

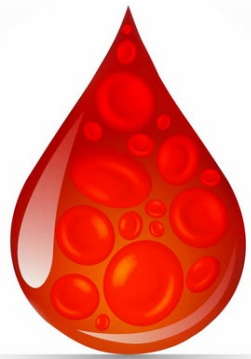


Iniciální resuscitace sepse - Individuální přístup

Martin HELÁN

ARK FNUSA v Brně

16.9.2022, ČSARIM



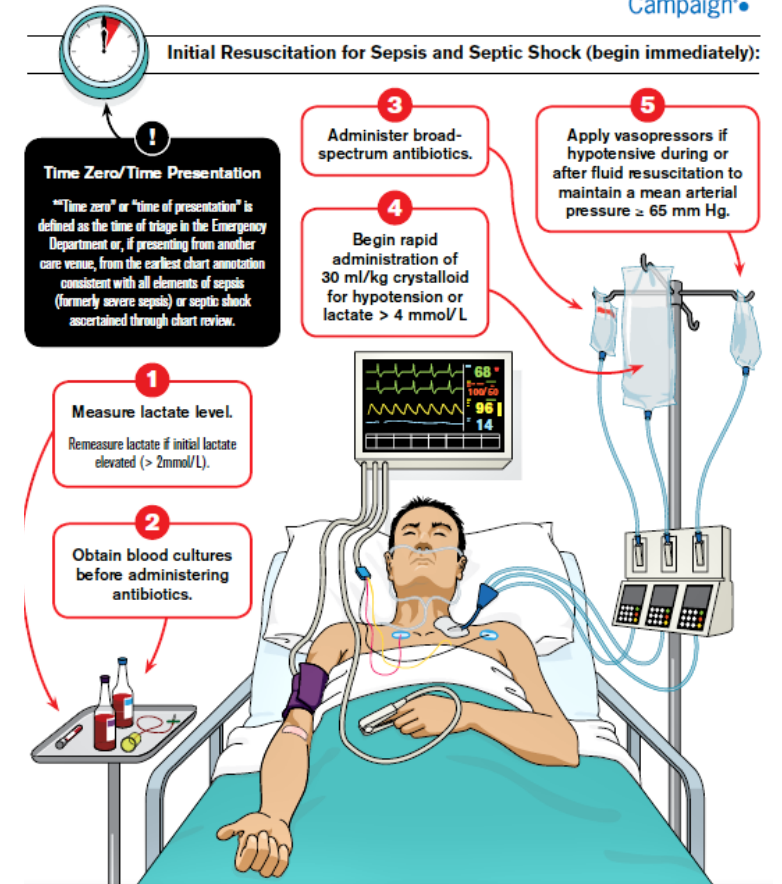
SEPTEMBER IS
SEPSIS AWARENESS
MONTH
🎗️

- Surviving sepsis campaign Vs. Individualizovaná terapie
 - Proč je potřeba individualizovat
 - One size fits all?
- Fenotypy sepse
- Nejohroženější skupina pacientů
- Lze iniciálně rozpoznat pacienta, který potřebuje „jinou“ terapii ?
- Možnosti jak individualizovat terapii

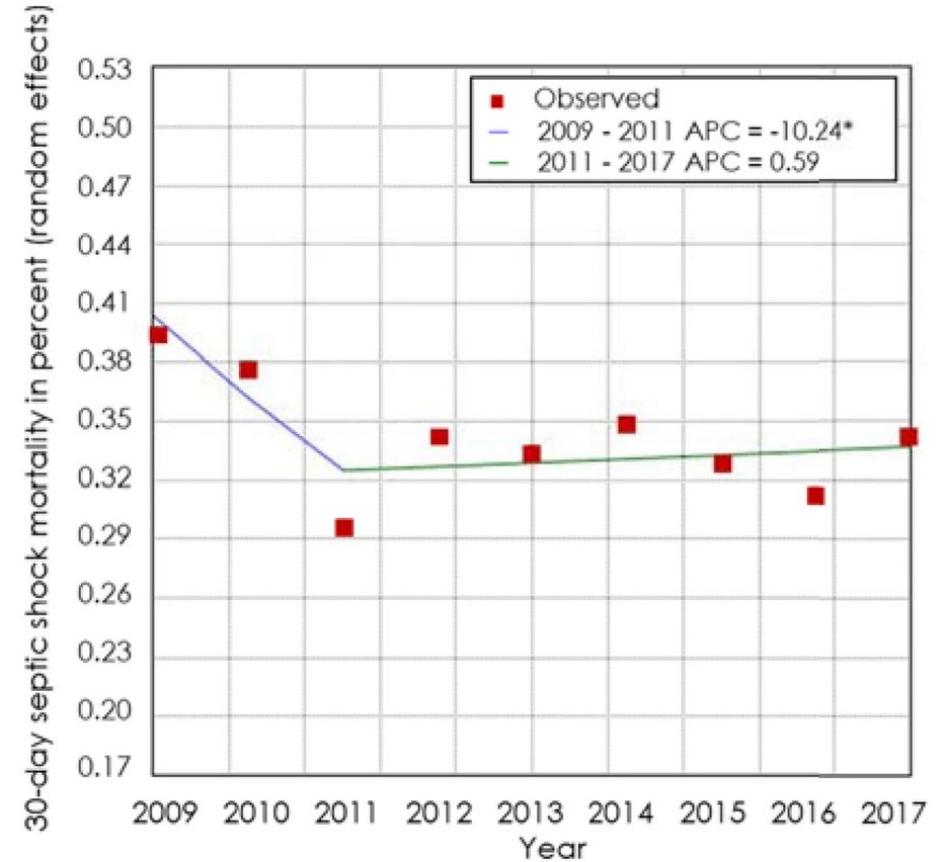
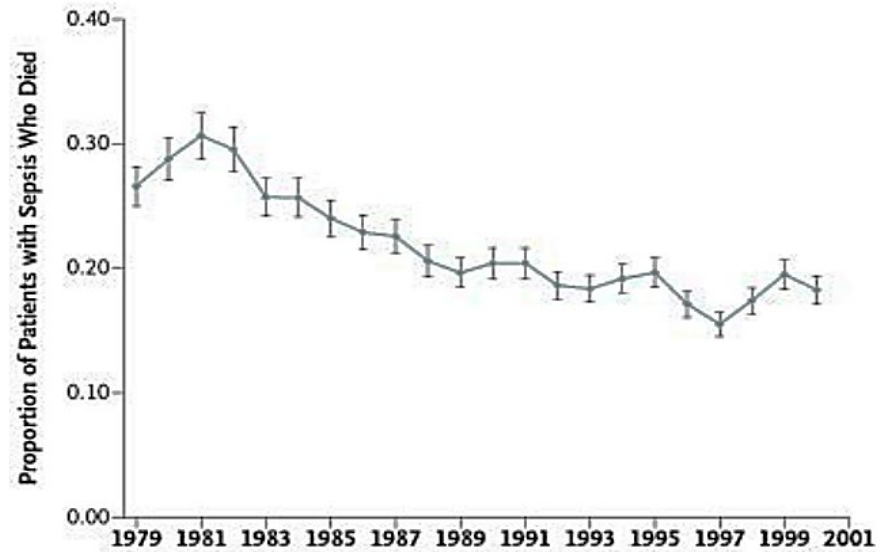
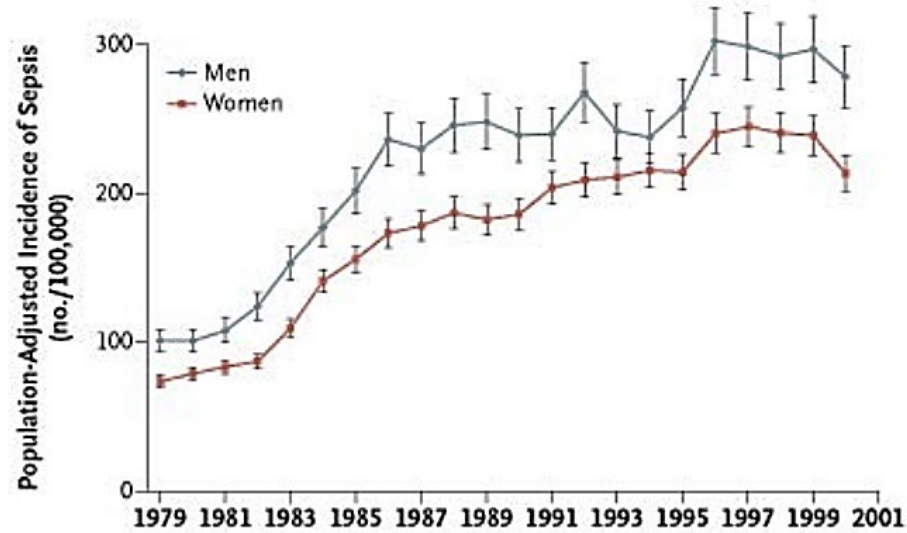
- No conflict of interest to declare!

Hour-1 Bundle

Surviving Sepsis Campaign



Jak se vyvíjí mortalita sepse?

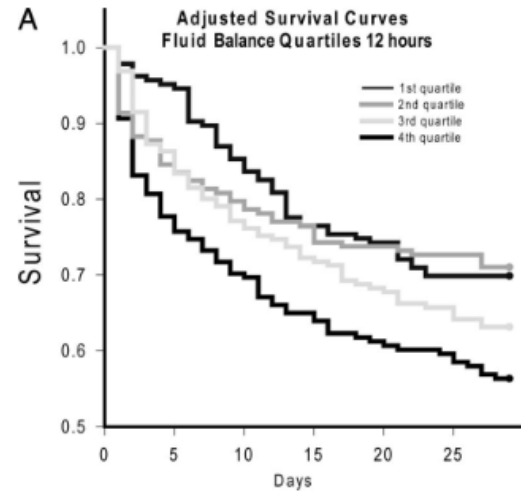


* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.

