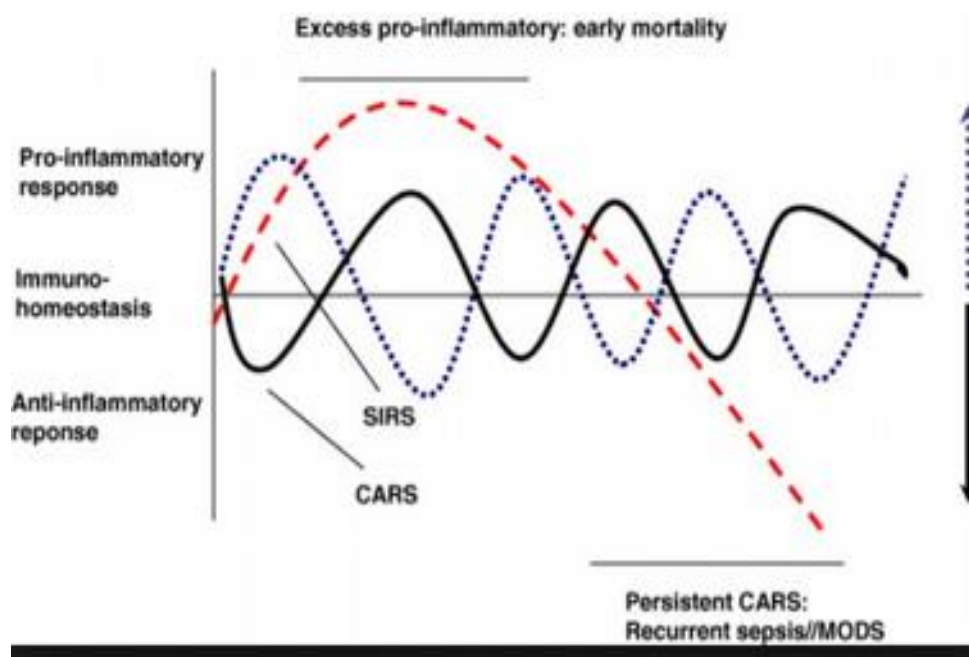
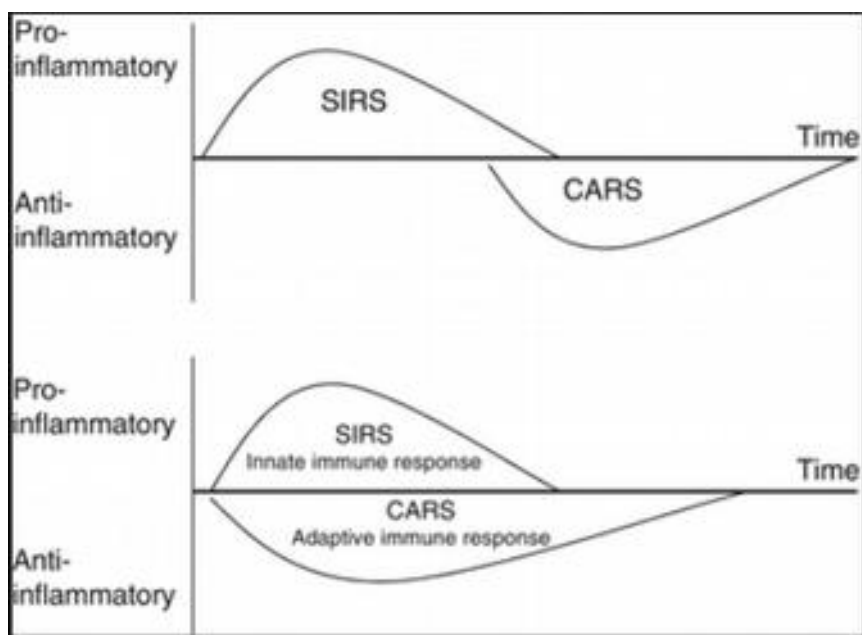
# Dynamika sepsy /SIRS

- Dynamika SIRS po veľkom op. Výkone
- Dynamika SIRS po reverzibilnom šoku, po nekomplikovanej traume
- Dynamika SIRS/sepsy po zmiešanej Infekcii





# Dynamika sepsy – včasná fáza, intermediárna, neskorá dynamický klinický syndróm – 1-3. deň, 4.-7. deň, po 7.-10. dni

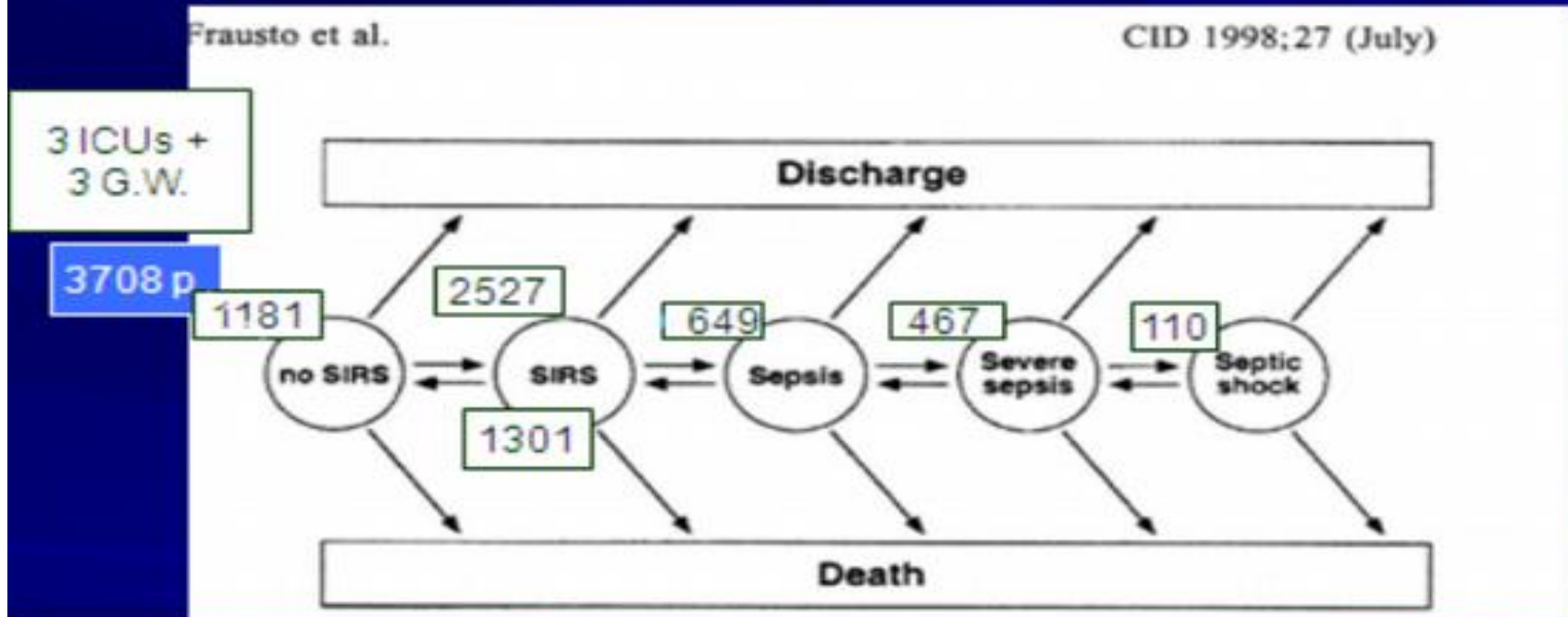


# EPIDEMIOLOGIA SEPSY



3-mesačná prospektívna epidemiologická štúdia z troch veľkých nemocníc v USA. Rangel-Frausto et al. 1995, 273:117-

## Rangel-Frausto MS: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 1995, 273 : 117 - 123



Rangel-Frausto MS et al : Dynamics of Disease Progression in Sepsis: Markov Modeling. Clin. Infect. Dis. 1998,27:.... In general the clinical trials have been conducted without clear understanding of the natural history of sepsis.

# Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units

691 pts had 752 episodes of SS.

23 ICUs  
 3-months  
 Incidence :  
 11,8 %  
 Hospital  
 Mortality:  
 37,5%

3547 pts:  
 No SIRS 8,6%  
 M. SIRS 44%  
 Sev. SIRS 26%  
 Sev. sepsis +  
 Sept. shock 19%

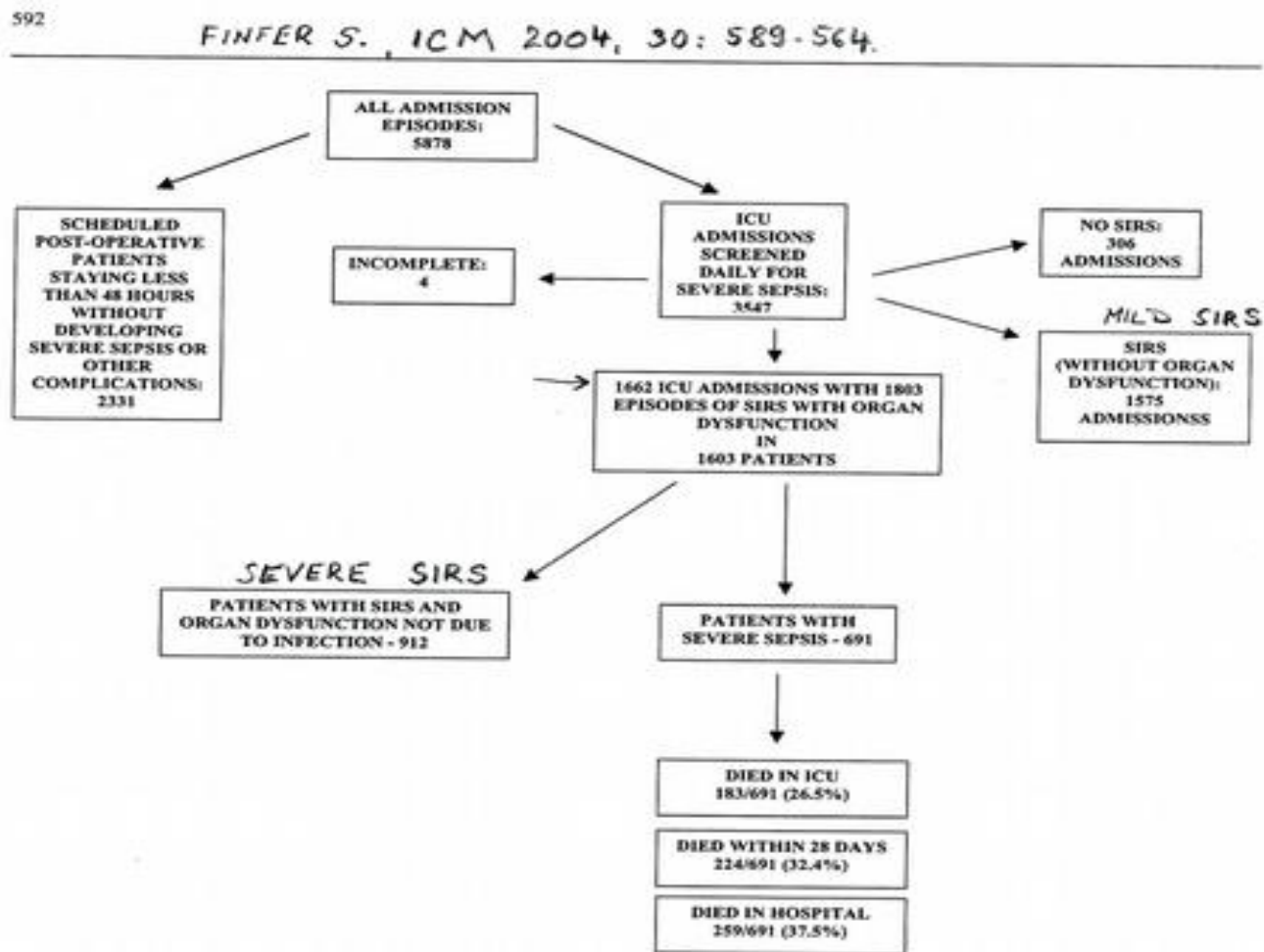
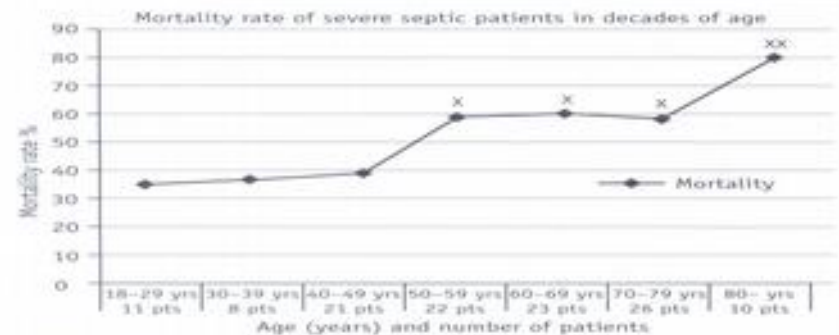


Fig. 1 Kaplan-Meier estimates of survival to day 28 in 691 patients with severe sepsis

# Epidemiology of Severe Sepsis in Intensive Care Units in the Slovak Republic

R. Záhorec, J. Firment, J. Straková, J. Mikula, P. Malik, I. Novák, J. Zeman, P. Chlebo

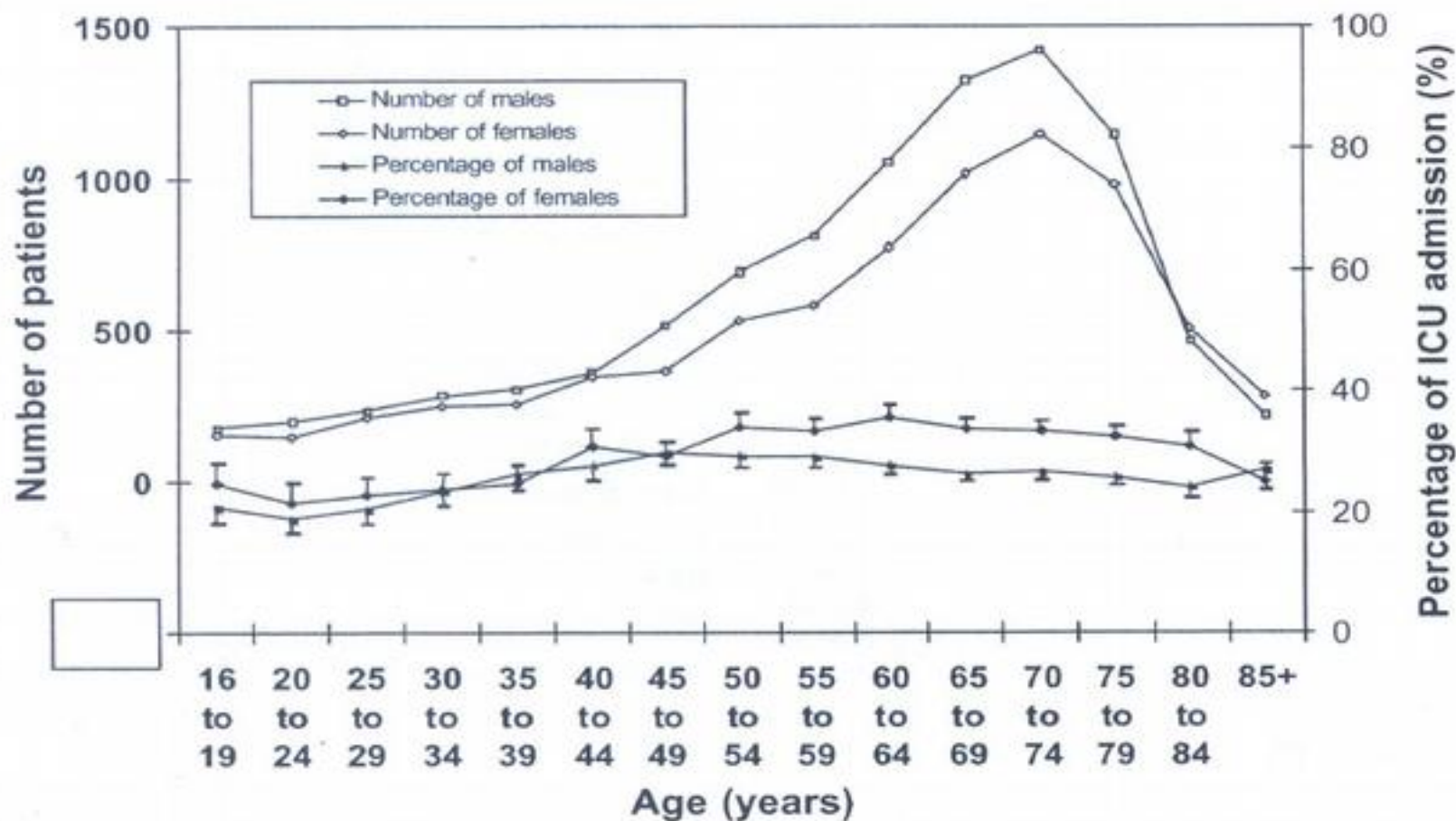
- 6-mesačná longitudinálna prospektívna epidemiologická štúdia na 14 OAIM/KAIM v SR v roku 2003.
  - **Incidenca ťažkej sepsy (s MODS) a septického šoku 8 %** zo všetkých kriticky chorých pacientov, extrapoláciou 3600 – 4000 prípadov/ročne
  - **Mortalita 51,2 %**, výskyt ťažkej sepsy/sept. šoku 90 prípadov /100 tis.ob.
  - **85 % septických pacientov bolo starších ako 45 rokov !!**
  - **Incidenca ťaž. sepsy i letalita na ťaž. sepsu sú spojené s vekom !!**
  - Všetci sept. pacienti pri prijíme mali **SOFA skóre > 4 body**
- Vstupná hodnota SOFA skóre > 10 bo diskriminovala letalitu !**



**Figure 1.** Mortality rates of severe septic patients in decades of age. Crude mortality is remarkably constant between 18 and 49-year-old septic patients and significantly lower than for 50–79-year-old patients ( $X - \chi^2 = 0.008$ ). The highest mortality rate is in septic patients above 80 years of age ( $XX - \chi^2 = 0.001$ ) when compared with younger adults < 50 years.

