Monitorování imunitního systému při sepsi

Miroslav Průcha

OKBHI

Nemocnice Na Homolce, Praha

Ostrava 2022

Definice sepse

- Sepsis is now defined as "**life-threatening organ dysfunction caused by a dysregulated host response to infection**."[4] (See Sepsis definitions, 1992-2016.) Sepsis is the result of an infection and encompasses the patient's response to that infection and resulting organ dysfunction.

Monitorování aktuálně

- Nekoná se ??

- Jsou PCT, IL-6, TNF, HLA-DR/CD14, CD64/CD45 biomarkery imunitní odpovědi na infekci?

1,036,071 results

Monitorování v rámci diagnostiky sepse

- BIOMARKERY SEPSE
- „Statimový režim“
- Dostupnost pokud možno 24 hod/7dnů v týdnu
- „Smysluplnost“ prováděných vyšetření (finanční náročnost)
- **Diagnostické a terapeutické konsekvence**

Diagnostika sepse
Infekce vs non-infekce

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Sepsis biomarkers

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[b] University College London Hospitals, 235 Euston Rd, London NW1 2PG, United Kingdom [1]
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Diagnostika sepse

Meta-Analysis › J Cell Biochem. 2019 Apr;120(4):5852-5859. doi: 10.1002/jcb.27870.
Epub 2018 Nov 11.

The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis

Meichun Tan [1], Yunxia Lu [1], Hao Jiang [1], Liandong Zhang [1]

Affiliations + expand

PMID: 30417415 DOI: 10.1002/jcb.27870

Results: At least nine studies were involved in the meta-analysis with 495 patients in the sepsis group and 873 patients in the nonsepsis group. In terms of the diagnostic accuracy of C-reactive protein (CRP) for sepsis, the overall area under the summary receiver operator characteristic (SROC) curve was 0.73 (95% confidence interval [CI], 0.69-0.77), with a sensitivity and specificity of 0.80 (95% CI, 0.63-0.90) and 0.61 (95% CI, 0.50-0.72) respectively, and the DOR was 6.89 (95% CI, 3.86-12.31). In terms of the diagnostic accuracy of procalcitonin (PCT) for sepsis, the overall area under the SROC curve was 0.85 (95% CI, 0.82-0.88), with a sensitivity and specificity of 0.80 (95% CI, 0.69-0.87) and 0.77 (95% CI, 0.60-0.88) respectively, and the DOR was 12.50 (95% CI, 3.65-42.80).

Conclusion: In this meta-analysis, our results together indicate a moderate degree of value of PCT and CRP for the diagnosis of sepsis in adult patients. The diagnosis accuracy and specificity of PCT are higher than those of CRP.

Meta-Analysis > BMC Infect Dis. 2021 Apr 26;21(1):384. doi: 10.1186/s12879-021-06064-0.

Diagnostic value of neutrophil CD64, procalcitonin, and interleukin-6 in sepsis: a meta-analysis

Shan Cong [1], Tiangang Ma [1], Xin Di [1], Chang Tian [1], Min Zhao [1], Ke Wang [2]

Affiliations + expand

PMID: 33902476 PMCID: PMC8072745 DOI: 10.1186/s12879-021-06064-0

Free PMC article

Results: Fifty-four articles were included in the study. The pooled sensitivity, specificity, and AUC of neutrophil CD64 for the diagnosis of sepsis were 0.88 (95% confidence interval [CI], 0.81-0.92), 0.88 (95% CI, 0.83-0.91), and 0.94 (95% CI, 0.91-0.96), respectively. The pooled sensitivity, specificity, and AUC of PCT for the diagnosis of sepsis were 0.82 (95% CI, 0.78-0.85), 0.78 (95% CI, 0.74-0.82), and 0.87 (95% CI, 0.83-0.89), respectively. Subgroup analysis showed that the AUC for PCT diagnosis of intensive care unit (ICU) sepsis was 0.86 (95% CI, 0.83-0.89) and the AUC for PCT diagnosis of non-ICU sepsis was 0.82 (95% CI, 0.78-0.85). The pooled sensitivity, specificity, and AUC of IL-6 for the diagnosis of sepsis were 0.72 (95% CI, 0.65-0.78), 0.70 (95% CI, 0.62-0.76), and 0.77 (95% CI, 0.73-0.80), respectively.