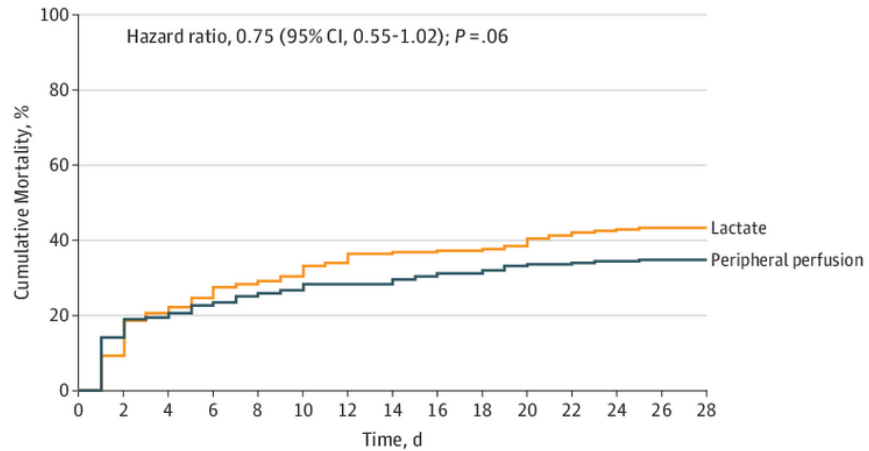
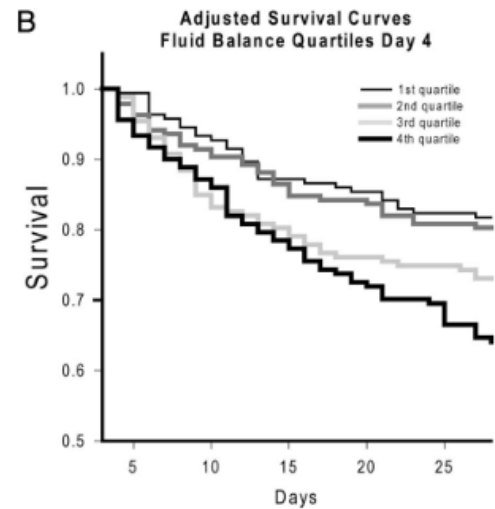
📖 Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003

📖 Bauer, M., Gerlach, H., Vogelmann, T. et al. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis. *Crit Care* 24, 239 (2020).

Tekutiny + Vasopresory



- určení hypovolemie
- určení fluid responsiveness
- sledování vývoje laktátu, capillary refill time, hypoperfuze
- vasoplegie
- kardiální funkce, pravostranná dysfunkce



Fluid infusion + Vasopressor (NE)

↗ ↗ Mean systemic pressure

↗ SVR

↗ Venous Return and CO
in preload responsive Patients

↗ MAP

Potential advantages of Fluid + NE combination

- 1) Increases the **mean systemic pressure** more than fluid alone (**better CO**)
- 2) **Corrects hypotension** better than fluid alone
- 3) **Limits fluid overload**
- 4) Produces **less hemodilution** than fluid alone (→ **increased DO₂**)
- 5) May **improve outcome**

Diastolic pressure

Patient of 70 years old and history of CAD with tachycardia (heart rate: 100 beats/min) and clinical signs of septic shock in spite of initial fluid resuscitation

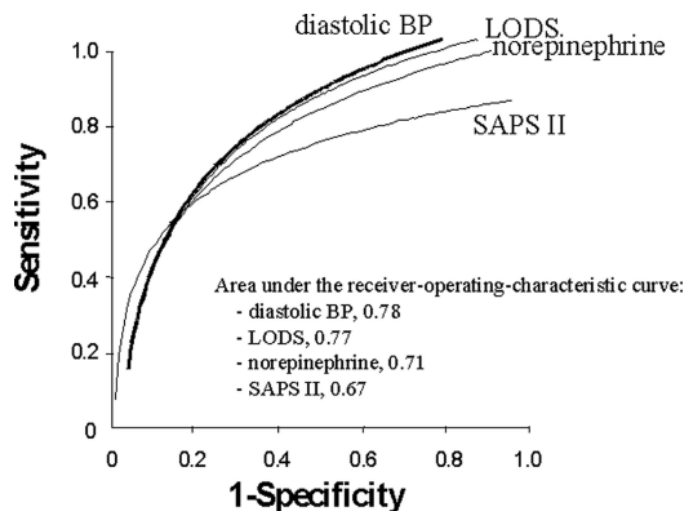
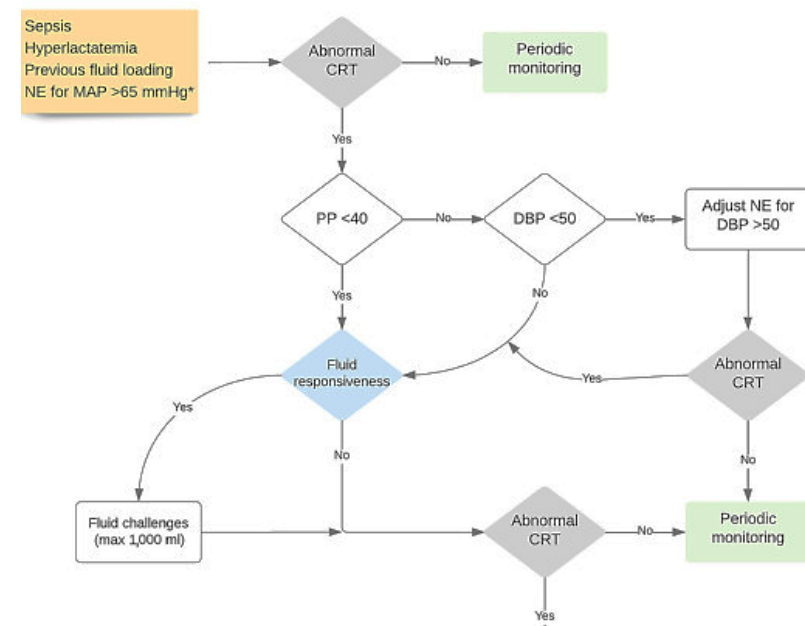


Fig. 3. Multivariate factors of survival. SAPS II was measured at the time norepinephrine was introduced; NE, norepinephrine; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; OR, odds ratios; 95% CI, 95% confidence interval.



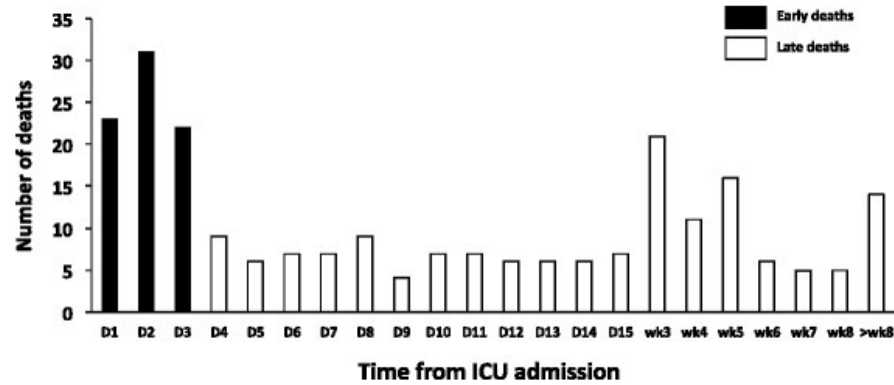
Hamzaoui O, Teboul JL. Importance of diastolic arterial pressure in septic shock: PRO. *J Crit Care.* 2019

Benchekroune, Karpati, Berton, Nathan, Mateo, Chaara, Riché, Laisné, Payen, Mebazaa. Diastolic Arterial Blood Pressure: A Reliable Early Predictor of Survival in Human Septic Shock. *The Journal of Trauma: Injury, Infection, and Critical Care.* 2008

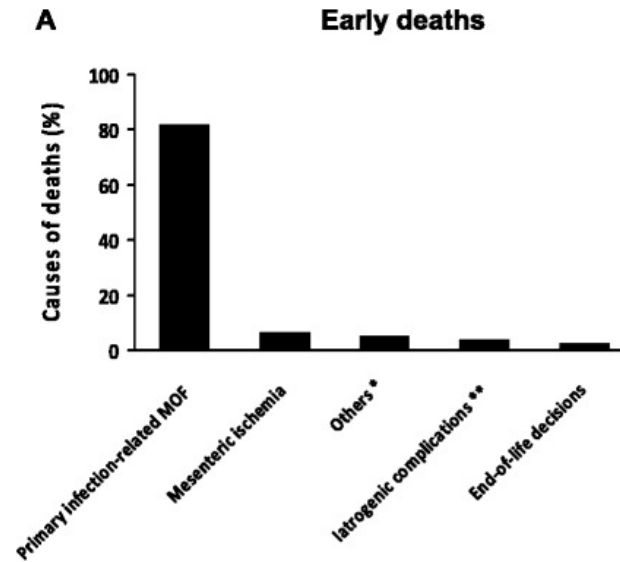
Kattan E, Bakker J, Estenssoro E, Ospina-Tascón GA, Cavalcanti AB, Backer D, Vieillard-Baron A, Teboul JL, Castro R, Hernández G. Hemodynamic phenotype-based, capillary refill time-targeted resuscitation in early septic shock: The ANDROMEDA-SHOCK-2 Randomized Clinical Trial study protocol. *Rev Bras Ter Intensiva.* 2022