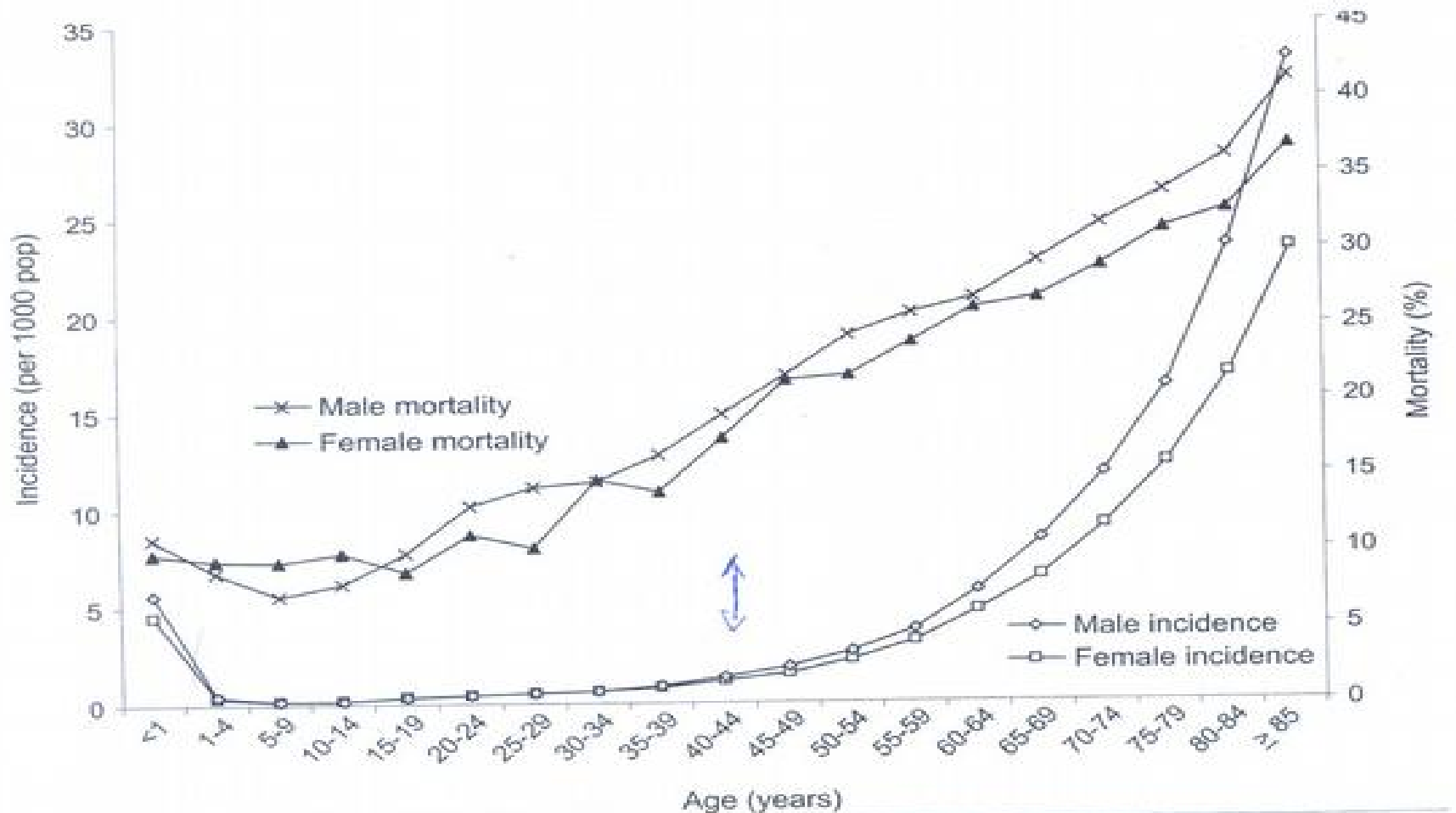
Vplyv veku na incidenciu sepsy v UK ,  
po 45. roku života !!!

Padkin A. et al: Epidemiology of severe sepsis occurring in the first 24 hours  
in ICUs in England, Wales and North. Ireland.  
Crit Care Med 2003, 31: 2332-2338.



Angus D. et al: Epidemiology of severe sepsis in the USA: analysis of incidence, outcome, and associated costs of care.

*Crit. Care Med.* 2001, 29: 1303-1310



# Immuno senescency , over 45 yrs. old

Innate Immunity	↓ function of macrophages
	↓ expression of TLRs
	↓ function of mitogen-activated protein kinases
	↓ production of TNF-alpha and IL-6
	↑ production of IL-10
	↓ bactericidal activity
T-cells	↓ naive cells
	↑ memory cells CD45Ro+
	↓ function of mitogen-activated protein kinases
	↓ type 1 cytokine response (IL-2, TNF-alpha)
	↑ type 2 cytokine response (IL-4, IL-10)
B-cells	↓ number of B-cells and plasma cells
	↑ polyspecific immunoglobulins with low affinity produced by B1-cells
	↓ response to neoantigens



A photograph of a forest stream with a waterfall. The water flows over mossy rocks, creating white rapids. The surrounding forest is dense with green foliage and moss-covered trees. The word "BIOMARKERY" is overlaid in white, bold, sans-serif font across the center of the image.

# BIOMARKERY

# Hlavné príznaky predchádzajúce sepse alebo vedúce k sepse.

V prednemocničných podmienkach

Wallgren U.M et al. Scand J Trauma, Resuscitation, Emergency Medicine, 2017,25:23-

- Náhla horúčka, triaška alebo rigor
- Náhle dyspnoe.  $fd > 24/min$
- Náhla akútna silná bolesť
- Náhla zmena mentálneho stavu
- Náhla svalová slabosť
- Strata svalovej sily, malátnosť
- Náhla nausea, alebo hnačka



Figure 7. Systemic symptoms seen in patients with sepsis. These symptoms vary between

## Varovné vitálne znaky na skorú identifikáciu pacientov so syndrómom sepsy na oddeleniach urgentnej medicíny.

- **SIRS kritéria 2/4** , variabilita výskytu jednotlivých kritérii od 42-78% , zmena teploty 51-65%, najpriekaznejší znak dyspnoe /tachypnoe > 24 d/min. a **tachykardia > 90/min.** (67-78 %)
- **NEWS** (Vedomie APUV, sTK, HR, SpO2 , ) , resp. **MEWS**
- **PRESEP skóre** , t > 38 C 4 body, srdc. Frekvencia > 90/min 2 body, hypotenzia sTK < 90 mmHg 2 body, tachypnoe > 22/min. 1 bod, hypoxémia SpO2 < 90 % 2 body. **PRESEP > 4 body** bola **senzitivita 0,85 a špecificita 0,86** .
- **BAS 90-30-90** , sAP < 90 mmHg, tachypnoe > 30/min, SpO2 < 90 % . Identifikácia 62-71% septických pacientov.
- **qSOFA** , sAP < 100 mmHg, alterácia vedomia , tachypnoe fd > 22 d/min. alebo SpO2 <92% - výťažnosť od 29 % po 42% (Williams ,2017), resp. 55% pre dg. ťažkej sepsy.

*Lars Ljungstrom , Community onset sepsis in Sweden. Univ Gothenburg 2017.*

# Biomarkery a dynamika sepsy /SIRS – 4 štádia sepsy:

skorá –hyperakútna, intermediárna, neskorá , chronická - PICS.

- Každá fáza sepsy /SIRS vyžaduje náležitú skupinu biomarkerov, resp. Správny - náležitý spôsob ich interpretácie , vychádzajúci z funkcie a vlastností sledovanej látky alebo parametra.
- **Včasná hyperakútna** fáza sepsy -prvých **24-72-96** hodín : IL-1, kyselina myristová, IL-6, IL-8, PCT, CRP, sCD14, nCD64, CD163 **NLR**, eosinofily, fbg. Počet trombocytov, **laktát, koagul. Faktory:** D-dimer, INR, aPTT. *Liu et al., 2016, Ljungstrom 2017*
- **Chronická fáza sepsy po 10.- 14 dňoch resp. PICS** vyžaduje : IL-6. CRP, PCT, IL-10. G-CSF, počet Lymfocytov, Treg lymfocytov. **Expresia HLA-DR na monocytoch.** *Monneret 2013*

# 7 Mechanizmov hyperlaktémie v sepe a septickom šoku

Vlessis 1995, Revely 2005, Levrant 2003, Mizock 2001, 2005, Levy 2005,

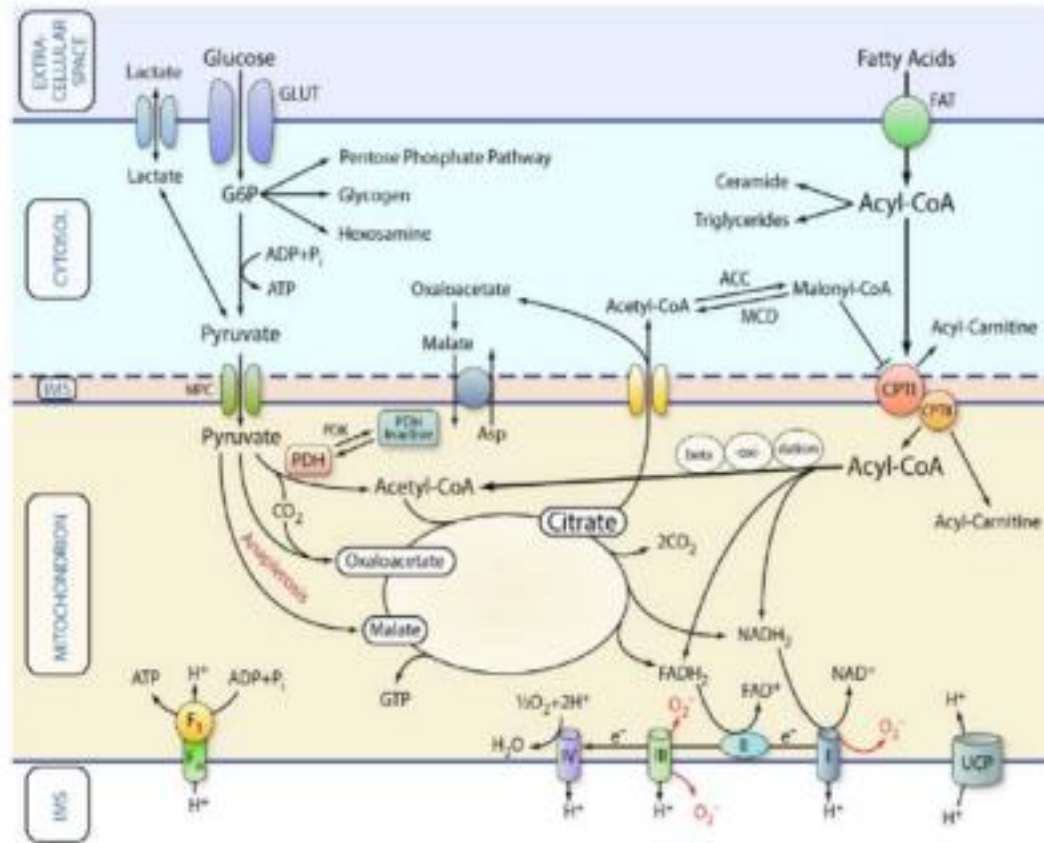


Figure 1.4 - Representation of classic pathways of cellular metabolism. Substrates (glucose and FAs) are transported across the cell membrane into the cytosol where they are activated to pyruvate and acetyl-CoA. These two metabolic intermediates are transported inside the mitochondrion by specific transport systems. Once inside, the substrates enter the Krebs Cycle and their reducing equivalents are used by the electron transport chain to generate a proton gradient which is used for ATP production. From Doenst et al [18].

Br. J Surg, 1995, 82: 870-876.

# Hematologické, imunologické a koagulačné parametre na diagnostiku septického syndrómu (Sepsa a SIRS)

Differentialny počet Leu : neutrophilia : lymphocytopenia = NLR ! Monocytopénia, and eosinopenia  
Leukocytárna aktivácia (IG- tyčinky, zvýšený objem monocytov a neutrofilov pri ich aktivácii v sepe)

**Trombocyty** počet a veľkosť, aktivita , **Anémia** , **erythrocyty** - Cell-free hemoglobin),

**Proteíny akútnej fázy** (PCT, CRP, SAA, orosomukoid, albumin : PINI,)

Aktivácia komplementu C3a, C5a, imunoglobulíny , Proteazy,elastáza, gelatináza, azurocidin -HBP, PLA2,  
Cell-free DNA, miRNA –Exosomes v Sepse, oligonucleotidy , mDNA, cDNA .

**Cytokíny**, IL-1, IL-6, IL-8, IL-10 , IL-17A, Th17 pathway

Neutrofilné granulocyty (CD64, CD62) **Lymphocyty**: lymphocytopenia - loss , **Treg** CD25+ , **CD39+**,  
**CD73+**, **PD-1 /PDL-1 pathway**, **BTLA** , **CTLA-4** , **Neu** : sCD14, nCD64, TREM-1, CD on **Mφ** ,HLA-DR,  
**Monocytes**, **CD14**, **sCD163** .