Conclusions: Of the three biomarkers studied, neutrophil CD64 showed the highest diagnostic value for sepsis, followed by PCT, and IL-6. On the other hand, PCT showed a better diagnostic potential for the diagnosis of sepsis in patients with severe conditions compared with that in patients with non-severe conditions.

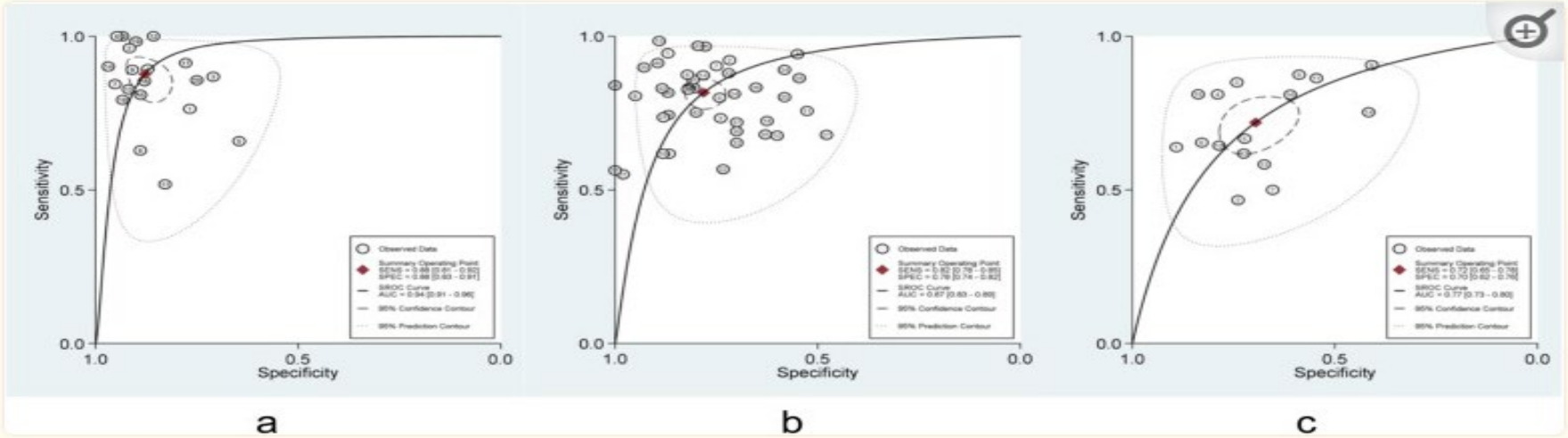
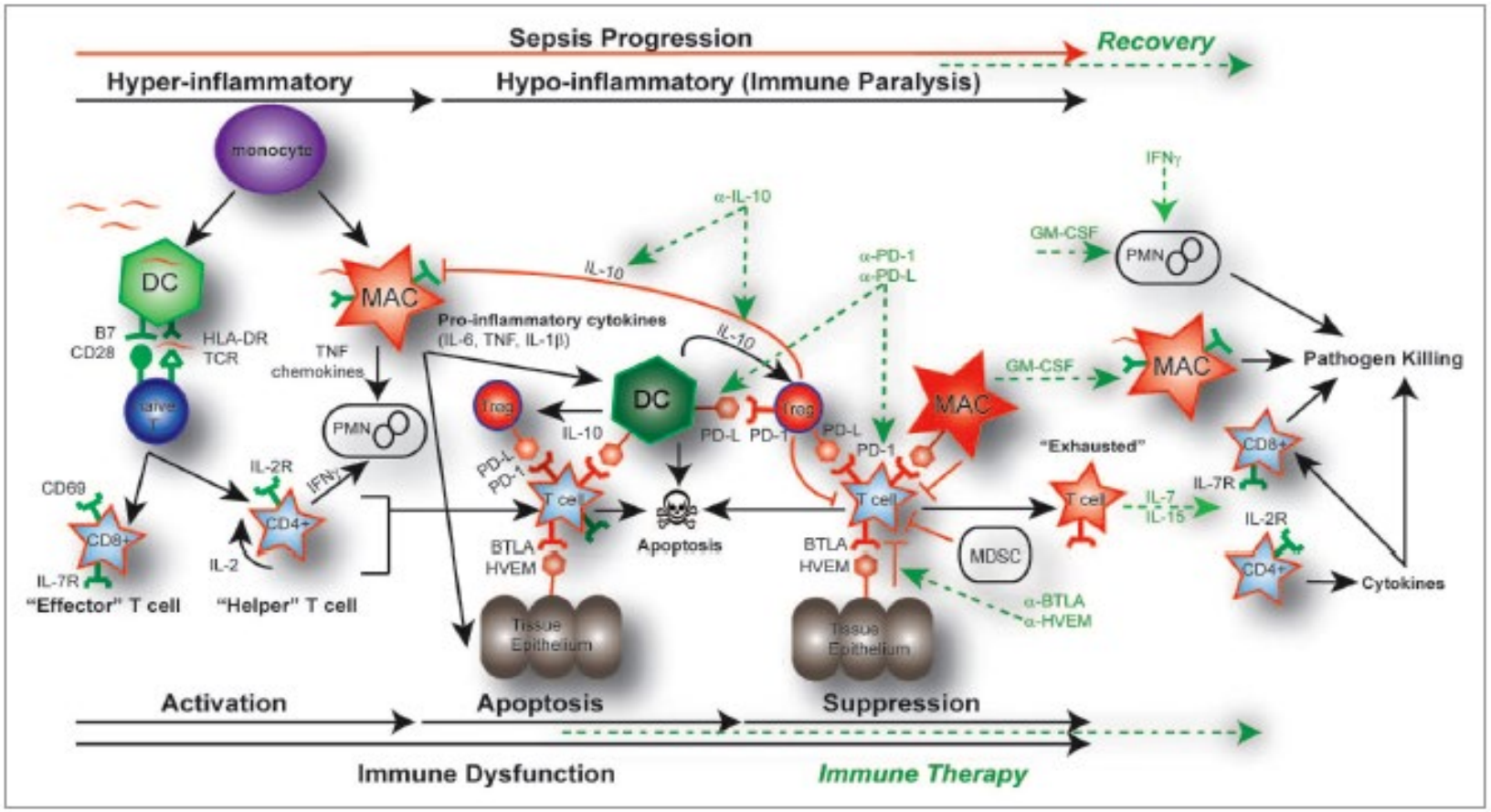