Časně zemřelí pacienti

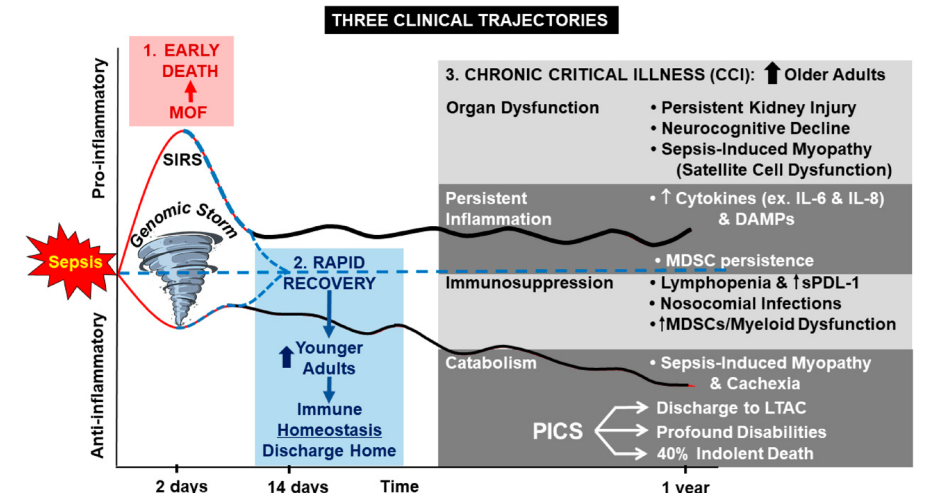
Fig. 2



Distribution of deaths according to time from ICU admission. Numbers of deaths are represented per day during the first 2 weeks and per week thereafter. Early (≤ 3 days) and late (> 3 days) deaths occurred in 78 (32 %) and 166 (68 %) patients, respectively



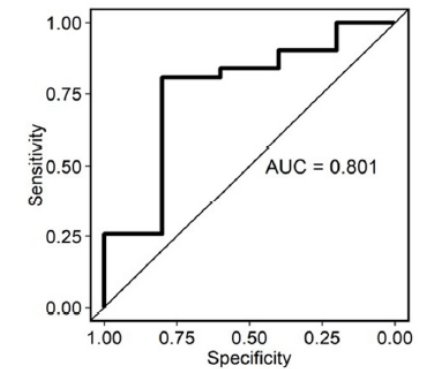
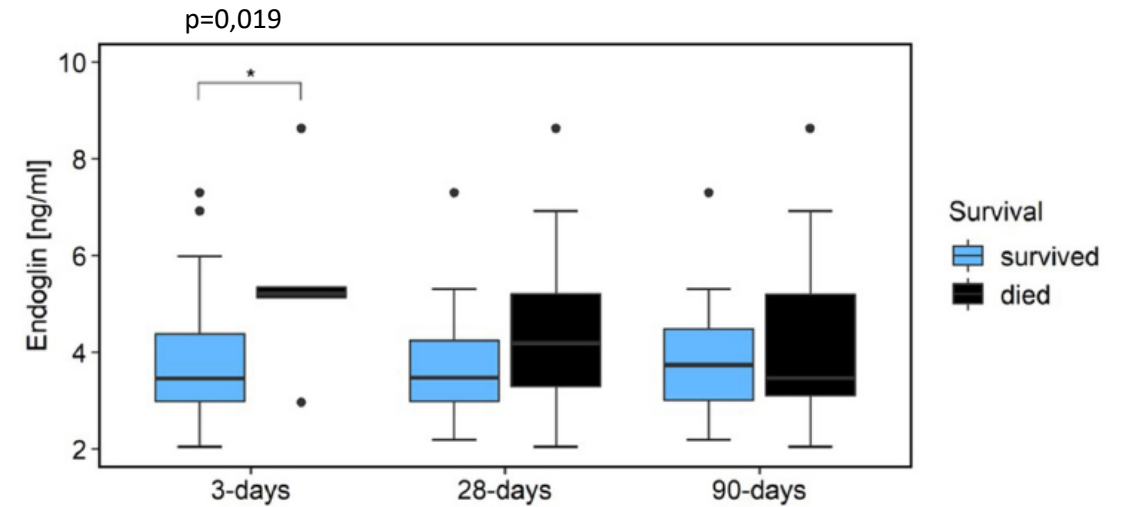
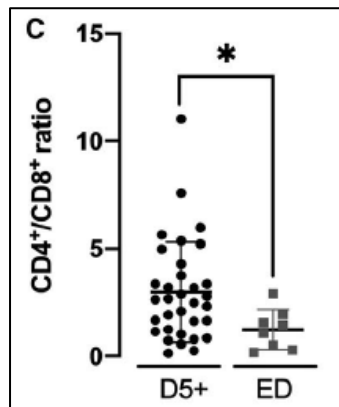
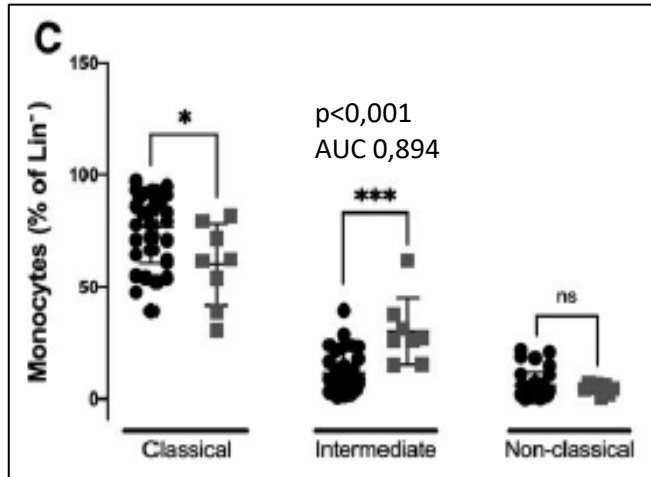
- Vysoký vstupní laktát, nízké vstupní pH, vysoké vstupní SOFA skóre – nezávislé prediktory časného úmrtí
- přetrvávající hodnota laktátu > 5
- Iničiálně pozitivní bakteremie



Daviaud F, Grimaldi D, Dechartres A, Charpentier J, Geri G, Marin N, Chiche JD, Cariou A, Mira JP, Pène F. Timing and causes of death in septic shock. Ann Intensive Care. 2015

Javed A, Guirgis FW, Sterling SA, Puskarich MA, Bowman J, Robinson T, Jones AE. Clinical predictors of early death from sepsis. J Crit Care. 2017

Časně zemřelí pacienti

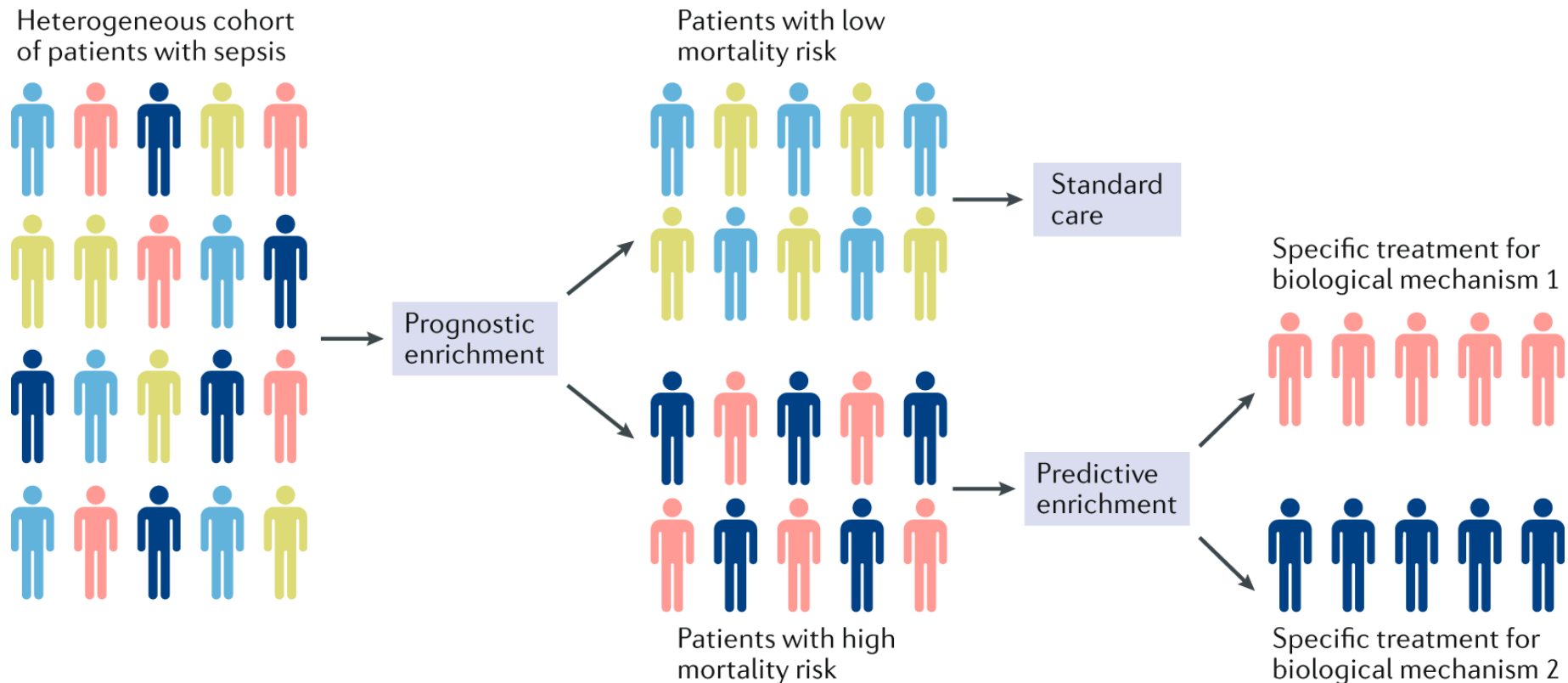


Tomášková V, Mytnikova A, Hortova Kohoutkova M, Mrkva O, Skotakova M, Šitina M, Helanova K, Fric J, Parenica J, Šramek V and Helan M (2022) Prognostic value of soluble endoglin in patients with septic shock and severe COVID-19. *Front. Med.*

Hortová-Kohoutková M, Lázníčková P, Bendíčková K, De Zuani M, Andrejčinová I, Tomášková V, Suk P, Šrámek V, Helán M, Frič J. Differences in monocyte subsets are associated with short-term survival in patients with septic shock. *J Cell Mol Med.* 2020.