**Koagulačné faktory** : **INR**, D-dimer, ATIII , **suPAR** , **fibrinogen**...

## Ratio of neutrophil to lymphocyte counts — rapid and simple parameter of systemic inflammation and stress in critically ill

Zaborec R

Pomer neutrofilov a lymfocytov — rýchly a jednoduchý ukazovateľ systémového zápalu a stresu v kritických stavoch

RESPIRATORY AND CRITICAL CARE MEDICINE VOL 159 1995

ZAHOREC R: RELATION OF NEUTROPHIL

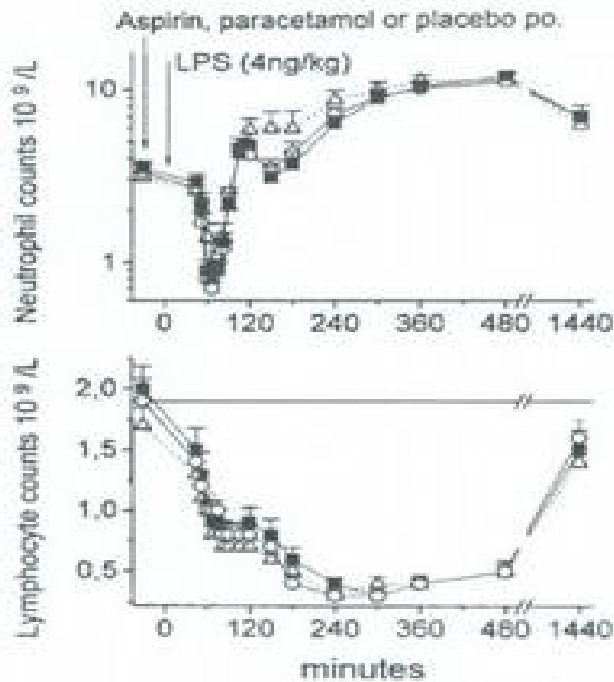
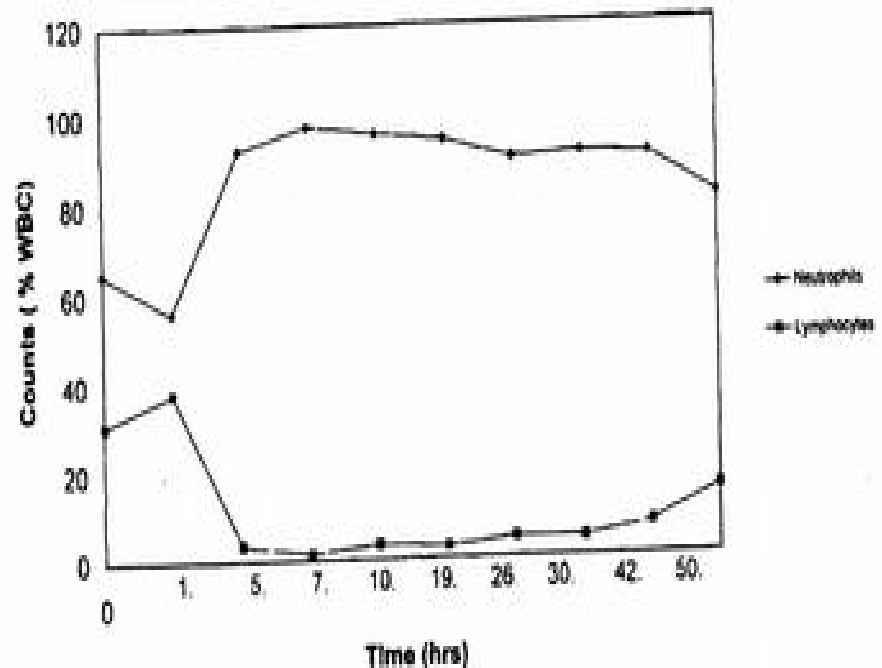


Fig 1. Neutrophil (top panel) and lymphocyte counts (bottom panel) observed before and after LPS administration (4 ng/kg), 300 mg aspirin (closed squares), 1,000 mg paracetamol (open triangles).



**Ratio of neutrophil to lymphocyte counts — rapid  
and simple parameter of systemic inflammation and stress  
in critically ill**

Zahorec R

**Pomer neutrofilov a lymfocytov — rýchly a jednoduchý ukazovateľ  
systémového zápalu a stresu v kritických stavoch**

Tab. 6. Inflammatory/immune response of circulating white blood cells, expressed as a Neutrophil-lymphocyte stress factor (NLSF), which is neutrophil-lymphocyte ratio.

Tab. 6. Návrh miery intenzity zápalu a stresu na relatívny počet neutrofilov a lymfocytov. NLSF — neutrofil-lymfocytový stresový faktor je pomer neutrofilov k lymfocytom vyjadrených v % z počtu leukocytov.

Differential white blood cell count (% relation of neutrophil/lymphocyte count), measured on blood cell counter SYSMEX SF 3000

Inflam/stress	Physiologic	Stress	Supraphysiolog.	Stress
Parameter	1-mild	2-moderate	3-severe	4-critical
Neutrophil %	78-84,9%	85-89,9%	90-94,9%	95 and higher %
Lymphoc. %	10,1-15%	5,1-10,0%	2,6-5,0%	2,5 and less %
NLSF	5,5-8,4	8,5-17,9	18-36	36 and higher

Vysvetlenie v texte

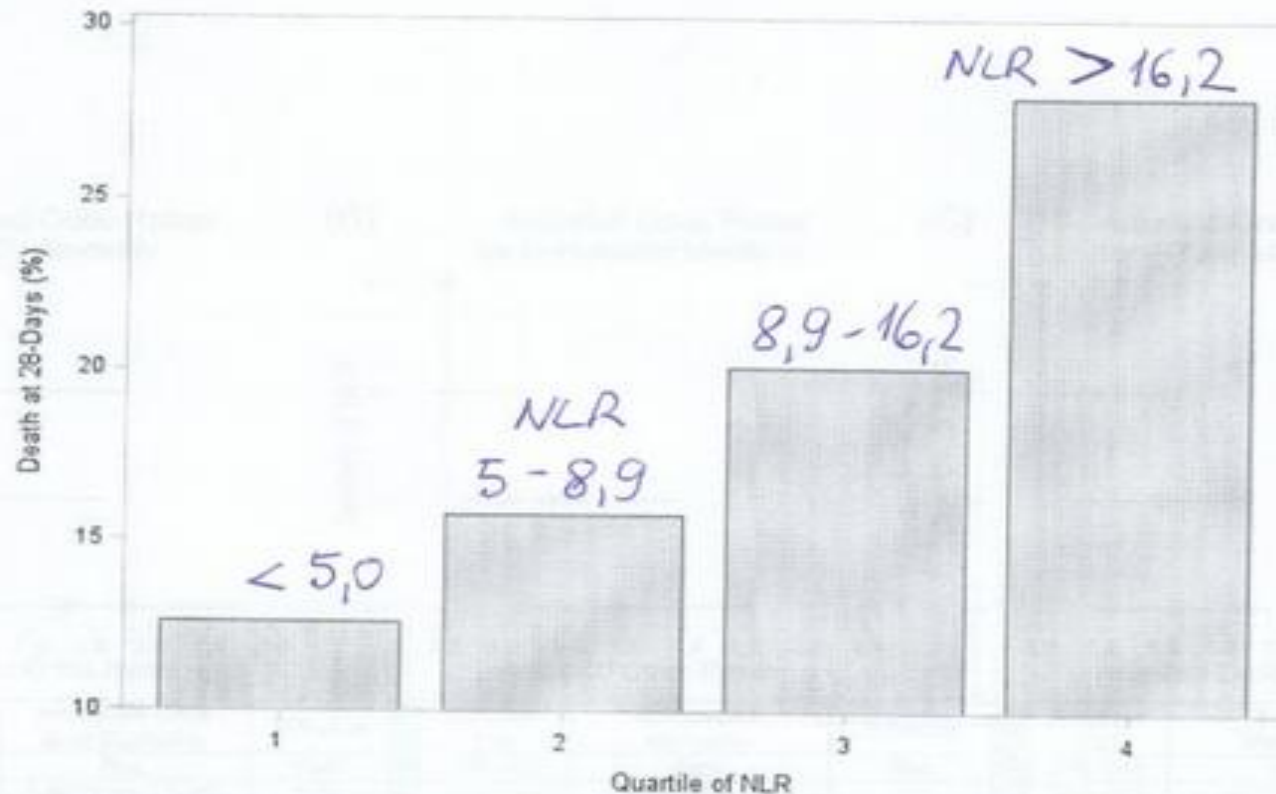


# The association between the neutrophil-to-lymphocyte ratio and mortality in critical illness: an observational cohort study

Critical Care 2015

doi:10.1186/s13054-014-0731-6

Justin D Saliccioli (justin.saliccioli12@imperial.ac.uk)  
 Dominic Marshall (dominic.marshall12@imperial.ac.uk)  
 Marco AF Dimentel (marco.dimentel@end.ox.ac.uk)



Quartile	Number Dead at 28-Days (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-Value
1	159 (13)	Ref.	Ref.	Ref.
2	199 (16)	1.30 (1.03 – 1.62)	1.32 (1.03 – 1.71)	0.03
3	254 (20)	1.75 (1.41 – 2.16)	1.43 (1.12 – 1.83)	0.004
4	354 (28)	2.70 (2.19 – 3.31)	1.71 (1.35 – 2.16)	< 0.001

CI, confidence interval; OR, odds ratio

NLR  
 < 5,0  
 5,0 - 8,9  
 8,9 - 16,2  
 > 16,2

## Reversal of neutrophil-to-lymphocyte count ratio in early versus late death from septic shock

*Florence Riché et al. 2015*

- Florence Riché **Affiliated with** Département d'Anesthésie - Réanimation - SMUR, Hôpitaux Universitaires Saint Louis – Lariboisière UFR de Médecine, Université Paris

### Key messages

- In patients admitted to the ICU for septic shock, a low NLCR at admission is associated with a risk of early death.
- In the same population, an increase in the NLCR during the first 5 days is associated with a risk of late death.
- Early and late death should be distinguished because they may involve different underlying mechanisms.

Published online 2010 Oct 29. doi: [10.1186/cc9309](https://doi.org/10.1186/cc9309)

### Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit

Cornelis PC de Jager,<sup>1</sup> Paul TL van Wijk,<sup>2</sup> Rejiv B Mathoera,<sup>1</sup> Jacqueline de Jongh-Leuvenink,<sup>3</sup> Tom van der Poll,<sup>4</sup> and Peter C Wever<sup>2</sup>

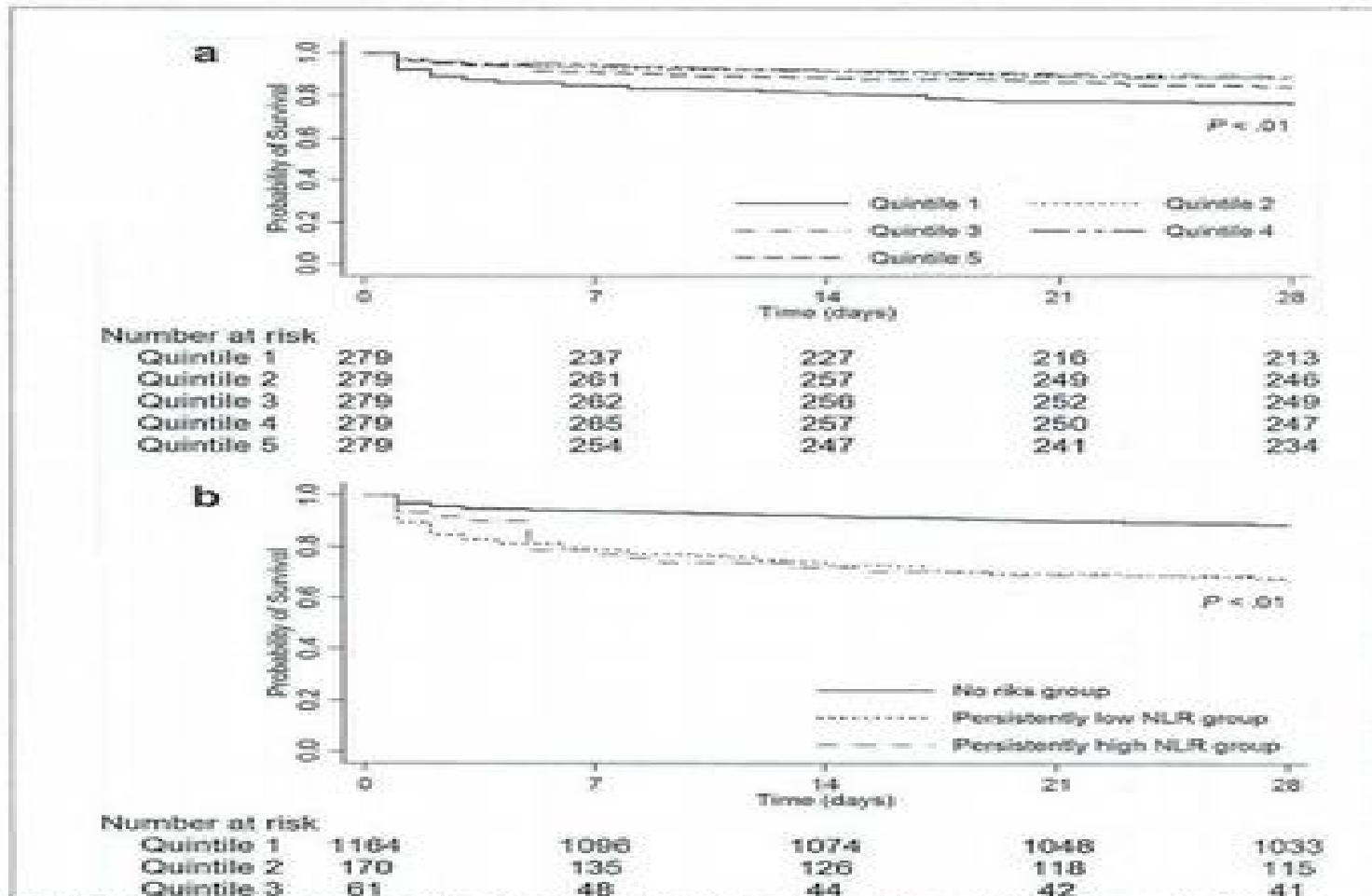
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<sup>2</sup>Department of Medical Microbiology and Infection Control, Jeroen Bosch Ziekenhuis, Tolbrugstraat 11, 5200 ME 's-Hertogenbosch, the Netherlands

<sup>3</sup>Department of Clinical Chemistry and Hematology, Jeroen Bosch Ziekenhuis, Tolbrugstraat 11, 5200 ME 's-Hertogenbosch, the Netherlands

# Neutrophil-to-lymphocyte ratio as a prognostic marker in critically-ill septic patients ☆

- Sung Yeon Hwang<sup>a,b</sup>,
- Tae Gun Shin<sup>c</sup>,
- Ik Joon Jo<sup>a</sup>,
- Kyeongman Jeon<sup>c,d</sup>,





# Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care

Lori F. Gentile, MD, Alex G. Cuenca, MD, PhD, Philip A. Efron, MD, Darwin Ang, MD, PhD, MPH, Azra Bihorac, MD, Bruce A. McKinley, PhD, Lyle L. Moldawer, PhD, and Frederick A. Moore, MD, Gainesville, Florida

Gentile et al.

Characterization and management of PICS will require new

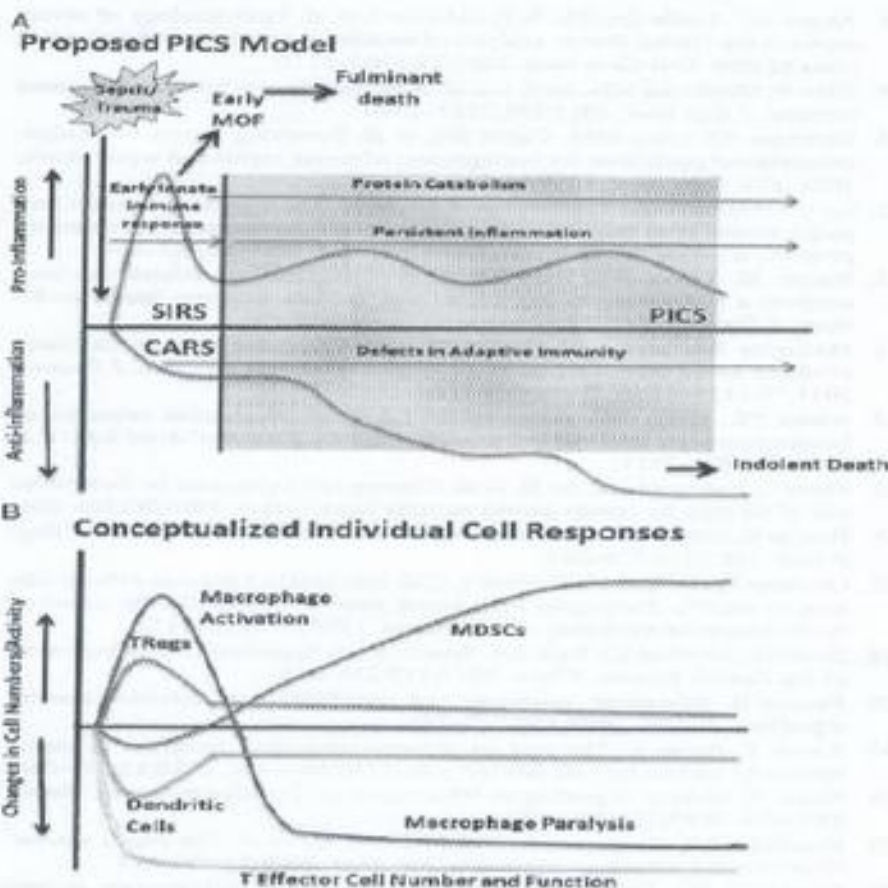


TABLE 3. PICS Criteria

Clinical Determinants of PICS	Measurements
Persistent Inflammation	Prolonged ICU stay >10 d
Immunosuppression	C-reactive protein >150 µg/dL
Catabolism	Total lymphocyte count <0.80 × 10 <sup>9</sup> /L
	Weight loss >10% during hospitalization or body mass index <18
	Creatinine height index <80%
	Albumin level <3.0 g/dL
	Prealbumin level <10 mg/dL
	Retinol binding protein level <10 µg/dL