Fig. 3

Summary receiver operator characteristic (SROC) of CD64 (**a**) across 20 studies, PCT (**b**) across 43 studies, and IL-6 (**c**) across 16 studies

Diagnostika imunoparalýzy



Vztah „imunoparalýzy a mortality

Mechanismy imunosuprese u sepse

Table 1. Mechanisms of sepsis-induced immune suppression with immune biomarkers, their measurement modalities and selected immune augmentation therapies.

Immune deficit	Biomarker	Measurement modality	Immune augmentation therapy
Macrophage/monocyte/ dendritic cells			
1. Monocyte deactivation	↓ HLA-DR expression	Flow cytometry, immunohistochemistry	INF-Ɣ, GM-CSF, G-CSF, IL-7, IL-15, Flt3 ligand
	↓ *ex vivo* LPS-induced TNF-α release	Sol TNF-α release by ELISA	
2. ↓ Co-stimulatory receptors	↓ CD80/CD86 – CD28 expression	Flow cytometry, immunohistochemistry	IL-7
3. Negative regulatory pathway	↑ PD-L1 expression	Flow cytometry, immunohistochemistry	Nivolumab (anti-PD-L1 monoclonal antibody), Flt3L

Mechanismy imunosuprese u sepse

Lymphocytes			
1. Lymphopaenia	↓ Circulating levels	Differential full blood count, flow cytometry	IL-7, Flt3 ligand
2. Apoptosis	↑ s-FAS, FAS-L	ELISA	IL-7, IL-15
3. ↑ Suppressor T-cells	↑ CD4+CD25+ (T-reg) lymphocytes	Flow cytometry	
	↑ myeloid depressor T-cells	Flow cytometry	
4. Negative regulatory pathway	↑ CTLA-4 and PD-1 cell surface expression	Flow cytometry, immunohistochemistry	Ipilimumab (anti-CTLA-4 monoclonal antibody)
Enhanced anti-inflammatory cytokine output	↑ TGF-β1, IL-10, IL-1ra TNF/IL-10 ratio	ELISA measurement of individual cytokines or within a cytokine panel	

JAMA Network Open

Original Investigation | Critical Care Medicine

Long-term Host Immune Response Trajectories Among Hospitalized Patients With Sepsis

Sachin Yende, MD, MS; John A. Kellum, MD; Victor B. Talisa, MS; Octavia M. Peck Palmer, PhD; Chung-Chou H. Chang, PhD; Michael R. Filbin, MD, MS; Nathan I. Shapiro, MD, MPH; Peter C. Hou, MD; Arvind Venkat, MD; Frank LoVecchio, MD; Katrina Hawkins, MD; Elliott D. Crouser, MD; Anne B. Newman, MD, MPH; Derek C. Angus, MD, MPH

Patogeneze:
Rozdílné fenotypy imunitní odpovědi

Abstract

IMPORTANCE Long-term immune sequelae after sepsis are poorly understood.

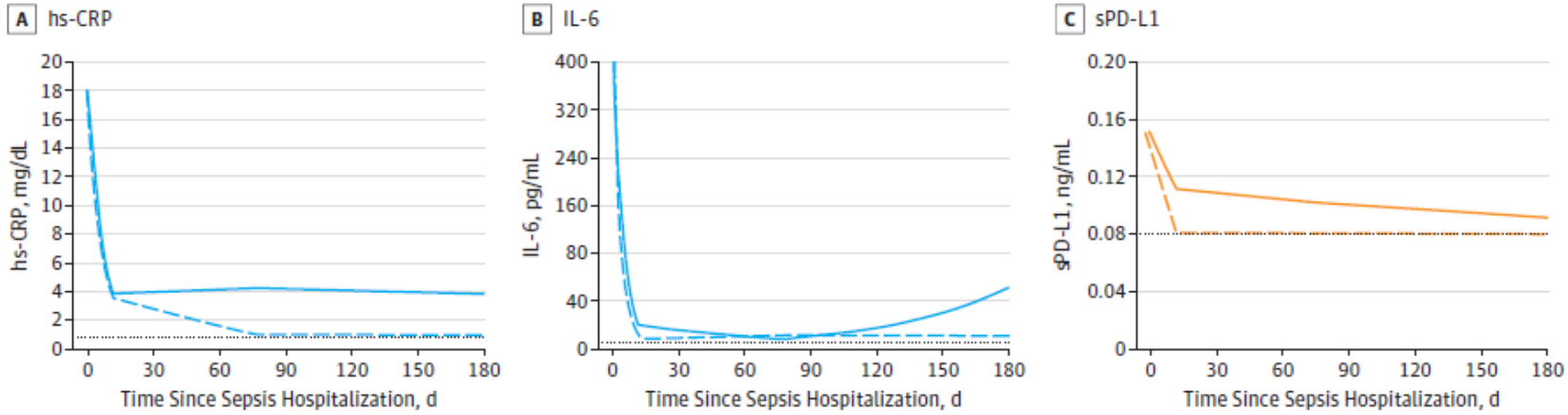
OBJECTIVE To assess whether abnormalities in the host immune response during hospitalization for sepsis persist after discharge.