Precision medicine

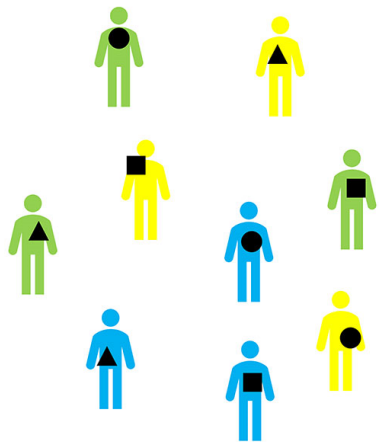
Prognostic/predictive enrichment



Artificial intelligence

Patients diagnosed with Sepsis

'Infection + Critical organ dysfunction'



●▲■ indicate pathophysiology underlying sepsis

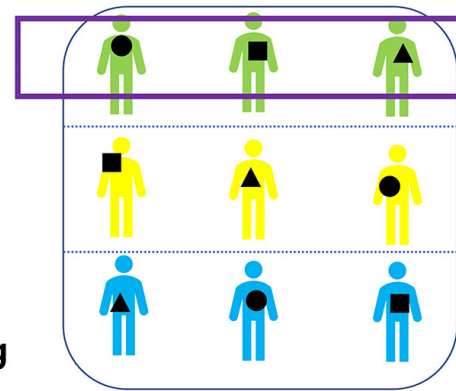
Subgrouping



'Within few hours'

Limited available parameters
• age
• sex
• vital signs
• blood examination
etc.

by Physician

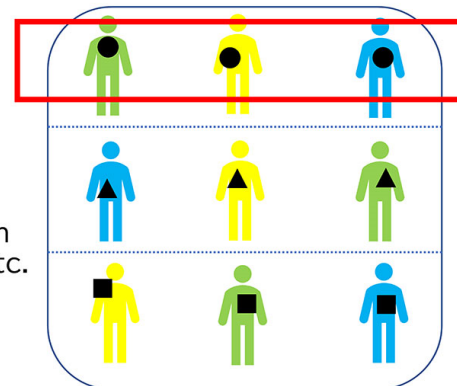


Including various underlying conditions



failed clinical trial

by AI



Uniform pathophysiology

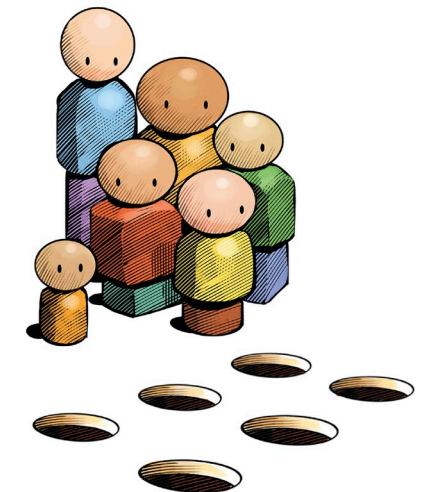


may follow the robust evidence from animal experiments

Fenotypy sepsis

Endotypes	Methodology	Studied group	Implications	References
Subclass A: repression of adaptive immunity and zinc-related biology Subclass B Subclass C	Genome-wide expression profiling, unsupervised hierarchical clustering of genes which expression was ≥ 2 -fold changed (comparing to controls) in 25-50% of patients	Children with septic shock ($n = 98$)	Identification of high-risk subpopulation by subclass An assessment identification of novel therapeutic targets	Wong <i>et al</i> (2009)
Subclass A Subclass B	Multiplex mRNA quantification platform to analyze the expression of the 100 subclass-defining genes	Children with septic shock ($n = 168$)	Development of a method for endotyping pediatric septic shock Identification of endotype (A) associated with the harmful effects of glucocorticosteroids	Wong <i>et al</i> (2015)
Mars1: immunosuppression, increase in heme biosynthesis pathway components Mars2: increased expression of genes related to pattern recognition, cytokines, cell growth Mars3: adaptive immunity; IL-4, NK-cell signaling Mars4: interferon signaling, pattern recognition, TREM1 signaling	Genome-wide expression	Sepsis ($n = 306$), validation cohort ($n = 216$), second validation cohort (CAP sepsis $n = 265$)	Mars1 type response is related to poor early- and long-term outcome	Scicluna <i>et al</i> (2017)
SRS1 (Sepsis Response Signature 1): immunosuppression, T-cell exhaustion, endotoxin tolerance SRS2: proliferation, immune response, cell adhesion	Genome-wide microchip array, variation in global gene expression by unsupervised hierarchical clustering	Sepsis due to CAP ($n = 265$ and validation cohort $n = 106$)	SRS1 is a predictor of high early mortality	Davenport <i>et al</i> (2016)
SRS1: cell death, apoptosis, endotoxin tolerance SRS2: cell adhesion, differentiation, proliferation, immune response	Genome-wide Microarray, variation in global gene expression	Fecal peritonitis sepsis ($n = 117$) (also comparison with CAP; $n = 126$)	SRS1 is a denominator of high early mortality, but the shift to SRS2 pattern is a marker of favorable prognosis	Burnham <i>et al</i> (2017)
Endotype A Endotype B	Retrospective analysis of transcriptomic data using pattern of 100 genes expression	Sepsis ($n = 549$)	Highest mortality in patients < 40 y.o. co-allocated into endotype A/SRS1. Suggestion of relationship between immunosuppressive response and mortality	Wong <i>et al</i> (2017a)
Endotype A Endotype B	Retrospective classification and regression tree analysis of retrospective data to find the smallest discriminatory set of genes	Septic children ($n = 300$); validation group ($n = 43$)	Development of four-gene based protocol for endotyping of septic children. Potential to identify glucocorticoid responses	Wong <i>et al</i> (2017b)
SRS1 SRS2	Genome-wide microarray, allocation based on the generalized linear model based on 7 genes (from Davenport <i>et al</i> , 2016)	Sepsis ($n = 177$)	Hydrocortisone treatment increases mortality in SRS2	Antcliffe <i>et al</i> (2019)
Inflammopathic: pro-inflammatory, complement pathways Adaptive: adaptive immunity and interferon signaling Coagulopathic: platelet degranulation, coagulation cascade	Genome-wide expression	Retrospective analysis of septic patients ($n = 700$) from 14 trials	Identification of major deregulated pathways in endotypes that can direct selective treatment	Sweeney <i>et al</i> (2018a)

CAP, community acquired pneumonia; SRS, sepsis response signature.