**Research or Laboratory Methodologies**

<b>Inflammation</b>	Luminex for cytokine concentrations (IL-6, IL-10, IL-1ra, and procalcitonin)
	Leukocyte genome expression patterns, e.g., <i>ARG1</i> , <i>NOS2</i> , <i>IL-1RA</i> , <i>SIR2</i> , <i>MMPS</i> , <i>MMP9</i> , <i>AIMP2</i>
<b>Immunosuppression</b>	
Paralyzed monocyte	Reduced ex vivo cytokine production
	Reduced HLA-DR expression
	Reduced phagocytosis
<b>Anergic or exhausted T cell</b>	Expression of suppressor molecules, e.g., <i>PDL-1</i> , <i>CTLA-4</i> , <i>BTLA</i> , and <i>HVEM</i>
	Reduced T cell proliferation
	T <sub>H</sub> 2 polarization
<b>Increased Treg numbers and suppressor activity</b>	

Figure 5. Persistent inflammation-immunosuppression catabolism syndrome (PICS) and the cellular constituents that contribute to its development. After the initial, simultaneous



# Immunoscore for early phase of sepsis

(suggestion, Záhorec 2018)

- PCT, CRP, IL-6, PreSepsin (CD14), Lymphocytes, (NLR), Eosinophils,

Parameter	0 point	1 point	2 points	3 points
PCT	0,4 – 1,0	1,0 – 1,9	2,0 – 4,9	> 5,0
CRP	< 10 mg/l	10-50	51- 150	> 150 mg/l
IL-6	< 30	31 - 200	201 – 399	> 400 pg/ml
PreSepsin sCD14	< 350	351- 600	601 – 800	> 801
Lymphocyte (NLR)	➤ 1500 ➤ <3,0	1000-1400 (3,0-5,0)	600-1000 (5,0-7,0)	< 600 /ul ( >7,1)
Eosinophils	200-1450 /ul	100 – 200 /ul	100-50	< 50 /ul

# Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker

Elliott D. Crouser, MD; Joseph E. Parrillo, MD; Christopher Seymour, MD; Derek C. Angus, MD, MPH; Kerl Bickling, PharmD; Liliana Tejdor, PhD; Robert Magari, PhD; Diana Carrasco, BS; JoAnna Williams, MD; Douglas R. Glasser, MD; Michael Samoszuk, MD; Luke Heron, BA; Emily Robert, BS; and Fernando Chaves, MD

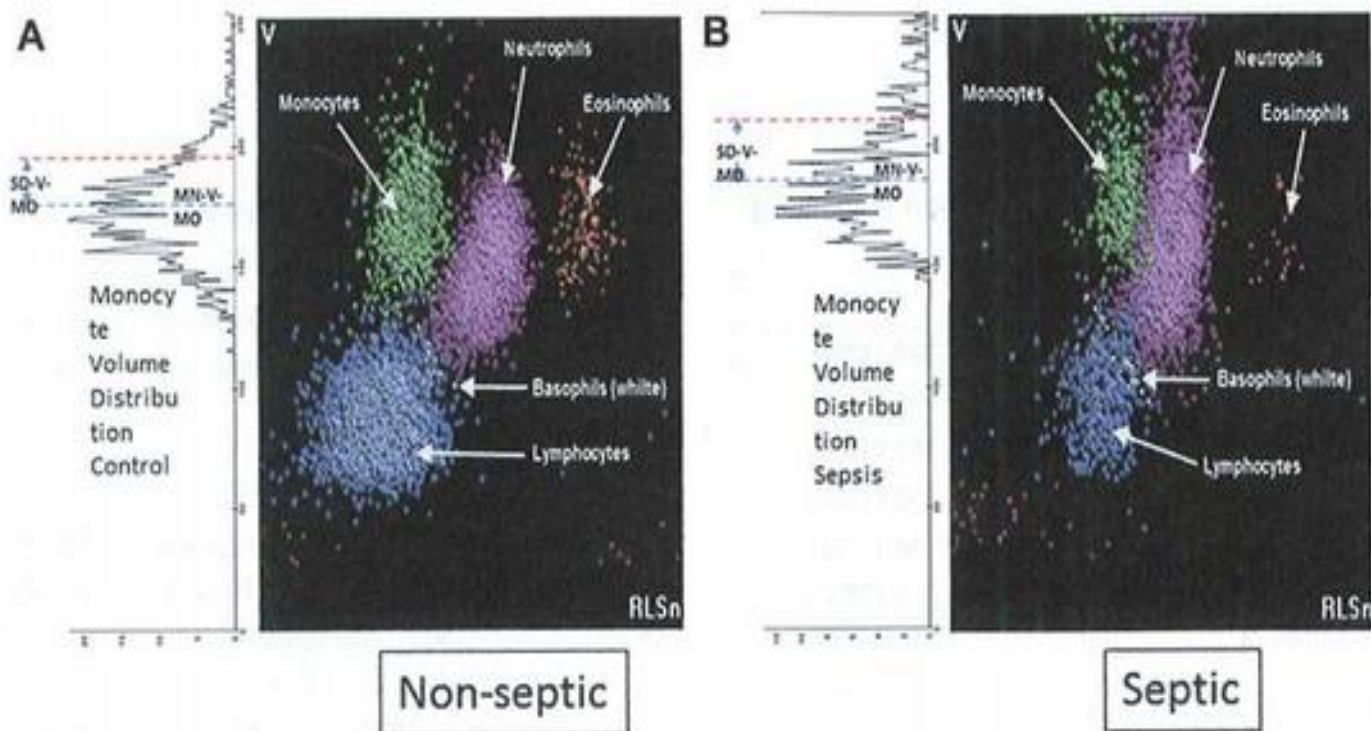
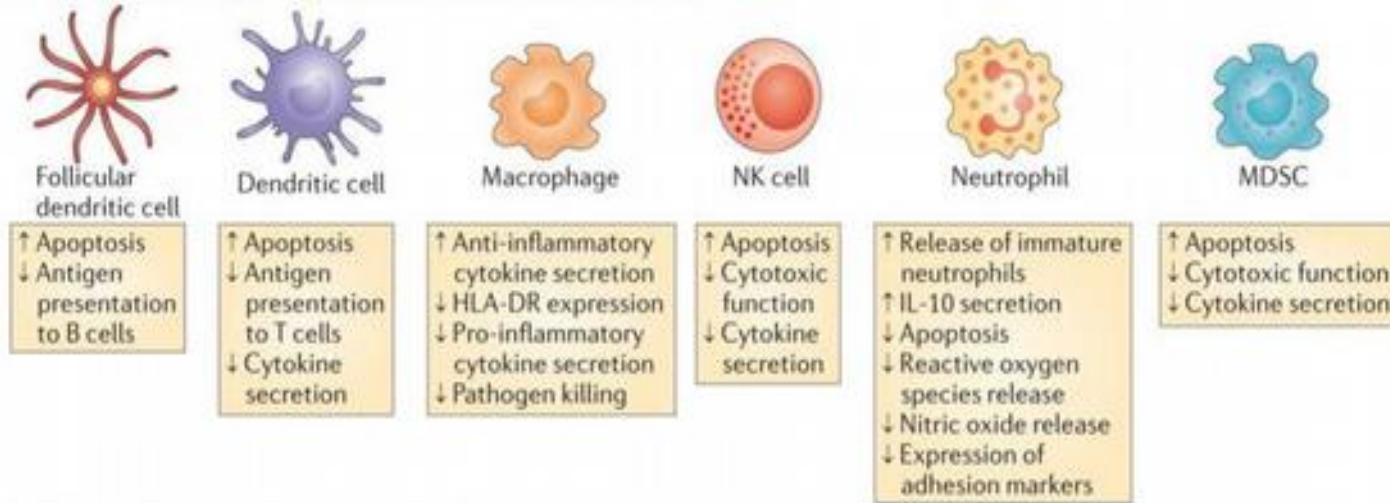


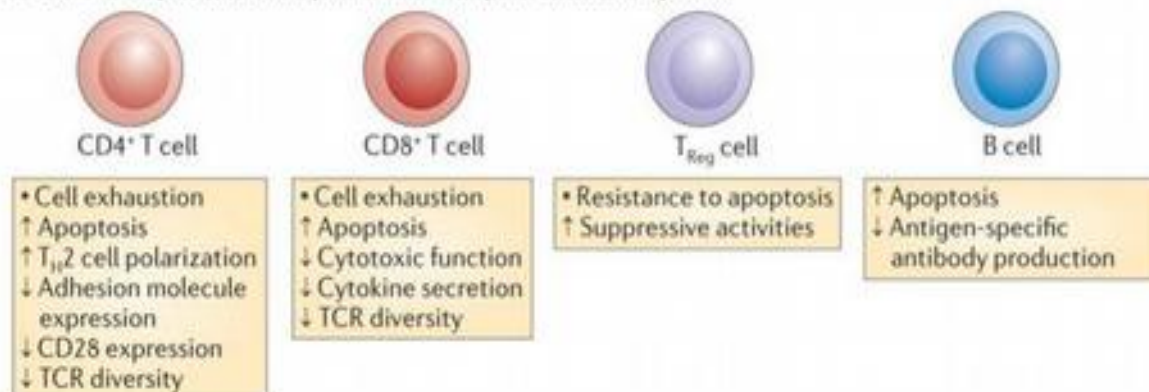
Figure 1 – A, B, Cell population distribution analysis. Representative histograms of WBC populations derived from the Beckman Coulter DxH 800 analyzer. (A) Example of a nonseptic donor. (B) Two-dimensional histogram corresponds to an example of a patient with septic shock. (A) The rotated one-dimensional histogram represents the distribution of the monocyte population volumes. The dotted blue line on top of the distribution represents the mean monocyte volume. The dotted red line represents 1 SD from the mean of the distribution (ie, monocyte distribution width), which is shown to be increased in the patient with sepsis.

# Populácie leukocytov, ktoré sa zúčastňujú v imunopatogenéze protrahovanej chronickej sepsy

## a Effects of protracted sepsis on the innate immune system



## b Effects of protracted sepsis on the adaptive immune system



# Immunoparalýza – parametre vhodné na dg. a monitoring

- Presmerovanie imunitnej dráhy z **Th1 na Th2**
- Vysoká koncentrácia s **IL-10, TGF-beta** uvoľňované z apoptotických bb...
- Zmena fenotypu makrofágov z **MΦ1 na MΦ2**
- **Lymfocytopenia** < 1,000-1200 /ul
- T-cell únava, vyčerpanie, strata adekvátnej T- bunkovej odpovede
- **Zvýšený počet a zastúpenie Treg lymfocytov** (CD4+ CD25+ CD39+)
- Zvýšená sekrécia molekúl **PD-1 prot, PDL-1**. monocytmi a dendrit.-bb DCs,
- Zvýšená sekrécia mediátorov **BTLA, CTLA-4**
- Nízka produkcia OFR, nízka syntéza a sekrécia TNF-alfa
- **HLA-DR < 30% na monocytoch, Makrofágoch**
- Nízka sekrécia a syntéza **INF-gamma**
- **Apoptóza lymfocytov** – relatívna i absolútna strata funkčných cirkulujúcich lymfocytov i lymforetikulárnych bb. v kostnej dreni - **loss of ly%, abs.**

*Monneret G. 2003, 2012, 2013*



# Immunescore for late chronic sepsis

(Monneret 2013, van Ton 2018)

- IL- 6, IL-10 , G-CSF, Lymphocyte count, HLA-DR % ,
- Treg /count /CD39+, CD73+. Ratio : CRP/alb , PCT/alb... PINI .

Parameter	0	1	2	3
IL-6	< 20	21 - 50	51 - 99	>100
IL-10	< 20	21 - 40	41 - 99	➤ 100
G-CSF	< 30	30 - 50	51 - 99	> 100
Lymph NLR	>1500 /ul < 2,8	1400-1000 2,81 – 5,0	600-1000 5.0- 7,0	<600 /ul > 7,0
HLA-DR % expres	?	< 90%	<50%	< 30%
Treg CD25+ CD39+	?			

# Využitie - omics pri výskume patofyziológie sepsy a ich aplikácie do klinickej praxe.

Fiehn O. **Metabolomics—the link between genotypes and phenotypes.** *Plant Mol Biol.* 2002;48:155–71