DESIGN, SETTINGS, AND PARTICIPANTS This prospective, multicenter cohort study enrolled and followed up for 1 year adults who survived a hospitalization for sepsis from January 10, 2012, to May 25, 2017, at 12 US hospitals.

EXPOSURES Circulating levels of inflammation (interleukin 6 and high-sensitivity C-reactive protein [hs-CRP]), immunosuppression (soluble programmed death ligand 1 [sPD-L1]), hemostasis (plasminogen activator inhibitor 1 and D-dimer), endothelial dysfunction (E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1), and oxidative stress biomarkers were measured at 5 time points during and after hospitalization for sepsis for 1 year. Individual biomarker trajectories and patterns of trajectories across biomarkers (phenotypes) were identified.

MAIN OUTCOMES AND MEASURES Outcomes were adjudicated centrally and included all-cause and cause-specific readmissions and mortality.

Figure 2. Latent Trajectory Classes for Biomarkers of Inflammation and Immunosuppression Estimated During 1 Year Using Joint Latent Class Mixture Models (JLCMM)



Horizontal dotted lines represent the estimated 95th percentile of biomarker distribution among individuals without an infection. The solid and dashed lines indicate latent mean longitudinal biomarker trajectories corresponding to the 2 classes identified by separate joint latent class mixture models fit to each set of biomarker data. hs-CRP indicates highly sensitive C-reactive protein; IL, interleukin; and sPD-L1, soluble programmed death ligand 1.

RESULTS A total of 483 patients (mean [SD] age, 60.5 [15.2] years; 265 [54.9%] male) who survived hospitalization for sepsis were included in the study. A total of 376 patients (77.8%) had at least 1 chronic disease, and their mean (SD) Sequential Organ Failure Assessment score was 4.2 (3.0). Readmissions were common (485 readmissions in 205 patients [42.5%]), and 43 patients (8.9%) died by 3 months, 56 patients (11.6%) died by 6 months, and 85 patients (17.6%) died by 12 months. Elevated hs-CRP levels were observed in 23 patients (25.8%) at 3 months, 26 patients (30.2%) at 6 months, and 23 patients (25.6%) at 12 months, and elevated sPD-L1 levels were observed in 45 patients (46.4%) at 3 months, 40 patients (44.9%) at 6 months, and 44 patients (49.4%) at 12 months. Two common phenotypes were identified based on hs-CRP and sPDL1 trajectories: high hs-CRP and sPDL1 levels (hyperinflammation and immunosuppression phenotype [326 of 477 (68.3%)]) and normal hs-CRP and sPDL1 levels (normal phenotype [143 of 477 (30.0%)]). These phenotypes had similar clinical characteristics and clinical course during hospitalization for sepsis. Compared with normal phenotype, those with the hyperinflammation and immunosuppression phenotype had higher 1-year mortality (odds ratio, 8.26; 95% CI, 3.45-21.69; $P < .001$), 6-month all-cause readmission or mortality (hazard ratio [HR], 1.53; 95% CI, 1.10-2.13; $P = .01$), and 6-month readmission or mortality attributable to cardiovascular disease (HR, 5.07; 95% CI, 1.18-21.84; $P = .02$) or cancer (HR, 5.15; 95% CI, 1.25-21.18; $P = .02$). These associations were adjusted for demographic

Otázky:
Genetická predispozice, přidružené faktory…

CONCLUSIONS AND RELEVANCE In this study, persistent elevation of inflammation and immunosuppression biomarkers occurred in two-thirds of patients who survived a hospitalization for sepsis and was associated with worse long-term outcomes.