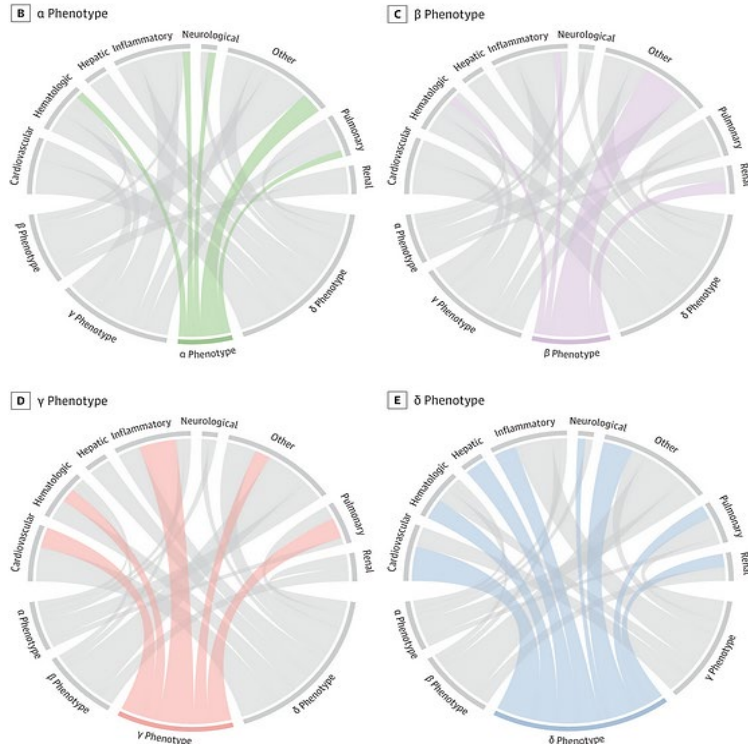


Terapie cílené na podskupiny pacientů

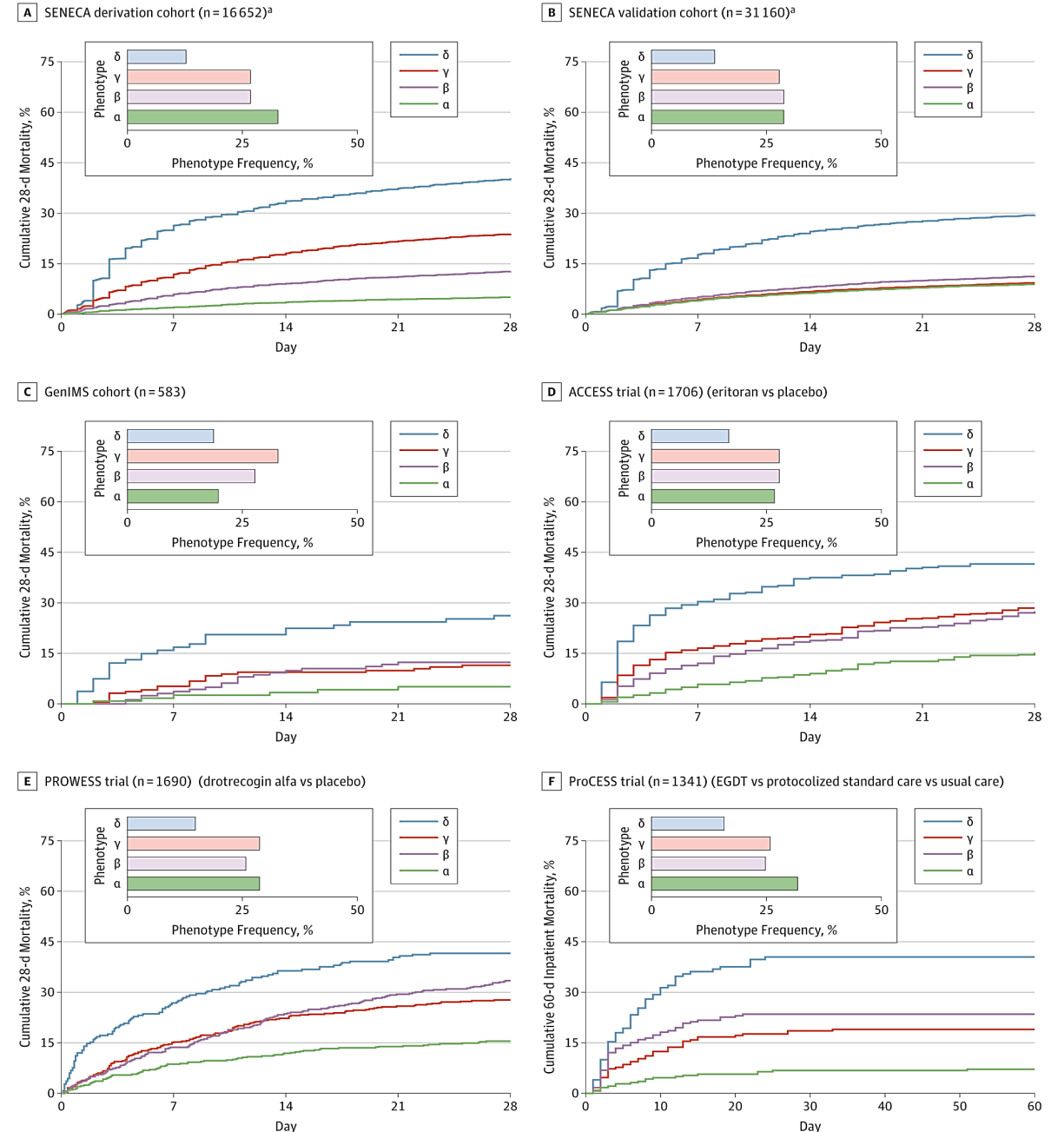
Table 2. Examples of clinical trials that showed benefits in subgroups of septic patients

Drug/intervention	Subgroups	Benefit	Mode of analysis	References
Afelimomab (anti-tumor necrosis factor F(ab') ₂ monoclonal antibody fragment)	IL-6 > 1,000 pg/ml	28-day mortality 43.6% vs. 47.6% placebo	Prospective	Panacek <i>et al</i> (2004)
GM-CSF	Monocytic HLA-DR < 8,000 antibodies per cell	Time of mechanical ventilation 148 ± 103 vs. 207 ± 58 h (placebo), <i>P</i> = 0.04	Prospective	Meisel <i>et al</i> (2009)
Anakinra (IL-1 receptor antagonist)	Features of hemophagocytic lymphohistiocytosis (disseminated intravascular coagulation (DIC), thrombocytopenia and hepatobiliary dysfunction)	28-day mortality 34.6% vs. 64.7% placebo	Re-analysis of de-identified data from the phase III randomized interleukin-1 receptor antagonist trial in severe sepsis	Shakoory <i>et al</i> (2016)
Trimodulin (polyclonal immunoglobulin preparation)	CRP ≥ 70 mg/l and IgM ≤ 0.8 g/l	28-day mortality 11.8% vs. 36.6% placebo (<i>P</i> = 0.006)	Exploratory <i>post hoc</i>	Welte <i>et al</i> (2018)

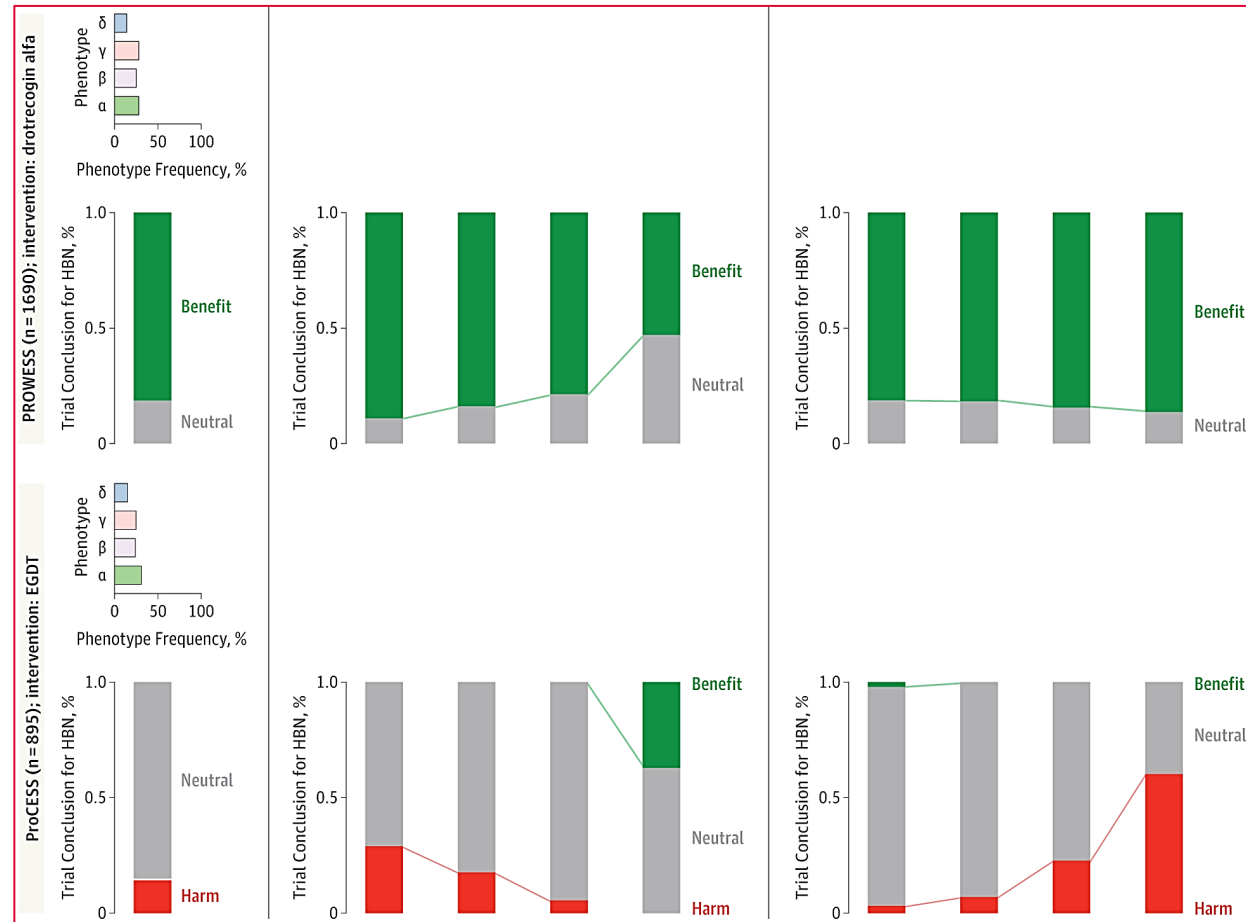
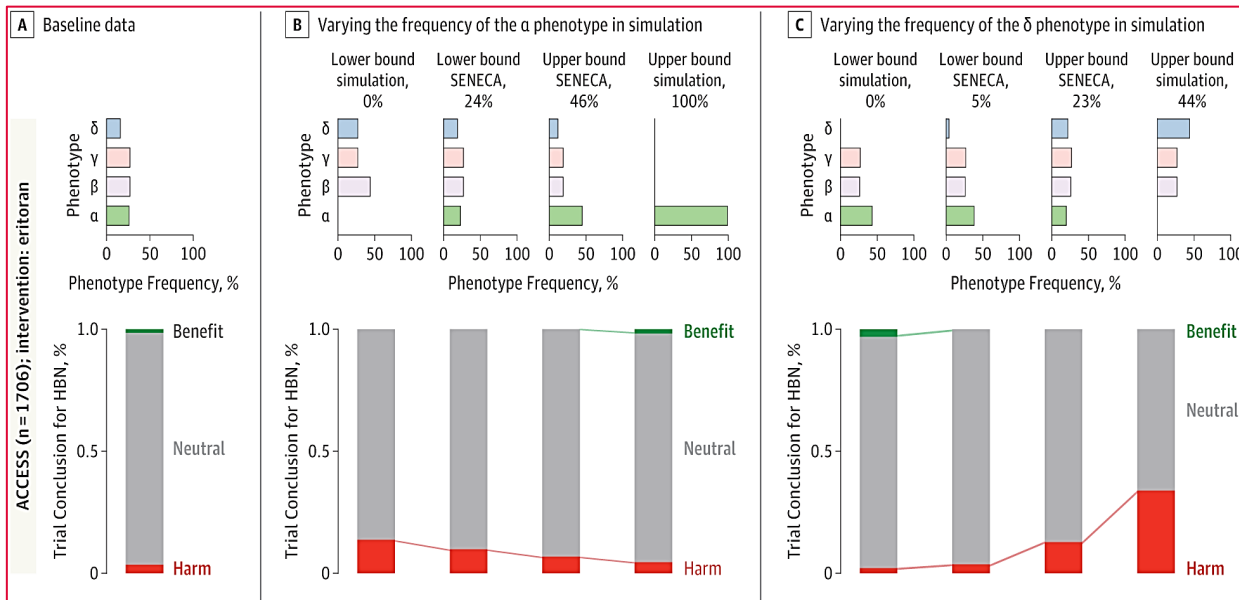
Phenotype sepsis $\alpha, \beta, \gamma, \delta$