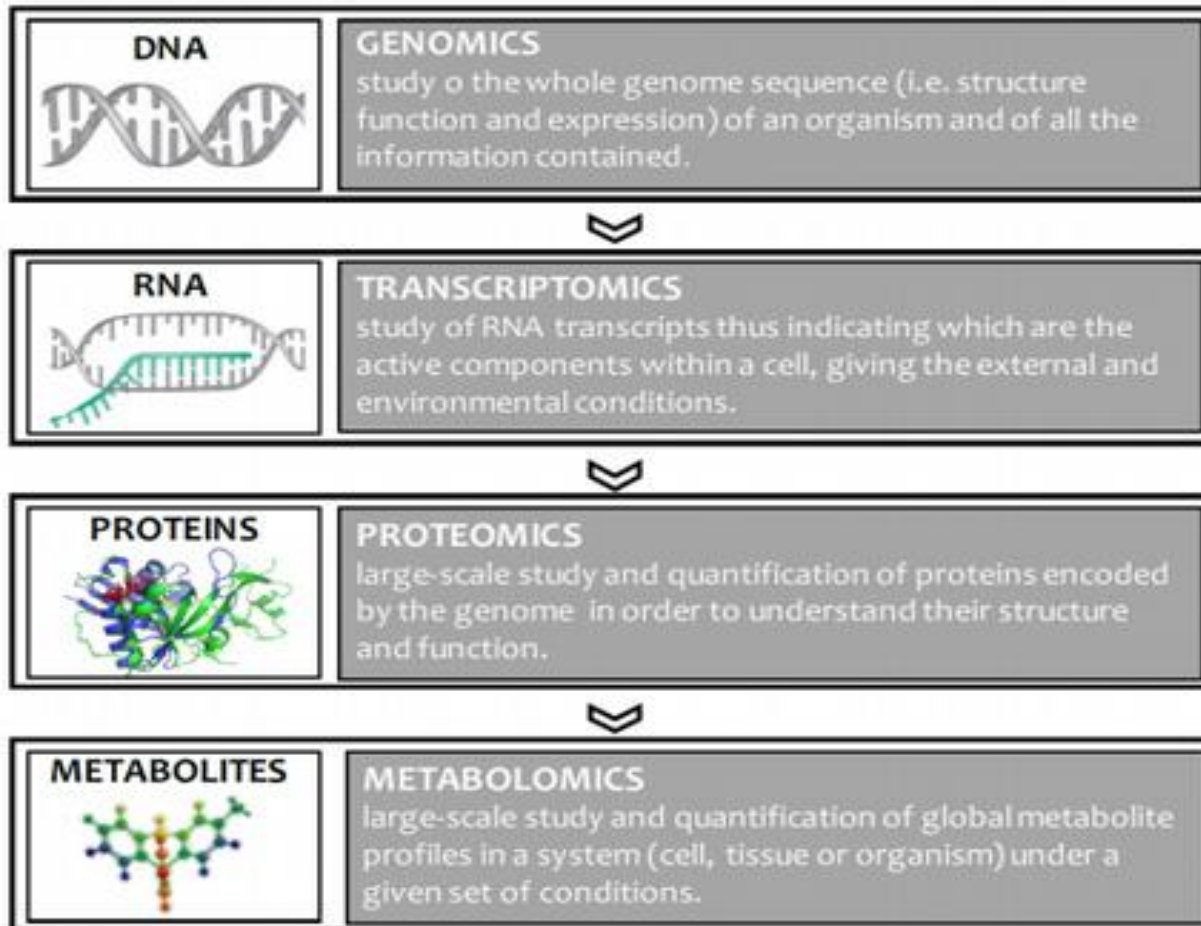


Figure 1.6 - Flow of biological information represented also as omics data

# Exosomes in Critical Illness

Nora Terrasini, MD<sup>1,2</sup>; Vincenzo Lionetti, MD, PhD, FAHA<sup>1,2</sup>

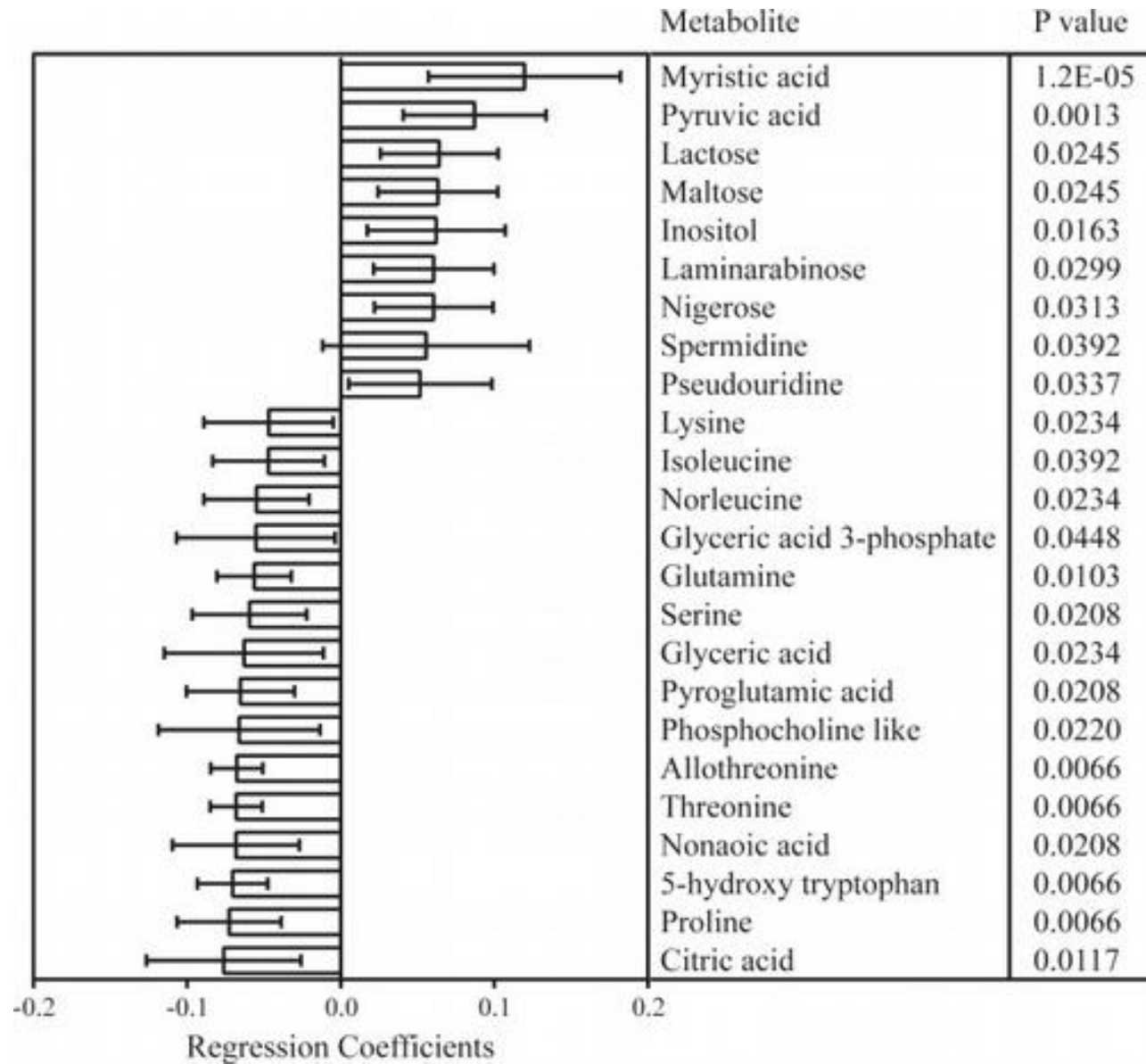
Sepsis	suppressor of cytokine signaling 1	Conditioned medium of alveolar macrophages	Inhibition of signal transducer and activator of transcription-1 activation in alveolar epithelial cells	Bourdonnay et al (14)
	Nicotinamide adenine dinucleotide phosphate hydrogen oxidase	Blood samples of 16 patients with early (< 24 hr) diagnosis of septic shock	Induced apoptotic death of endothelial and smooth muscle cells in culture	Janiszewski et al (15)
	-	Blood samples of 55 patients with diagnosis of septic shock	Decreased myocardial contractility in isolated heart and papillary muscle preparations	Azevedo et al (16)
	miR-223	Conditioned medium of MSCs	Attenuated cardiac dysfunction and improve animal survival in polymicrobial sepsis in vivo	Wang et al (17)
	Milk fat globule epidermal growth factor-factor VIII	Conditioned medium of bone marrow dendritic cell	Attenuation of the systemic inflammatory response and overall beneficial effect in sepsis	Miksa et al (18)

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# Metabolites in Blood for Prediction of Bacteremic Sepsis in the Emergency Room.

PLOS ONE 2016.

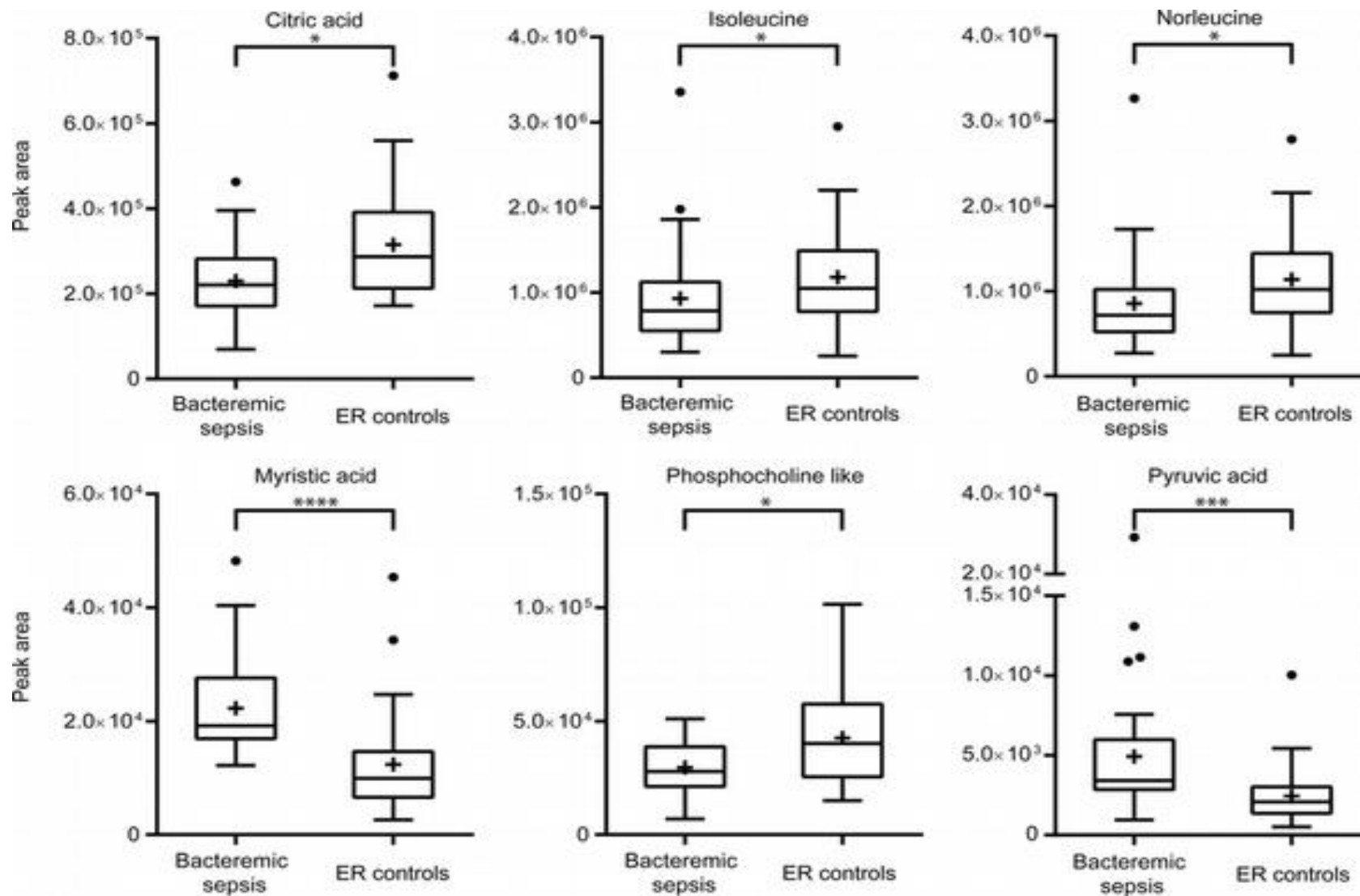
[Kauppi AM](#)<sup>1</sup>, [Edin A](#)<sup>1</sup>, [Ziegler I](#)<sup>2</sup>, [Mölling P](#)<sup>3</sup>, [Sjöstedt A](#)<sup>1</sup>, [Gylfe Å](#)<sup>1</sup>, [Strålin K](#)<sup>4</sup>, [Johansson](#)



# Metabolites in Blood for Prediction of Bacteremic Sepsis in the Emergency Room.

[Kauppi AM](#)<sup>1</sup>, [Edin A](#)<sup>1</sup>, [Ziegler I](#)<sup>2</sup>, [Mölling P](#)<sup>3</sup>, [Sjöstedt A](#)<sup>1</sup>, [Gylfe Å](#)<sup>1</sup>, [Strålin K](#)<sup>4</sup>, [Johansson](#)

PLOS ONE, 2016.



# Kinetika organickej kyseliny myristovej v sepe

$\text{CH}_3-(\text{CH}_2)_{12}-\text{COOH}$  , najrýchlejší vzostup koncentrácie v plazme

- **Myristic acid, selected organic acids ratio and their significance in sepsis diagnosis**

Moravec M, Zazula R, Průcha M a kol. , SepsEast Budapest 2018.

**A new lead in the sepsis diagnosis – Myristic acid levels following parenteral self-administration of Hylak forte.**

Nejtek T, Průcha M., ... Zazula R. , SepsEast Budapest 2018

## Záver:

Kyselina myristová sľubný biomarker systémovej bakteriálnej infekcie (BSI) a sepsy v prvých hodinách bakteriálnej sepsy spolu s kopeptínom

# Characterization of metabolomic signatures in septic shock patients .

Alica Cambiaghi, 2017, Milan,

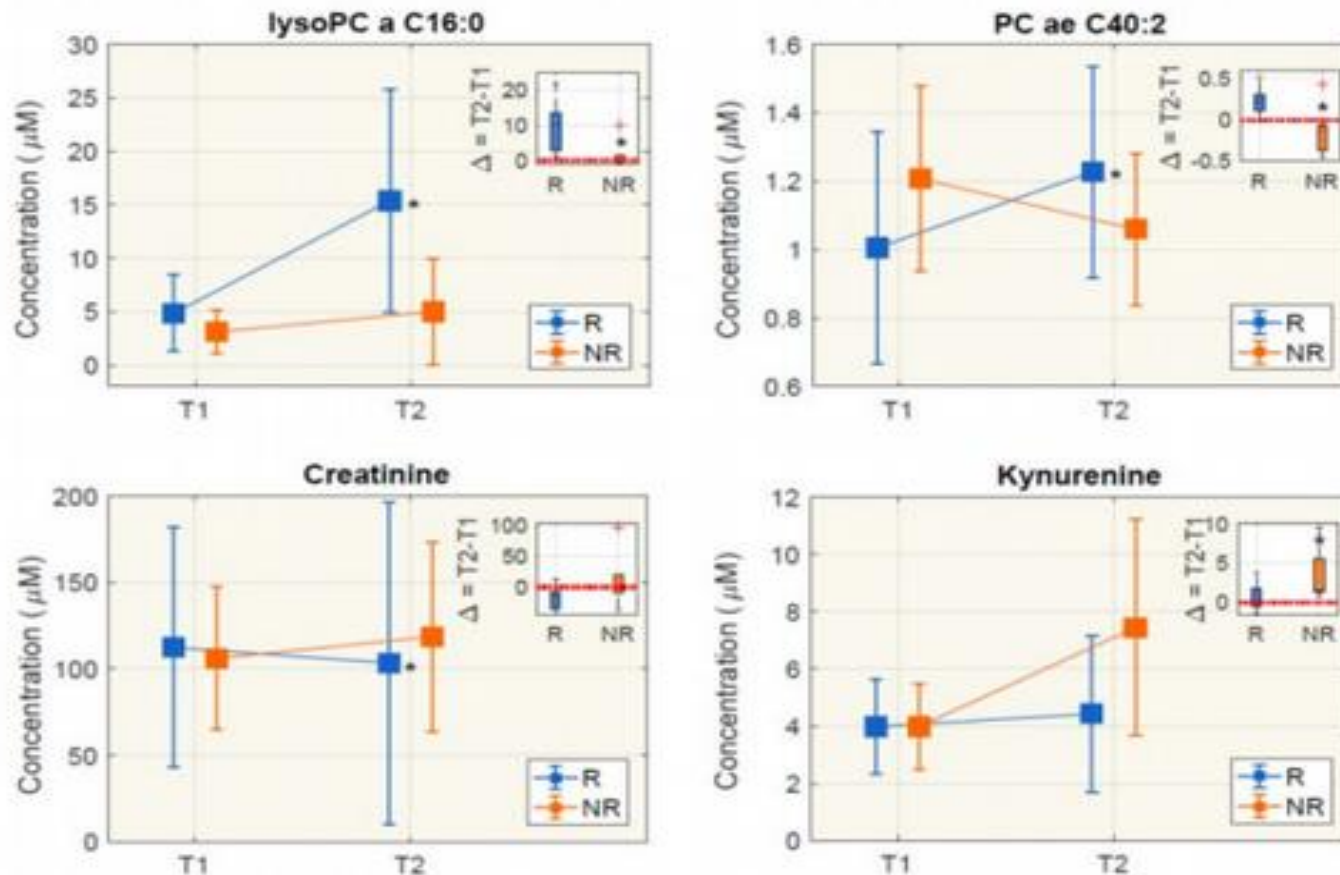
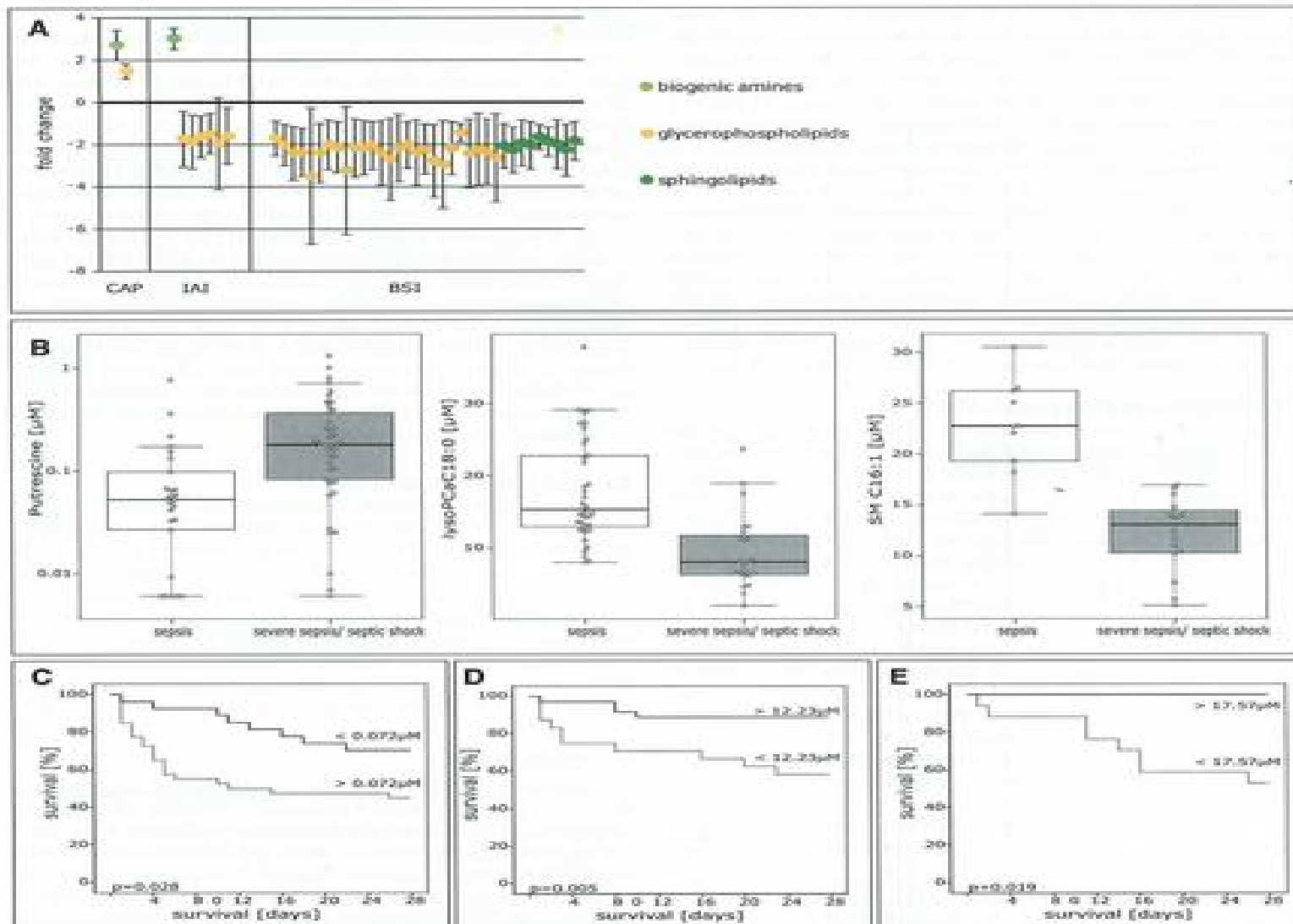


Figure 5.7 - Trends of metabolites concentration from T1 to T2 in the two groups. Box-plots in the top right corner show the difference in metabolite concentration between T1 and T2 expressed as delta ( $\Delta = T2 - T1$ ). We performed Wilcoxon rank-sum test between the delta of the two groups and Wilcoxon signed rank between T1 and T2 in each group separately. Significant differences are marked with \* ( $p$ -value $<0.05$ ). Only four metabolites have been plotted as an example.