JAMA Network Open. 2019;2(8):e198686. doi:10.1001/jamanetworkopen.2019.8686

Table 3. Association Between the Hyperinflammation and Immunosuppression and Normal Phenotypes and Long-term Outcomes

Variables	No. of Events/No. at Risk (%)		Adjusted OR, HR, or SHR (95% CI)[a]	P Value
	Hyperinflammation and Immunosuppression Phenotype	Normal Phenotype		
All-cause 1-y mortality	77/326 (23.4)	6/141 (4.3)	8.26 (3.45-21.69)	<.001
All-cause readmission or death, d				
0-180	144/326 (44.2)	48/141 (34.0)	1.53 (1.10-2.13)	.01
181-365	30/182 (16.5)	15/93 (16.1)	1.18 (0.64-2.20)	.59
Readmission or death due to infection, d				
0-180	79/326 (24.2)	27/141 (19.1)	1.35 (0.87-2.10)	.18
181-365	22/217 (10.1)	5/114 (4.5)	2.00 (0.75-5.36)	.17
Readmission or death due to cardiovascular disease, d				
0-180	22/326 (6.7)	2/141 (1.4)	5.07 (1.18-21.84)	.02
180-365	6/258 (2.3)	7/139 (5.0)	0.42 (0.14-1.28)	.13
Readmission or death due to cancer, d				
0-180	25/326 (7.7)	2/141 (1.4)	5.15 (1.25-21.18)	.02
180-365	7/269 (2.6)	5/139 (3.6)	0.67 (0.20-2.27)	.53

Abbreviations: HR, hazard ratio; OR, odds ratio; SHR, subdistribution hazard ratio.

[a] The ORs were estimated using logistic regression model for all-cause 1-year mortality. The HRs were estimated using a Cox proportional hazards regression model for all-cause 1-year readmission or death. The SHRs were estimated using the Fine-Gray model for cause-specific analyses of death or readmission. Covariates included age, sex, race/ethnicity, Charlson Comorbidity Index score, APACHE II score, infection site, mechanical ventilatory support, vasopressor use, and dialysis.

Otázky

- Jak intenzivně a „rozumně“ pacienty se sepsí monitorovat?
- Věk, komorbidity…

- Je to nutné ve vztahu k mortalitě v některých zemích??
- Úroveň intenzivní péče…..
- Australská studie …

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

IMPORTANCE Severe sepsis and septic shock are major causes of mortality in intensive care unit (ICU) patients. It is unknown whether progress has been made in decreasing their mortality rate.

OBJECTIVE To describe changes in mortality for severe sepsis with and without shock in ICU patients.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, observational study from 2000 to 2012 including 101 064 patients with severe sepsis from 171 ICUs with various patient case mix in Australia and New Zealand.

MAIN OUTCOMES AND MEASURES Hospital outcome (mortality and discharge to home, to other hospital, or to rehabilitation).