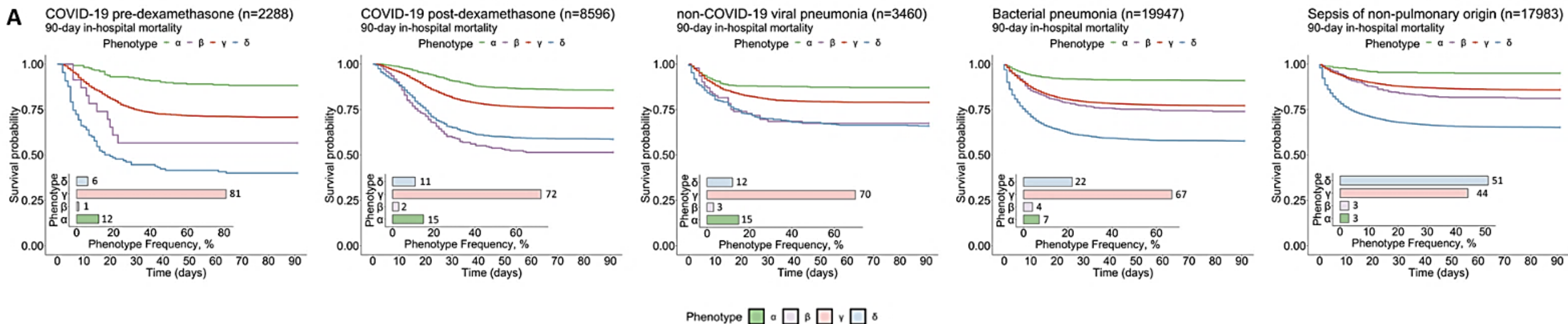
- **alpha (α):** having the fewest abnormal laboratory test results, the least organ dysfunction, and the lowest in-hospital death rate (23%)
- **beta (β):** older age, more chronic illness, and kidney dysfunction
- **gamma (γ):** elevated inflammation and primary pulmonary dysfunction
- **delta (δ):** least common and most deadly phenotype; characterized by liver dysfunction and shock and the highest in-hospital mortality (32%)



Phenotype sepsis $\alpha, \beta, \gamma, \delta$



Fenotypy sepsy při Covid-19 ?



Individualizovaná resuscitace sepse

Ma et al. *Crit Care* (2021) 25:243
<https://doi.org/10.1186/s13054-021-03682-7>

Critical Care

RESEARCH

Open Access



Individualized resuscitation strategy for septic shock formalized by finite mixture modeling and dynamic treatment regimen

Penglin Ma^{1†}, Jingtao Liu^{2†}, Feng Shen³, Xuelian Liao⁴, Ming Xiu⁵, Heling Zhao⁶, Mingyan Zhao⁷, Jing Xie⁸, Peng Wang⁹, Man Huang¹⁰, Tong Li¹¹, Meili Duan¹², Kejian Qian¹³, Yue Peng¹⁴, Feihu Zhou¹⁵, Xin Xin¹⁶, Xianyao Wan¹⁷, Zongyu Wang¹⁸, Shusheng Li¹⁹, Jianwei Han²⁰, Zhenliang Li²¹, Guolei Ding²², Qun Deng²³, Jicheng Zhang²⁴, Yue Zhu²⁵, Wenjing Ma²⁶, Jingwen Wang²⁷, Yan Kang²⁸ and Zhongheng Zhang^{29*}

- Identifikováno 5 fenotypů:

1. **baseline class** - majority of patients
2. **critical class** - had the highest severity of illness
3. **renal dysfunction class** - was characterized by renal dysfunction
4. **respiratory failure class** - was characterized by respiratory failure
5. **mild class** - was characterized by the lowest mortality rate (21%)

While class 1 transitioned to de-resuscitation phase on day 3, class 3 transitioned on day 1.

- Classes 1 and 3 might benefit from **early use of norepinephrine**,
- Class 2 can benefit from delayed use of norepinephrine while waiting for **adequate fluid infusion**.

Vývoj hyper-/hypotermie

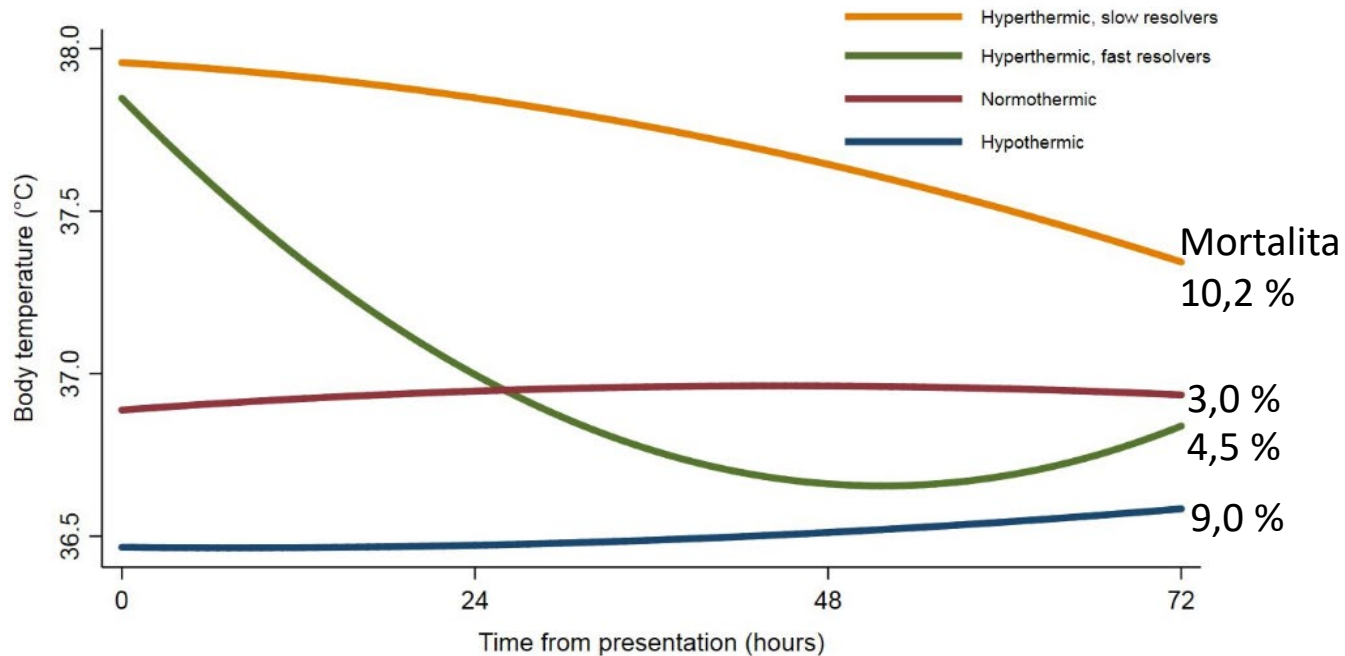
Identifying Novel Sepsis Subphenotypes Using Temperature Trajectories

 Sivasubramaniam V. Bhavani¹, Kyle A. Carey¹, Emily R. Gilbert², Majid Afshar²,  Philip A. Verhoef^{1,3}, and Matthew M. Churpek¹

+ Author Affiliations

<https://doi.org/10.1164/rccm.201806-1197OC> PubMed: [30789749](https://pubmed.ncbi.nlm.nih.gov/30789749/)

Received: June 29, 2018 Accepted: February 20, 2019



RESEARCH SNAPSHOT THEATER: SEPSIS III

1649: IMMUNOLOGIC PHENOTYPING OF FEBRILE AND AFEBRILE CRITICALLY ILL SEPTIC PATIENTS

Drewry, Anne¹; Morris, Robert²; Doctor, Rebecca¹; Dalton, Catherine³; Hotchkiss, Richard¹

[Author Information](#)