# Metabolite Profiles in Sepsis: Developing Prognostic Tools Based on the Type of Infection\*

Sophie Neugebauer, MSc<sup>1,2</sup>; Evangelos J. Giamarellos-Bourboulis, MD<sup>3,2</sup>; Aimilia Pelekanou, MD<sup>2</sup>; Androniki Marioli, MD<sup>4</sup>; Fotini Baziaka, MD<sup>5</sup>; Iraklis Tsangaris, MD<sup>6</sup>; Michael Bauer, MD<sup>2,6</sup>







**SPÄT K TERAPII SEPSY**

# **Resuscitácia sepsy /septického šoku, 7 krokov,** personalizovaný prístup vs. protokolizovaná med. (EBM)

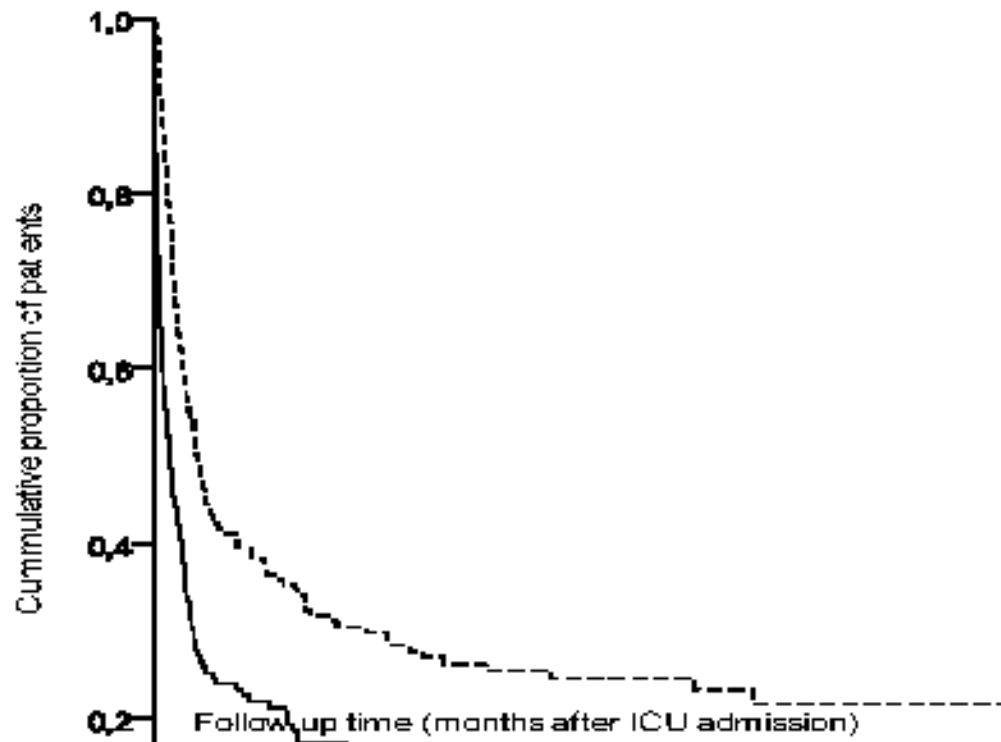
- **Resuscitácia obehu** – obnovenie funkčnej hemodynamiky
- **Resuscitácia respirácie** - ventilácie a oxygenácie, SpO<sub>2</sub> >93%
- **Kauzálna antimikrobiálna liečba** – odstránenie ložiska infekcie, eliminácia mikrobiálneho pôvodu, ATB /antivirotiká
- **Resuscitácia renálnych funkcií** - udržanie diurézy, „renal rescue protokol“ , hodinová diuréza vyše 1,0-1,5 ml/kg/hod.
- **Korekcia - Homeostáza** vnútorného prostredia – Na, K, Ca, Mg
- Energetická a endokrinná podpora metabolizmu –  
**Metabolická resuscitácia + Výživa** – nutričná podpora
- **Imunoterapia - imunomodulácia** kortikoidy, IVIG, noradrenalín,  
**imunostimulácia** – GM-CSF, IFN-gamma. Vitamín D/D<sub>3</sub>,

# Základné postupy v terapii septického šoku

12 hlavných zásad - Nandhabalan et al. Crit Care 22:215, 2018

- **1. Infúzna liečba** - iníciaľne balancované kryštaloidy alebo Hartman roztok, nižší objem 20 ml /kg t.hm. / 2 – 3 hod inf. koloidov transf ČMP a inf. **20% albumínu 100 ml, R:10-14 ml/hod.** , pozor na bilanciu tekutín : udržať **BT < 2800 ml/24 hod.**,
- **2. Zaistiť žilové vstupy** 2-3, CVK 2-3 lumen , invazívne monitorovanie aTK (sAP, MAP, dAP) , CVP , perf. tlak= MAP-CVP
- **3. EKG, teplota , SpO<sub>2</sub>** , hodinová diuréza, **invaz. art femoralis.** CVP,
- **4. ATB antimikrobiálna** liečba napr. Klindamicin /Klimicin 3x600 mg inf. a 8 hod. , rýchla mkb diagnostika PCR , SepsFast, Bactec, priama mikroskopia,
- **5. Hydrocortisón** –denná dávka 200 mg iv., 4 x 50 mg iv a 6 hod. alebo kontinuálna infúzia HCT 8 mg /hod.
- **6. Udržať akceptovateľný dAP > 40 mmHg** a MAP tlak > 55 mmHg, tak aby sa nemuseli zvyšovať dávky vazopresorov, optimálne:
- **7. Noradrenalín** v dávke 0,07 – 0,15 ug/kg/min. Včas spolu s inf. objemovou terapiou , pri dosiahnutí **dávky 0,21-0,3 ug/kg/min zväžiť kombináciu** s dobutamínom, alebo vazopresínom
- **8. Vazopresín (Empresín)** alebo **terlipresín** 0,02 -0,03 ug/kg/min. riedenie Terlipresínu 1 mg/50 ml rozt. R: 6 – 4 - 3 ml/hod. Riedenie arg/vazopresínu 40 IU /50 ml rozt. R: 1,5-2,0 ml/h.
- **9. Substitúcia /hradenie vitamínu B1 a C** - vysoké dávky **thiaminu 3x200 mg iv.**, a **Acidum ascorbicum 3x 1,0 g a 8 hodín alebo až 4x1,0 g iv.** a 6 h.

## Dlouhodobé přežívání dle max. dávky noradrenalinu za 24 h



	30 days	90 days	p (log rank test)
----- Noradrenalin T24 ≤ 0.3 ug/kg/min (N=182)	0.47 (0.40; 0.55)	0.35 (0.28; 0.42)	<b>&lt;0.001</b>
———— Noradrenalin T24 > 0.3 ug/kg/min (N=162)	0.26 (0.20; 0.33)	0.17 (0.11; 0.23)	

# Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic?

Heitor Pons Leite<sup>1</sup>, Lúcio Flávio Peixoto de Lima<sup>2</sup>

<sup>1</sup>Discipline of Nutrition and Metabolism, Department of Pediatrics, <sup>2</sup>Pediatric Intensive Care Unit, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil

*Correspondence to:* Heitor Pons Leite. Discipline of Nutrition and Metabolism, Department of Pediatrics, Federal University of São Paulo, Rua Loefgreen 1647, São Paulo, Brazil. Email: heitorpons@gmail.com.

- **Thiamin inj.** 2 – 3 x 200 mg /die , *Donnino CCM 2016, Moskowitz 2017, Woolum CCM 2018,*
- **Acidum ascorbicum , L-ascorbát , 3-4 x 1,0 g i.v.** *P. Marik Chest 2017,*
- **Vitamin D /D3 – 25-OH cholekalciferol,** *Holick NEJM 2013*
- **Selen, zinok ,** *Manzanares 2016 , Angstwurm 2007, Valenta 2011.*
- **Nutrícia (diéta) bohatá na cholesterol, thiol (S) – taurín., cysteín,**

# Metabolic resuscitation in sepsis

**Vitamins : B1, B6,  
C vit, E vit,  
25OH-D3 vitamin**

**Cholesterol - rich  
Thiol – rich Nutrition ,  
L-carnitin,  
phosphate CrP,**

Mitochondria

Krebs cycle,  
RC, AOX,

**Micronutrients :  
Selenium, Zinc**

**Endocrine support:  
Insulin, T3-trijodtyronin,  
GH, oxandrolone,  
melatonin**

Woolum J.A. et al. Crit Care Med. 2018, 46: : 1747 -

## Effect of Thiamine Administration on Lactate Clearance and Mortality in Patients With Septic Shock\*

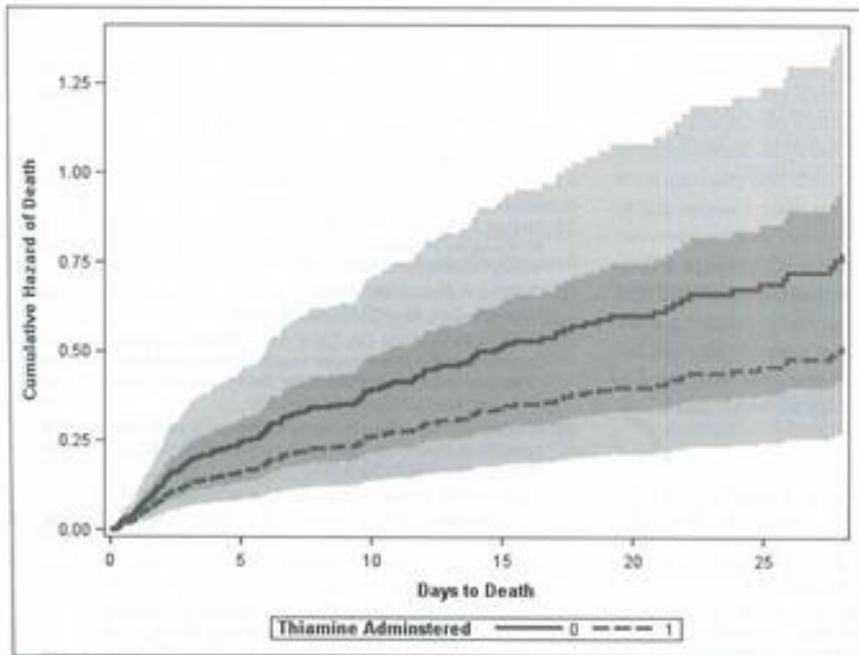


Figure 3. Cumulative hazard of death over time. 0 = no thiamine, 1 = thiamine.

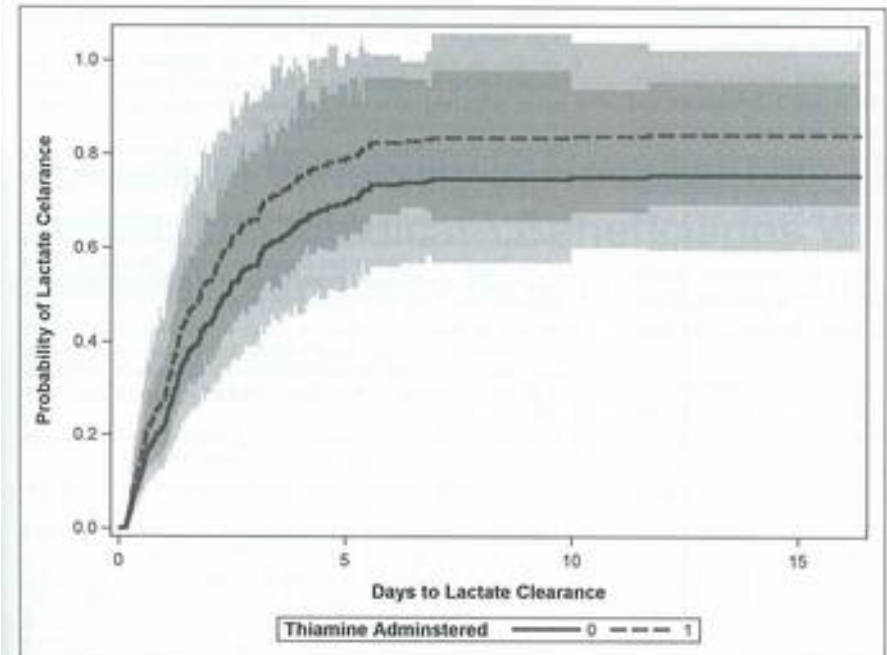


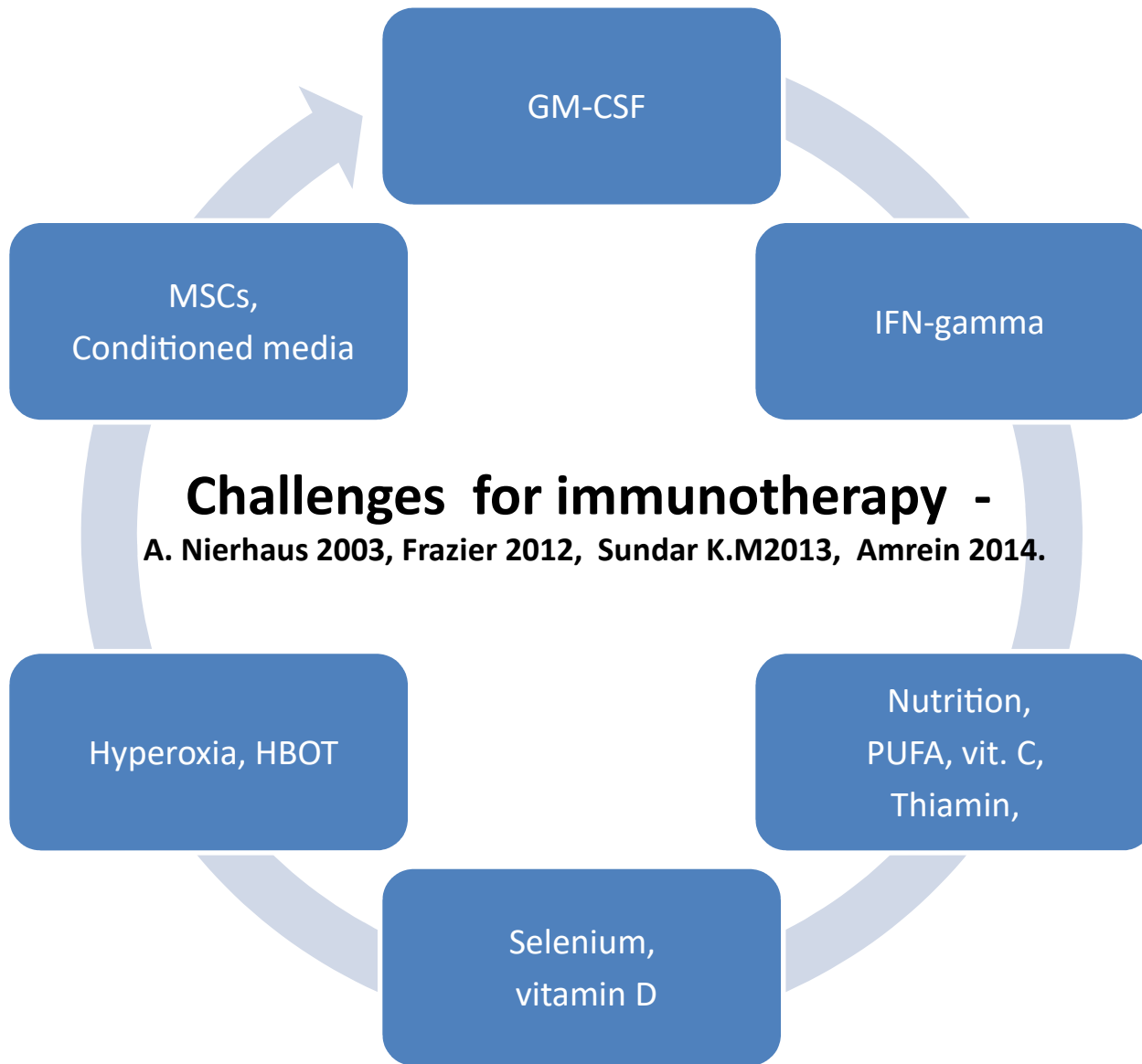
Figure 2. Probability of lactate clearance over time. 0 = no thiamine, 1 = thiamine.