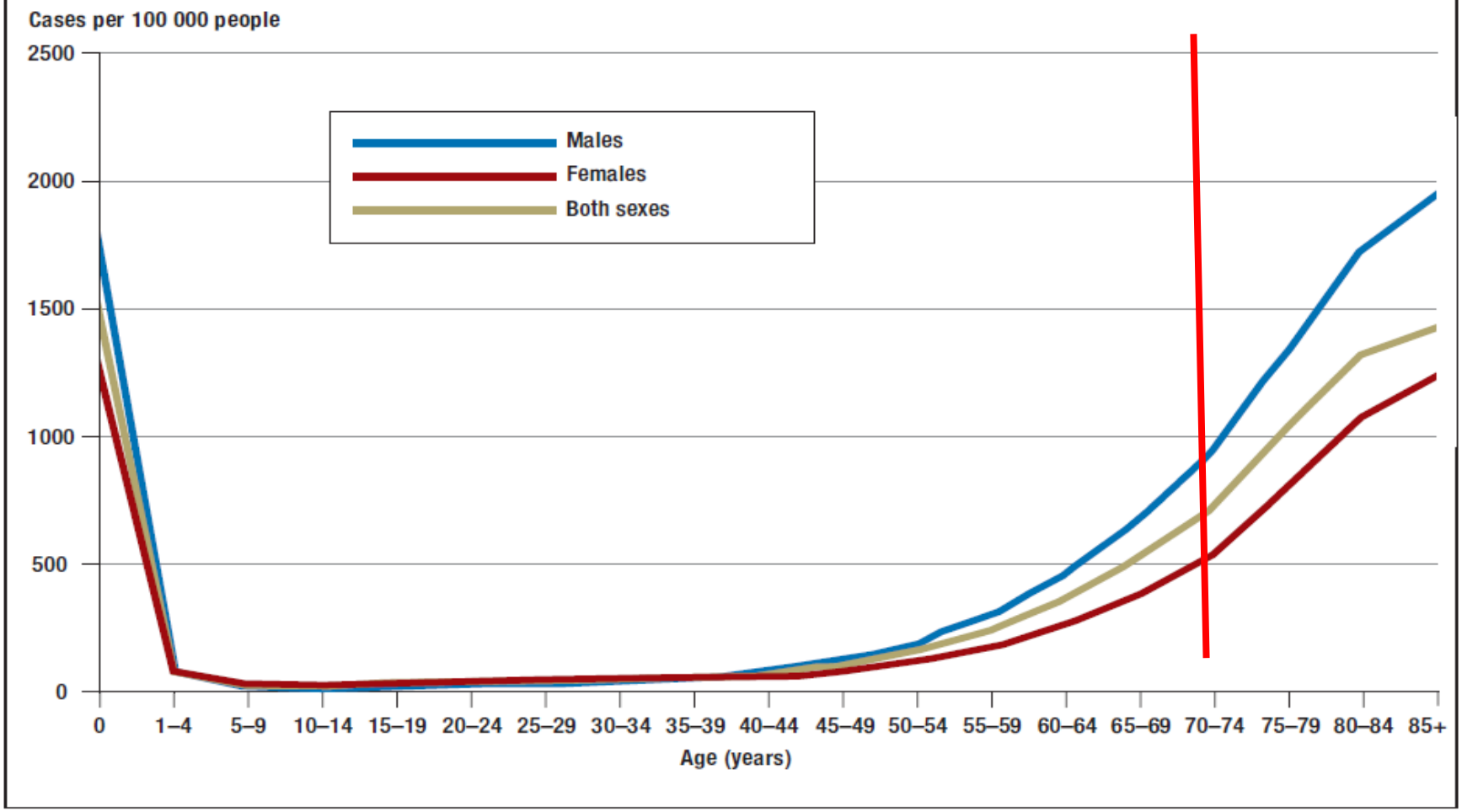
RESULTS Absolute mortality in severe sepsis decreased from 35.0% (95% CI, 33.2%-36.8%; 949/2708) to 18.4% (95% CI, 17.8%-19.0%; 2300/12 512; $P < .001$), representing an overall decrease of 16.7% (95% CI, 14.8%-18.6%), an annual rate of absolute decrease of 1.3%, and a relative risk reduction of 47.5% (95% CI, 44.1%-50.8%). After adjusted analysis, mortality decreased throughout the study period with an odds ratio (OR) of 0.49 (95% CI, 0.46-0.52)