Critical Care Medicine: January 2020 - Volume 48 - Issue 1 - p 800

doi: [10.1097/01.ccm.0000648500.25500.65](https://doi.org/10.1097/01.ccm.0000648500.25500.65)

RESEARCH SNAPSHOT THEATER: SEPSIS

1483: MONOCYTE FUNCTION AND CLINICAL OUTCOMES IN FEBRILE AND AFEBRILE PATIENTS WITH SEVERE SEPSIS

Drewry, Anne; Ablordeppey, Enyo; Murray, Ellen; Fuller, Brian; Kollef, Marin; Hotchkiss, Richard

[Author Information](#)

Critical Care Medicine: January 2018 - Volume 46 - Issue 1 - p 725

doi: [10.1097/01.ccm.0000529485.65268.b2](https://doi.org/10.1097/01.ccm.0000529485.65268.b2)

Vývoj hyper-/hypotermie

FEATURE ARTICLES

Therapeutic Hyperthermia Is Associated With Improved Survival in Afebrile Critically Ill Patients With Sepsis: A Pilot Randomized Trial

Drewry, Anne M. MD, MSCI¹; Mohr, Nicholas M. MD, MS²⁻⁴; Ablordeppey, Enyo A. MD, MPH^{1,5}; Dalton, Catherine M. BA¹; Doctor, Rebecca J. BA¹; Fuller, Brian M. MD, MSCI¹; Kollef, Marin H. MD⁶; Hotchkiss, Richard S. MD¹

[Author Information](#) ☺

Critical Care Medicine: June 2022 - Volume 50 - Issue 6 - p 924-934

doi: 10.1097/CCM.00000000000005470

- maximum temperature **less than 38.3°C** within the 24 hours prior to enrollment
- External warming using a forced-air **warming blanket for 48 hours**, with a goal temperature **1.5°C above** the lowest temperature documented in the previous 24 hours.
- We enrolled 56 participants
- Participants allocated to external warming had **lower 28-day mortality** (18% vs 43%).

Kortikoidy ?

- Stále kontroverzní

SSC – „For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids. **Weak** recommendation; moderate quality of evidence“

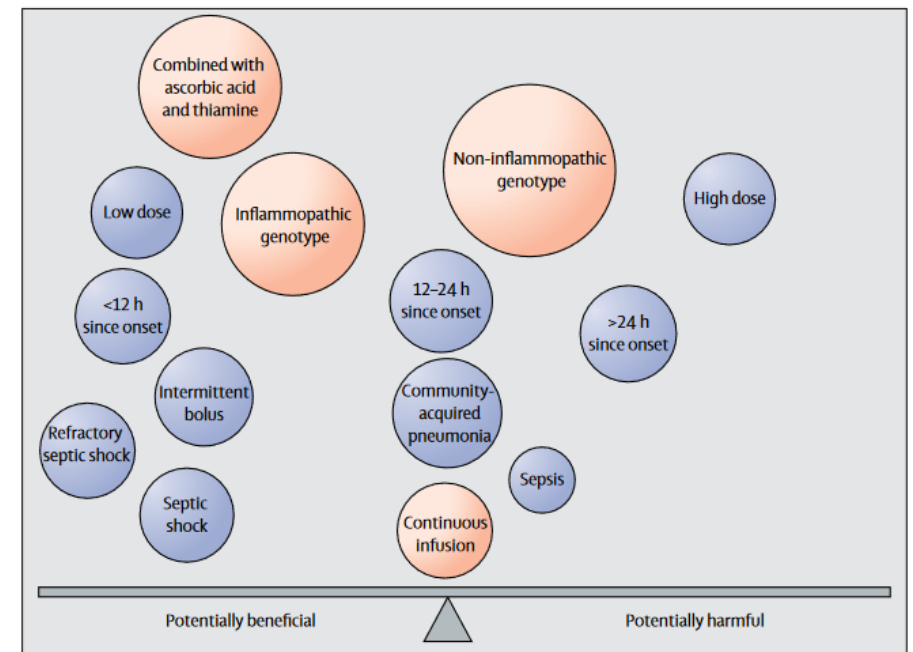
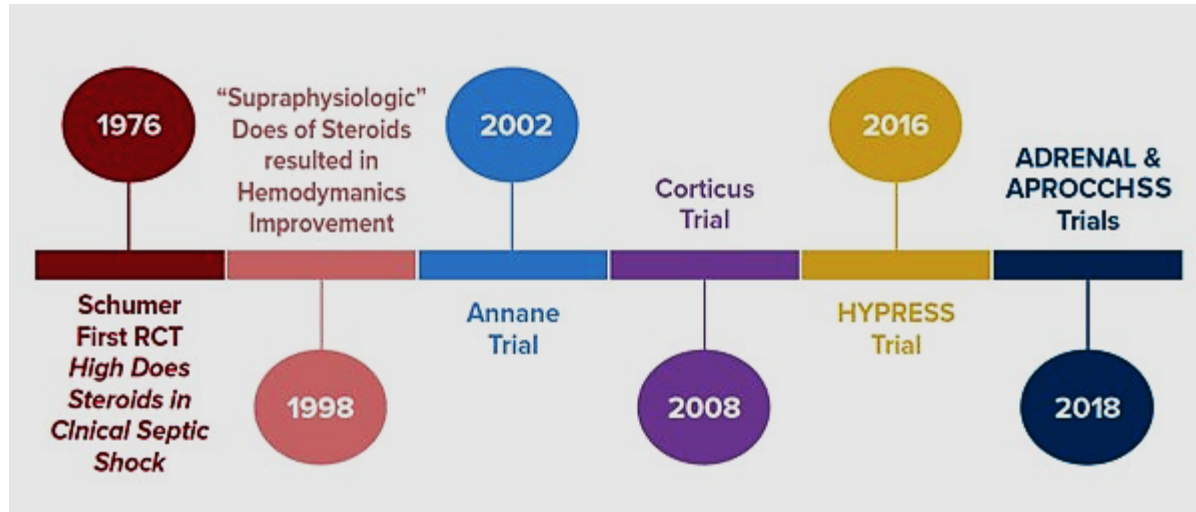


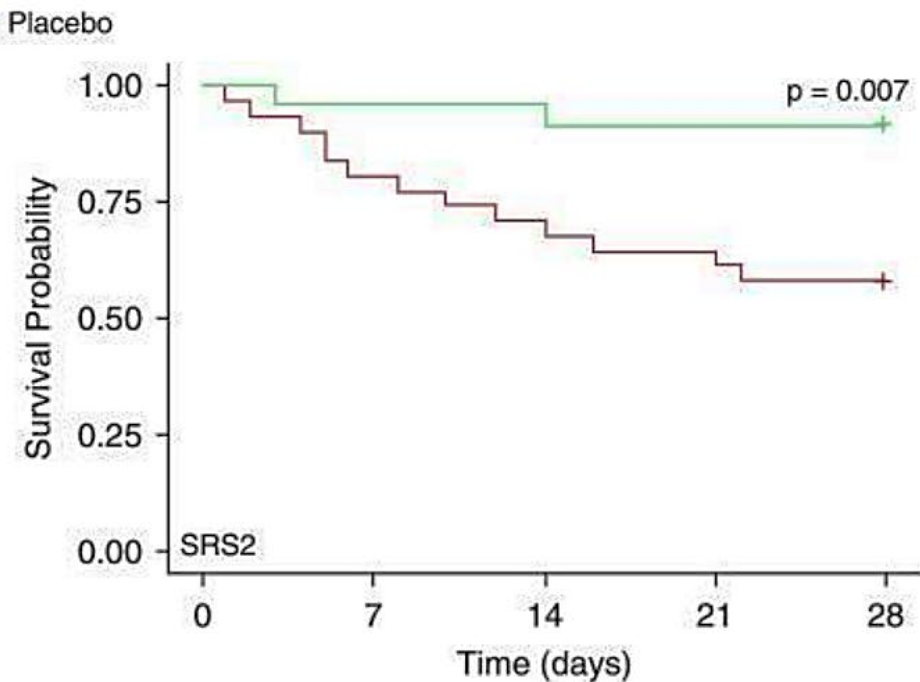
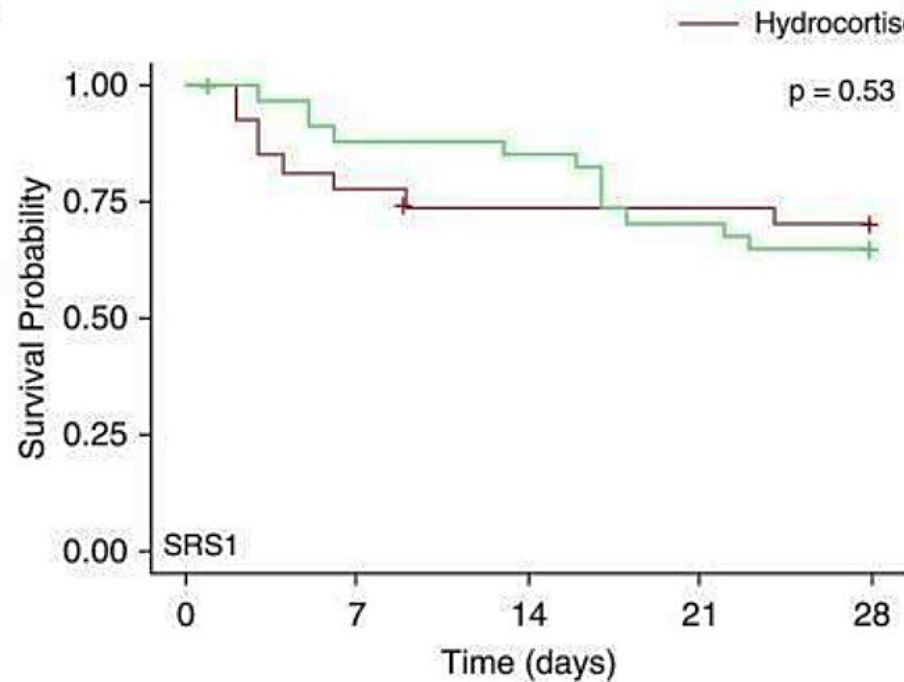
Figure: Balance of the benefits and potential harms associated with the use of glucocorticoids in patients with sepsis and septic shock

The orange bubbles are those with lower certainty of evidence. The blue bubbles are those with higher certainty of evidence.