## Thiamine: An Essential Component of the Metabolic Resuscitation Protocol\*

- Thiamin deficiencia vs Wernicke encefalopatia, možná asociácia s delíriom a **septicou encefalopatiou** .
- Odpor. Dávka **3 x 200 – 500 mg iv. a 8 hodín** , *Flannery CCM 2016, 44:1545-*

*Paul Marik , Crit Care Med 2018, 46: 1869-70.*





# Čo ma naučila sepsa

*Rýchle rozpoznanie a diagnostika sepsy na základe patofyziológie a imunopatogenézy sepsy*

*Komplexná terapia a intenzívna starostlivosť v závislosti od dynamiky sepsy*

*Pokora , ponímanie septického pacienta v jeho celistvosti*

*Zaangažovanie pacienta a rodiny v ozdravných procesov a rehabilitácie*

*Spoznanie nových ľudí, nových priateľov, zdieľanie nových Poznatkov a dobrej praxe s kolegami.* **21. Colours of Sepsis , Ostrava 2019**



*Bienále výstavy textilu ,  
10.10. 2018 , Bratislava Čunovo*



**ĎAKUJEM**

# Humanizmus a všeobímajúca láska človeka k človeku – etický a duchovný základ medicíny

Srdce - svätyňu kreatívneho pokladu  
a intuície duše vedie **láska - jediná  
a skutočná sila**, ktorá môže utvoriť  
lepší svet.

Všetci ľudia predstavujú prvky  
božskej a prírodne jedinečnej  
štruktúry labyrintu, spojenej  
tenkým vláknom porozumenia.

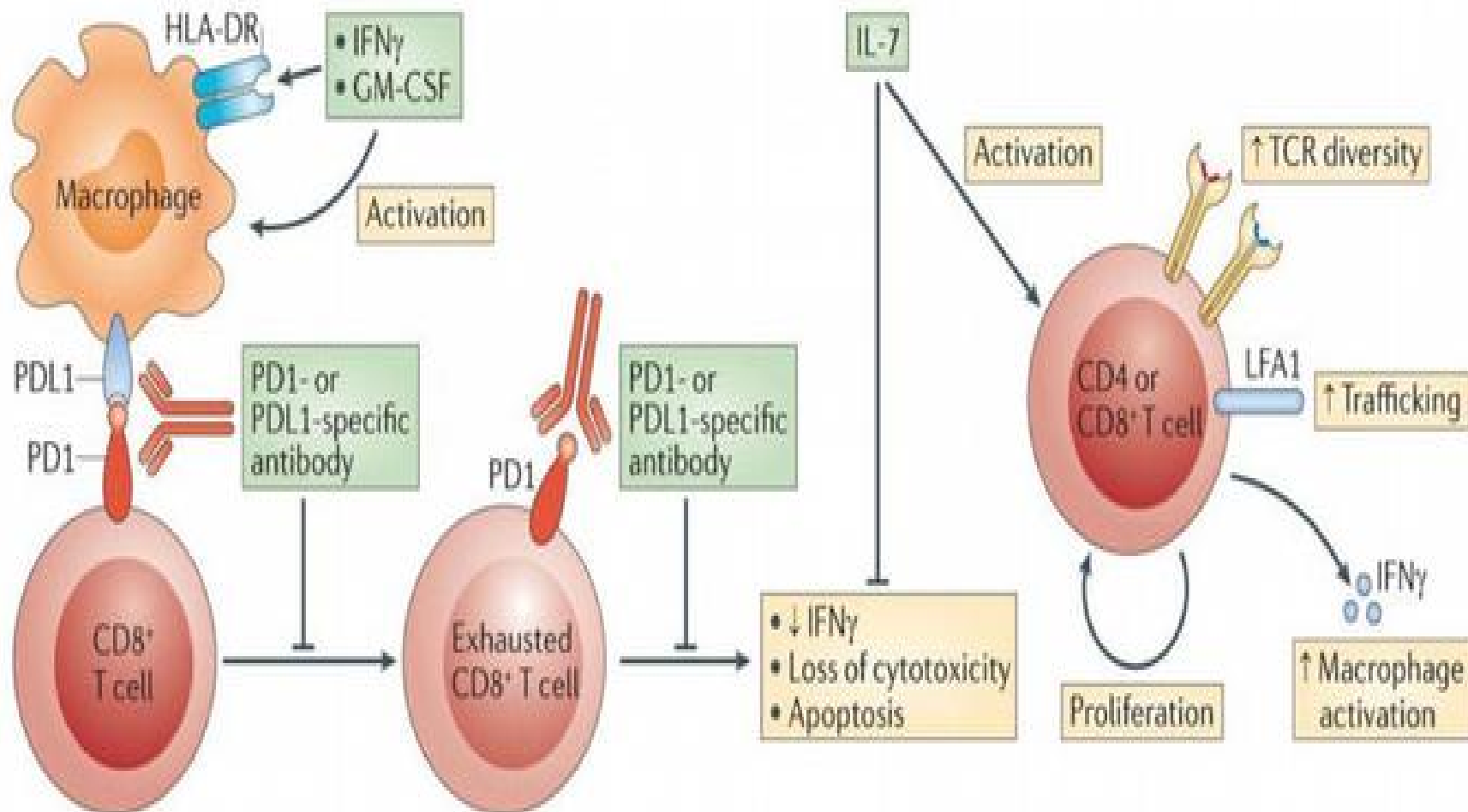
*Bienále výstavy textilu ,  
Danubiana 10.10. 2018 , Bratislava Čunovo*



# Precision Immunotherapy for Sepsis

Annemieke M. Peters van Ton<sup>1</sup>, Matthijs Kox<sup>1,2</sup>, Wilson F. Abdo<sup>1</sup> and Peter Pickkers<sup>1,2\*</sup>

<sup>1</sup>Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, Netherlands, <sup>2</sup>Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, Netherlands



TNF $\alpha$ , tumor necrosis factor alpha; IL1RA, Interleukin-1 receptor antagonist; IL-1, interleukin-1; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN $\gamma$ , interferon gamma; IL-7, interleukin-7; anti-PD-L1, programmed death-1 ligand antagonist; OR, odds ratio.

# Resuscitácia septického šoku

II.KAIM LFUK, Zámorec Január 2019

- 2019 Január

- ❧ Resuscitácia cirkulácie - obnovenie funkčnej hemodynamiky (koncept prof. M. Pinsky 2002,2007)
- ❧ Odstránenie ložiska infekcie - chirurgická liečba, radiodg intervencia, agresívna antimikrobiálna terapia
- ❧ Resuscitácia respiračného systému - udržanie suffic ventilácie a oxygenácie,  $SpO_2 > 92-93\%$ .
- ❧ Resuscitácia renálnych funkcií - udržanie diurézy, renal rescue protocol, hodin diur  $> 1,5 \text{ ml/kg/hod}$ .
- ❧ Resuscitácia metabolizmu - „metabolická resuscitácia“
- ❧ Úprava a korekcia poruchy vnútorného prostredia

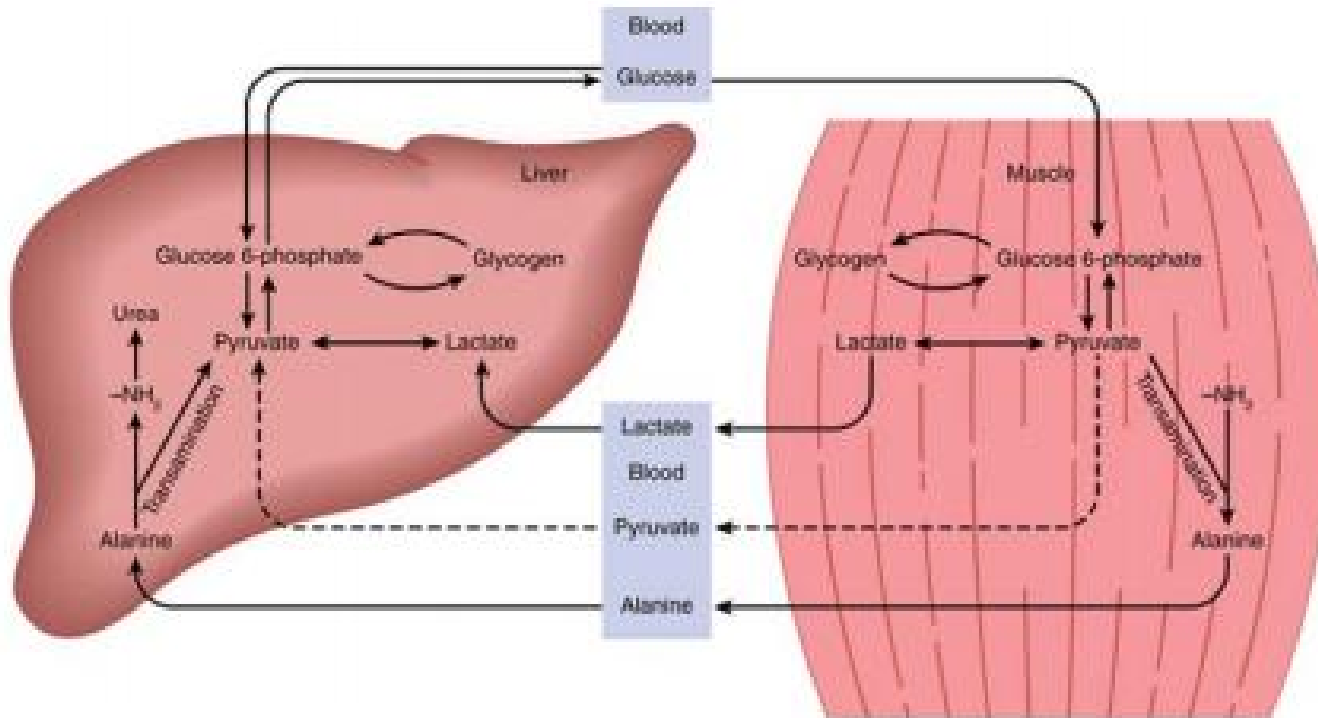
# Sepsis-induced immune dysfunction: can immune therapies reduce mortality?

Matthew J. Delano, Peter A. Ward

Immune modulator	G-CSF	GM-CSF	IFN- $\gamma$	PD-1 and PD-L1	IL-3	IL-7	IL-15
Proposed benefit	Improves neutrophil and monocyte production and release	Improves neutrophil and monocyte production and function	Improves monocyte HLA-DR expression and function	Biomarkers to identify candidates for immune-modulatory therapy	Promotes stem cell and progenitor development	Increases T cell proliferation and recruitment	Decreases NK cell, T cell, and NKT cell apoptosis
	Improves myelopoiesis and granulopoiesis	Enhances monocytic and lymphocytic cytotoxicity	Reduces infection and related complications	Reverse T cell exhaustion	Enhances lymphopoiesis in combination with IL-7	Decreases lymphocyte apoptosis	Increases NK cell, T cell, and NKT cell proliferation and activation
		Augments T cell responses	Improves immunity against fungal infections	Promote lymphocyte proliferation		Increases T cell IFN- $\gamma$ secretion	
		Reduces nosocomial infection acquisition		Augment neutrophilic and monocytic cytotoxicity		Improves T cell homing and pathogen clearance	
		Reduces ventilator days		Reduce opportunistic infections		Increases T cell receptor diversity	

# Characterization of metabolomic signatures in septic shock patients .

*Alica Cambiaghi, 2017, Milan,*



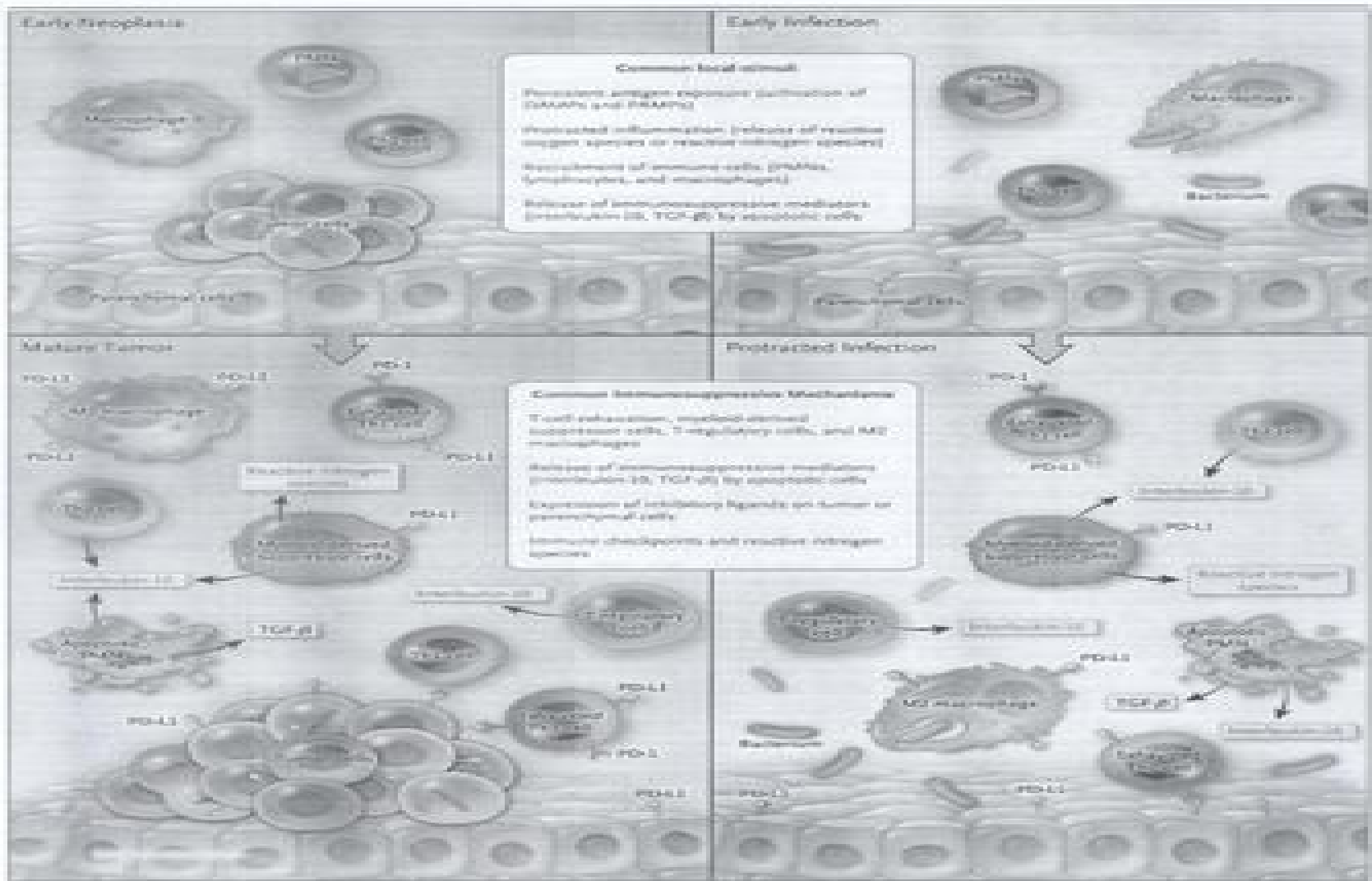
*Figure 5.13– Schema of the glucose-alanine cycle.*



Elizabeth G. Plimster, Ph.D., Editor

# Parallels between Cancer and Infectious Disease

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# Základné postupy v terapii septického šoku

12 hlavných zásad - Nandhabalan P. et al. Crit Care 22:215, 2018

- **9. Levosimendan** - inf. kontinuálna levosimedanu , zvýšiť substitúciu **kalcia** (cave: hypokalcémia ! a hypoalbuminémia ! ) a albumínu 20% R: 10-12 ml/hod.
- 10. V refraktérnom šoku s poruchou mikrocirkulácie a mikrotrombózy treba zvážiť „low-dose“ kontin. Infúziu **prostacyklínu – epoprostenol** prípadne nízke dávky kontin. Infúzie heparínu 300-500 j/hod. za kontroly aPTT, INR.
- 11. Minimálna Analgo-sedácia Sedácia – režim založený na **opioidoch a low-dose propofolu 20- 30 mg/hod.**
- **12. RRT –vs. renal rescue protokol** (M.Palazzo 1998) , pri cytokínovej búrke, hyperinflatórnej mediátorovej reakcii včasná hemodiafiltrácia , vhodné kapsle – Cytosorb.
- Špeciálne prípady refrakt. šoku - **ECMO, Extrakorpor. Podpora obehu**

# Incidence of severe sepsis /per 1000 adults

*Shen : Chest 2010.*

**Table 2. Reported population incidence of severe sepsis**

Country or region	Year	Incidence (per 1000 population)
Australia and New Zealand <sup>12</sup>	1999	0.77
United States <sup>6</sup>	1995	3
United States <sup>8</sup>	2000	2.4
Norway <sup>22</sup>	1999	1.49
France <sup>23</sup>	2001	0.95
The Netherlands <sup>20</sup>	2001	0.54
England, Wales, Northern Ireland <sup>10</sup>	2003	0.66

the number of gram-positive infections, with over 50% of infections in 1995–2000 related to gram-positive organisms, contrasting with over 50% caused by gram-negative organisms in the period 1979–1984.