Vanish study re-analysis

Antcliffe et al., 2019 - *Transcriptomic Signatures in Sepsis and a Differential Response to Steroids. From the VANISH Randomized Trial*

- Patients with the **SRS2** phenotype had worse mortality when receiving corticoids as part of septic shock treatment



Macrophage activation-like syndrom - MALS

= Secondary Hemophagocytic lymphohistocytosis (sHLH)

- fulminant cytokine storm and fatal cause of MODS
- Fever, pancytopenia, tissue hemophagocytosis, liver dysfunction, coagulopathy
- uncontrolled activation and proliferation of macrophages, and T lymphocytes, with a marked increase in circulating cytokines, such as IFN-gamma, and GM-CSF.
- increased levels of Ferritin, IL-6, IL-18, INF- γ , ...
- H Score

Sepsis (defined as total SOFA score ≥ 2 points for new admissions or as increase of total SOFA score ≥ 2 points for hospitalized patients)

		+ either positive HSscore or both HBD and DIC	
HSscore (more than 151 points are needed)		HBD	
	Points	Presence of at least 2 of the following:	
• Infection by HIV or long term immunosuppressive treatment e.g., cyclosporine, glucocorticoids, azathioprine	18	• Serum bilirubin > 2.5 mg/dl	
• Core temperature		• Aspartate aminotransferase $\geq 2 \times$ upper normal limit	
<38.4°C	0	• International normalized ratio (INR) > 1.5	
38.4–39.4°C	1		
>39.5°C	2		
• Organomegaly			
Hepatomegaly or splenomegaly	1		
Hepatomegaly and splenomegaly	2		
• Number of cytopenias			
1 lineage	0		
2 lineages	24		
3 lineages	34		
• Ferritin (ng/ml)			
<2,000	0		
2,000–6,000	35		
>6,000	50		
• Triglycerides (mmol/l)			
<1.5	0		
1.5–4	44		
>4	64		
• Fibrinogen (mg/l)			
>2.5	0		
≤ 2.5	30		
• Serum aspartate aminotransferase (U/l)			
<30	0		
≥ 30	19		

DIC, disseminated intravascular coagulation; HBD, hepatobiliary dysfunction; HIV, human immunodeficiency virus; HS, hemophagocytosis; SOFA, sequential organ failure asses; <, less than; >, more than; \leq , less than or equal to; \geq , more than or equal to.

Macrophage activation-like syndrom - MALS

- Ferritin levels above 4420 ng/ml
- The frequency of MALS was 3.7% and 4.3%
- MALS was an independent risk factor for 10-day mortality
- less than 15% decrease of ferritin on day 3 was associated with more than 90% sensitivity for unfavorable outcome

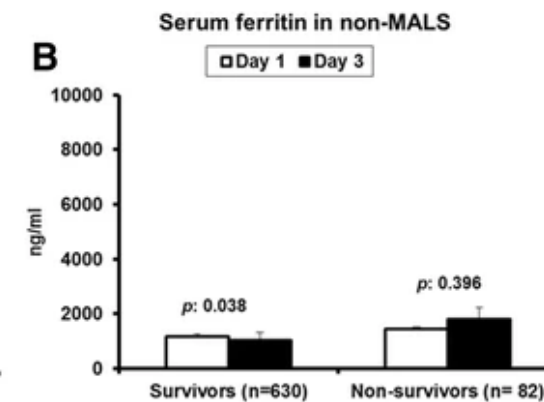
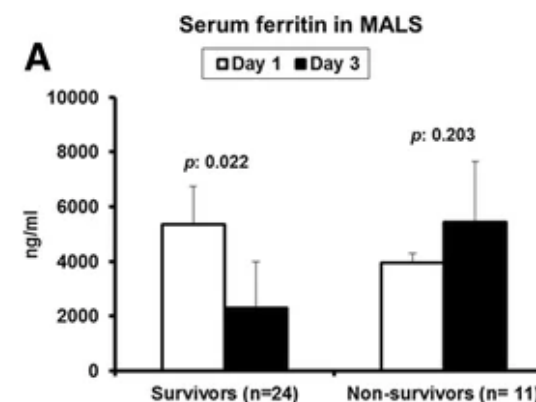
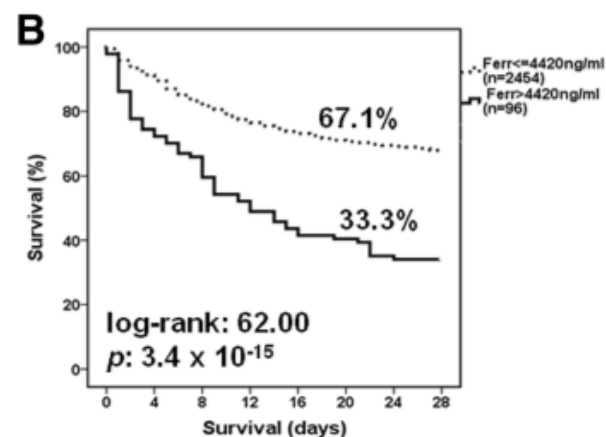
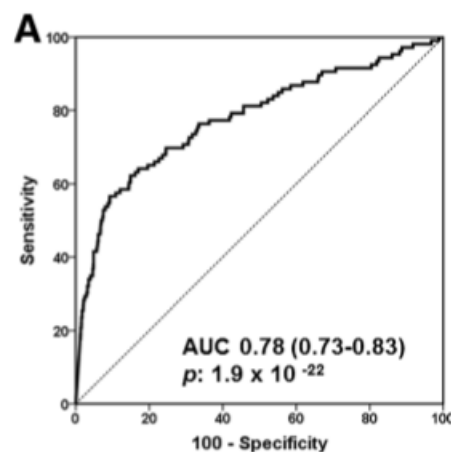
RESEARCH ARTICLE

Open Access

Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis

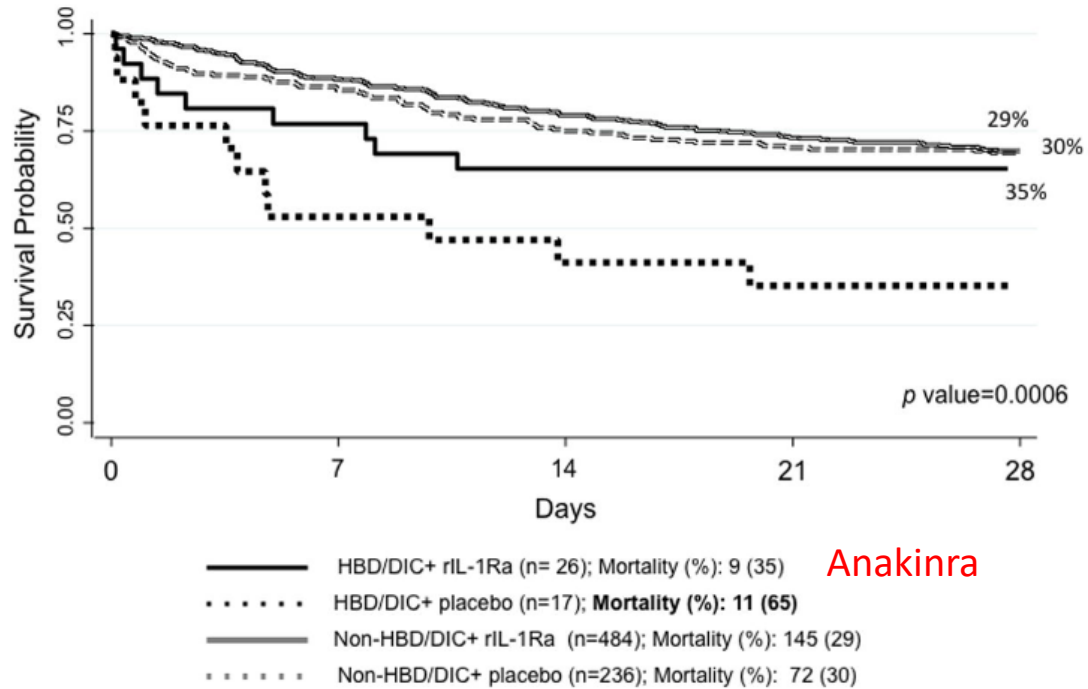


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- *A Trial of Validation and Restoration of Immune Dysfunction in Severe Infections and Sepsis (PROVIDE, NCT03332225) – Athens, Greece – recruitment completed, not yet published.*
 - 3 arms (Anakinra, Recombinant human interferon-gamma, placebo)

Study Re-analysis



Critical care medicine
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Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: Re-analysis of a prior Phase III trial

B. Shakoory, M.D., J.A. Carcillo, M.D., [...], and S.M. Opal, M.D.

- HBD/DIC group (MAS): patients with severe sepsis who demonstrate BOTH hepatobiliary dysfunction and DIC features

Děkuji za pozornost !



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