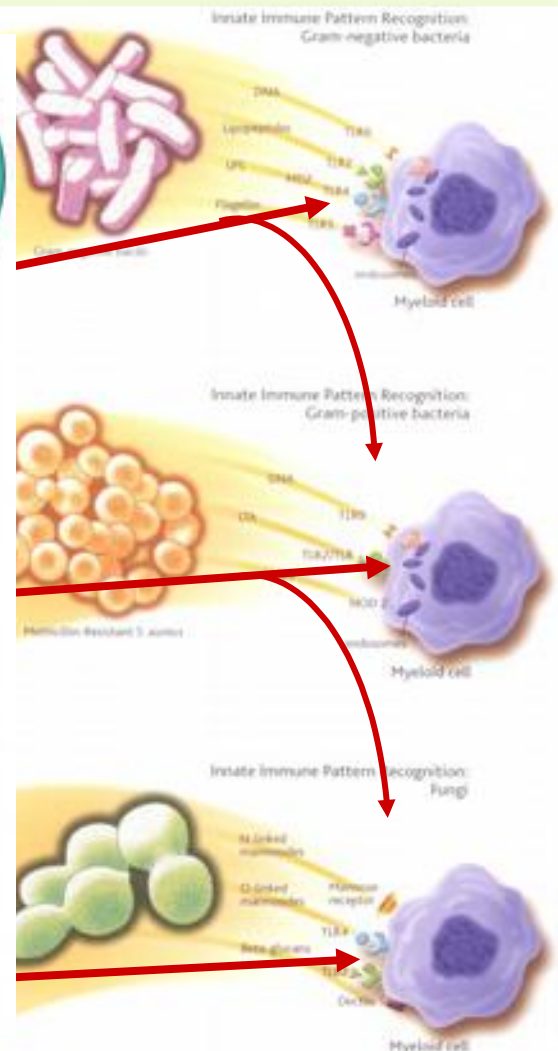
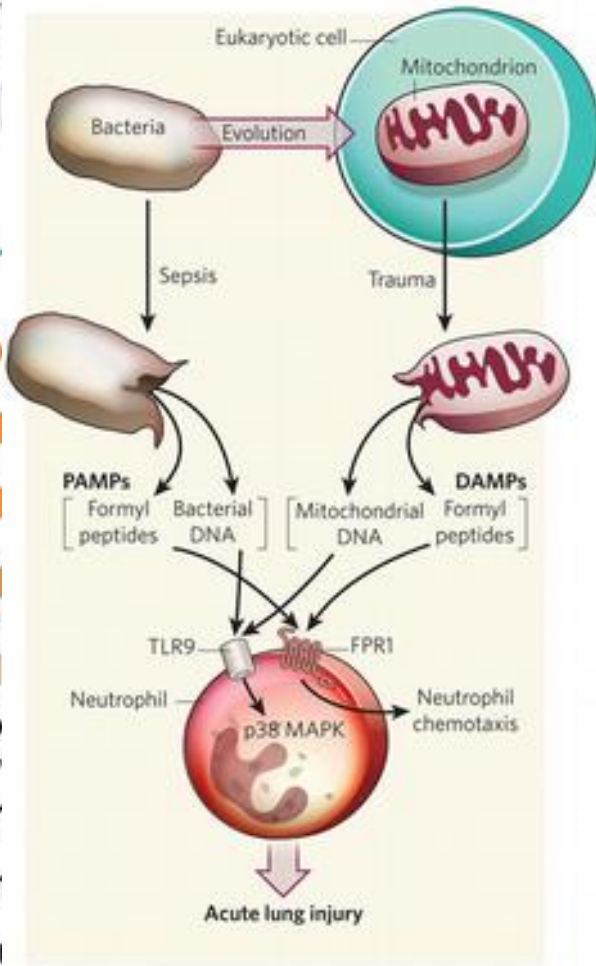
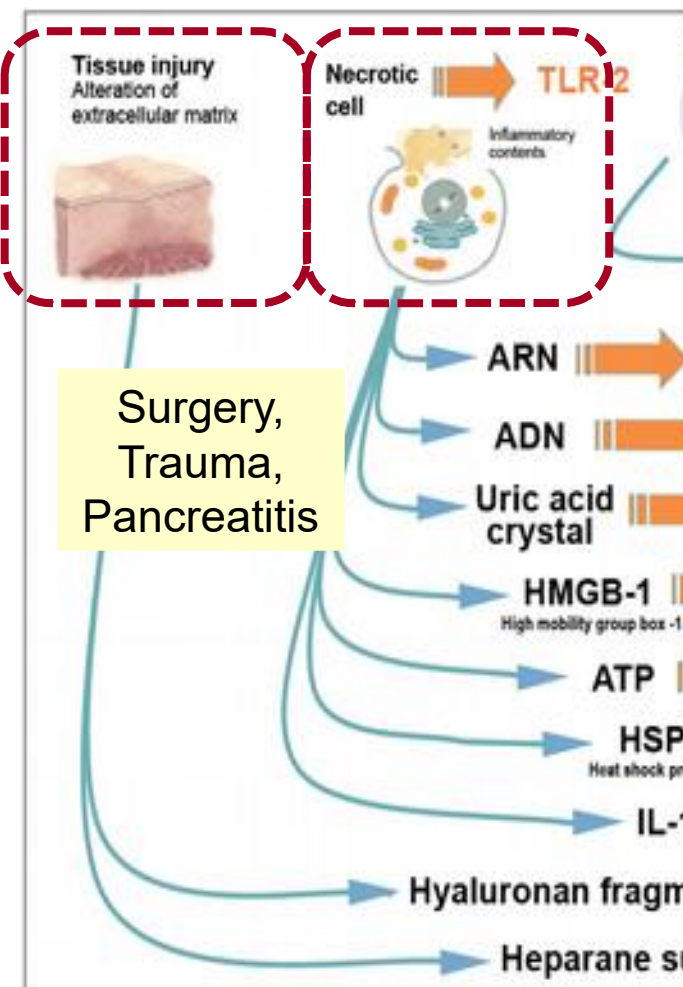
# The cause of the innate immune response

DAMP and / or PAMP and / or MAMP

Innate immune response = „DAMP → SIRS“

versus

„PAMP → SIRS“



Biomarkers of sepsis (RZ 2000) :  
PCT and lymphocyte counts

- Instead of WBC count we should  
Use PCT & lymphoc. counts
- by means of Bayesian method  
Procalcitonin !
- PCT > 1,0 ng/ml in medical pts
- PCT > 2,0 ng/ml in surgical pts
- Lymphocyte count !
- Lymph < 1,000 cells/ul in med
- Lymph < 600 cells/ul in surg.

Intensive Care Med (2000) 26: 1870  
DOI 10.1007/s001340000738

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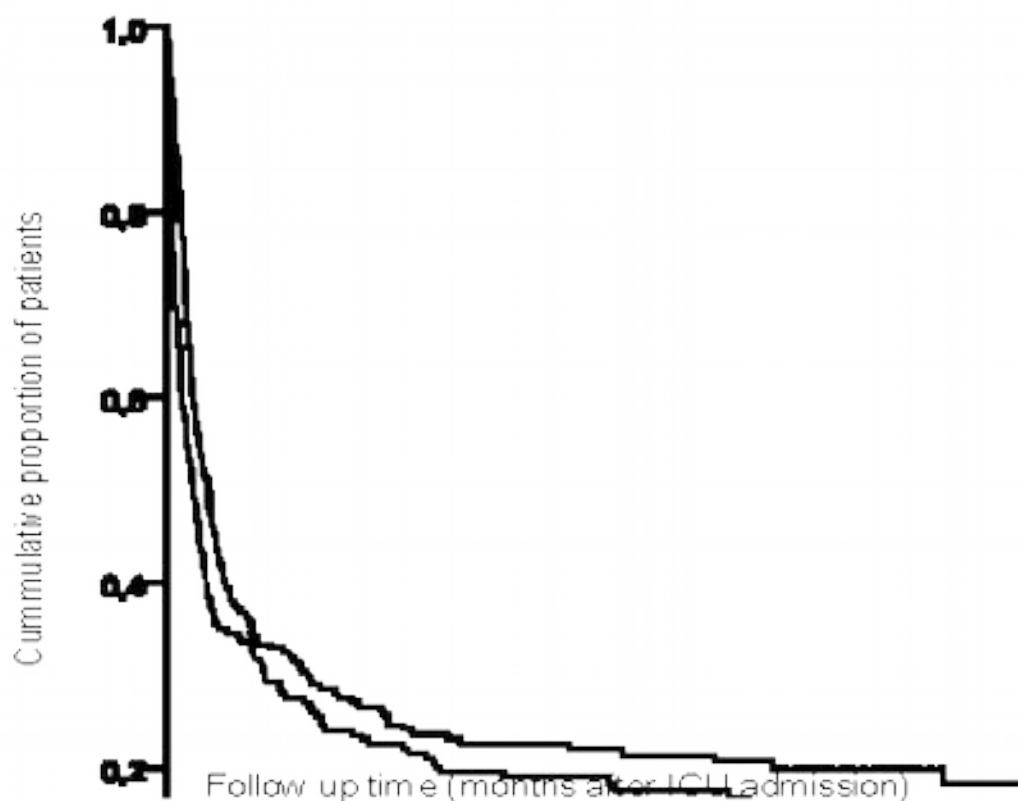
**R. Zahorec**

**Definition for septic syndrome  
should be re-evaluated**

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## Dlouhodobé přežívání dle 24h tekutinová bilance

- RZ



		30 days	90 days	p (log rank test)
---	Fluid balance T24 up to 3.5l (N=242)	0.45 (0.39; 0.52)	0.29 (0.23; 0.35)	<b>0.041</b>
—	Fluid balance T24 over 3.5l (N=216)	0.36 (0.29; 0.42)	0.26 (0.20; 0.32)	

# The grading of sepsis

**Table I: SCORING OF LOCAL EFFECTS OF TISSUE INFECTION**

Attribute	Score
Wound infection with purulent discharge/enterocutaneous fistula	
Requiring only light dressing changed not more than once daily	2
Requiring to be dressed with a pack, dressing needing to be changed more than once daily, requiring application of a bag and/or requiring suction	4
Peritonitis	
Localized peritonitis	2
Generalized peritonitis	6
Chest infection	
Clinical or radiological signs of chest infection without productive cough	2
Clinical or radiological signs of chest infection with a cough producing purulent sputum	4
Full clinical manifestations of lobar/bronchopneumonia	6
Deep-seated infection (e.g. subphrenic abscess, pelvic abscess, empyema thoracis, acute or chronic osteomyelitis)	6

**Table II: SCORING OF PYREXIA (ORAL TEMPERATURE)**

Attribute	Score
Maximum daily temperature ( $^{\circ}\text{C}$ )	
36-37.4	0
37.5-38.4	1
38.5-39	2
> 39	3
< 36	3
	Add
Minimum daily temperature $> 37.5^{\circ}\text{C}$	1
If 2 or more temperature peaks above $38.4^{\circ}\text{C}$ in 1 day	1
If any rigours occur in a day	1

Temperature should be recorded at least 4 times in 24 h. The record for the 24 h period is assessed as above and 'pyrexia score' computed.

**Table III: SCORING OF SECONDARY EFFECTS OF SEPSIS**

Attribute	Score
Obvious jaundice (in the absence of established hepatobiliary disease)	2
Metabolic acidosis	
Compensated	1
Uncompensated	2
Renal failure	3
Gross disturbance of mental orientation/level of consciousness (e.g. delirium, coma) and/or other focal neurological manifestations of pyaemia/septicaemia (having excluded other causes)	3
Bleeding diathesis (from disseminated intravascular coagulation)	3

It is frequently said, and with some truth, that You cannot begin to investigate something until You can measure it.

*Grading of Sepsis,*

*Elebute, Stoner 1983*

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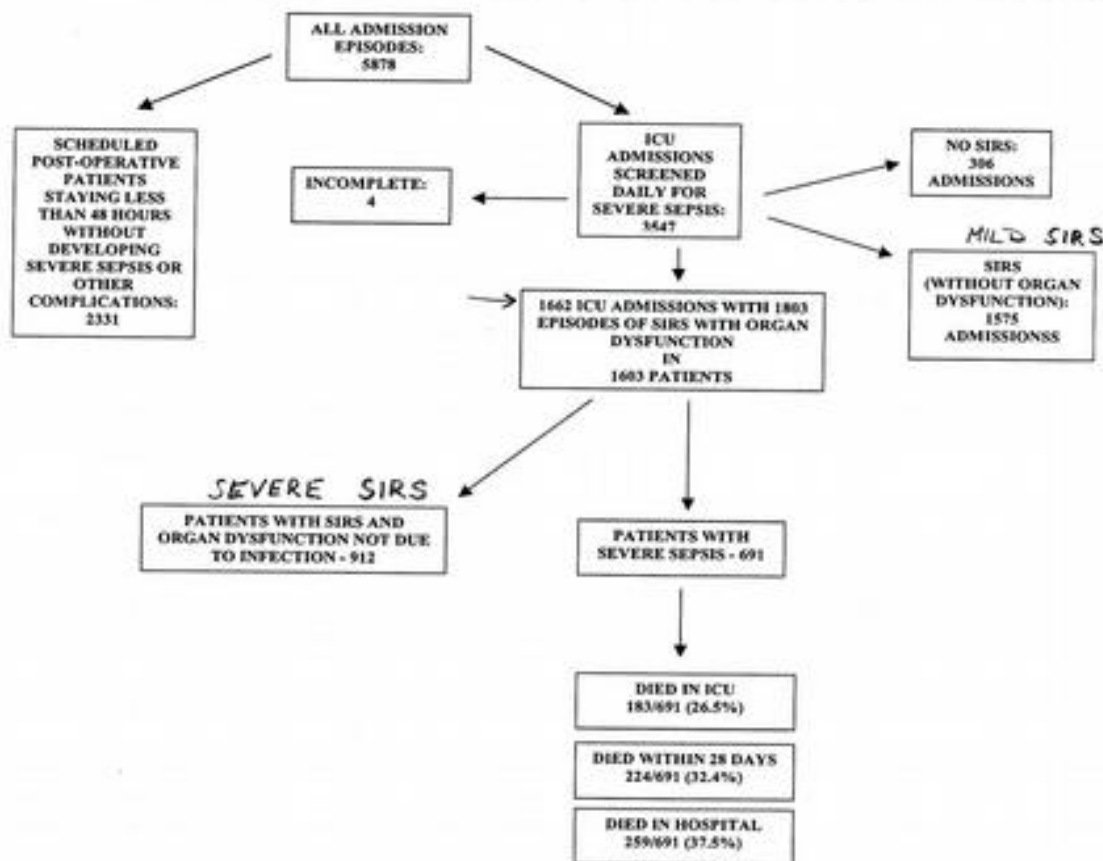


# Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units

691 pts had 752 episodes of SS.

592

FINFER S., ICM 2004, 30: 589-564.



23 ICUs  
 3-mesačná  
 Incidencia :  
 11,8 %  
 Hospitalizačná  
 Mortalita:  
 37,5%

3547 pacientov:  
 žiaden SIRS 8,6%  
 Mierny SIRS 44%  
 Ťažký SIRS 26%  
 Ťažká sepsa +  
 Septický šok 19%

Fig. 1 Kaplan-Meier estimates of survival to day 28 in 691 patients with severe sepsis