Editorial page 1295

Supplemental content at jama.com

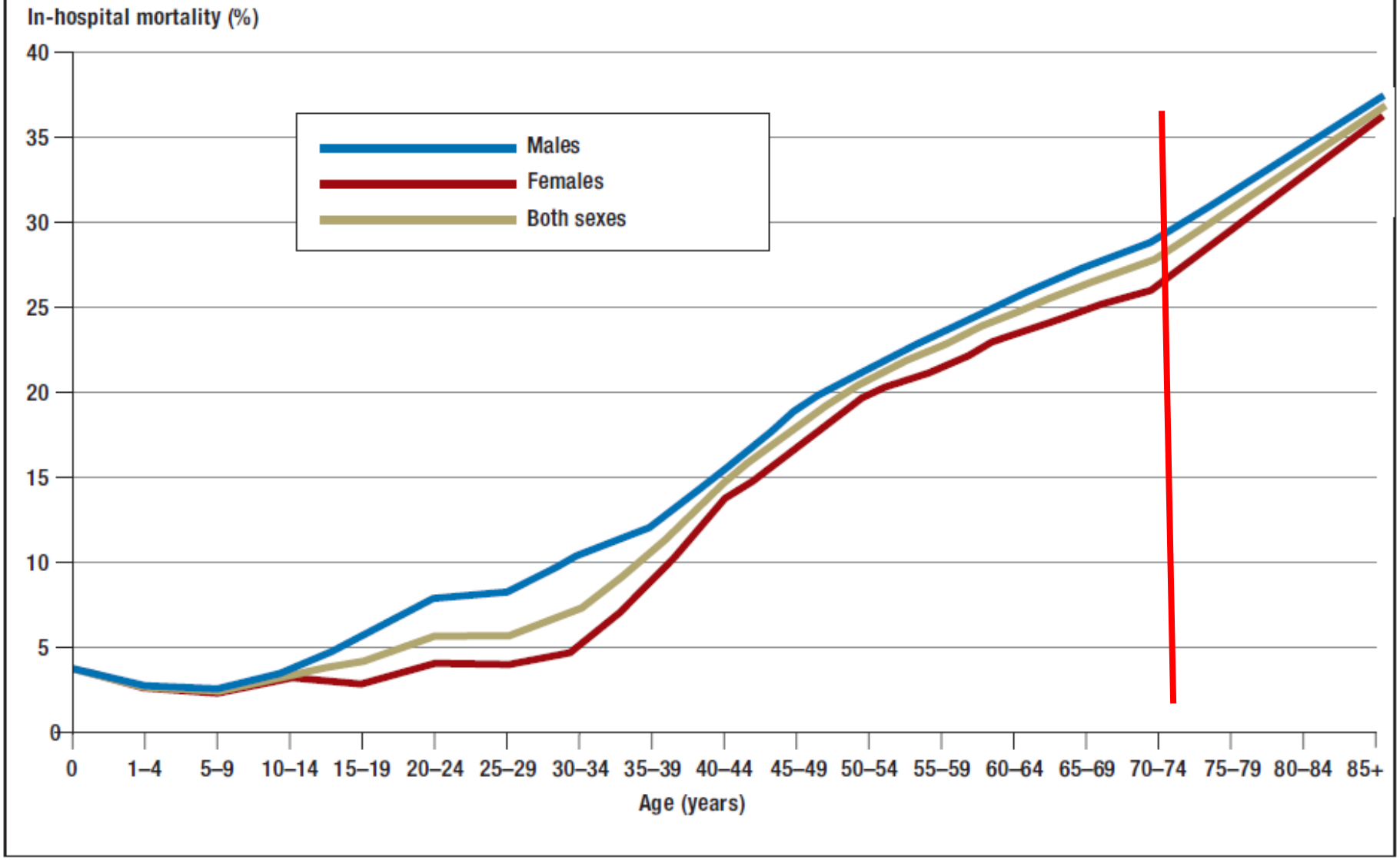
Senescence imunitního systému, komorbidity … Analogie COVID-19

FIGURE 2



In-hospital incidence of sepsis per 100 000 persons per year, by age group and sex, in the period 2007–2013 (clinical and pathogen-based sepsis codes)

FIGURE 3



In-hospital mortality of patients with sepsis, by age group and sex, in the period 2007–2013 (clinical and pathogen-based sepsis codes)

Monitorace všech?

Research | Open Access | Published: 20 June 2015

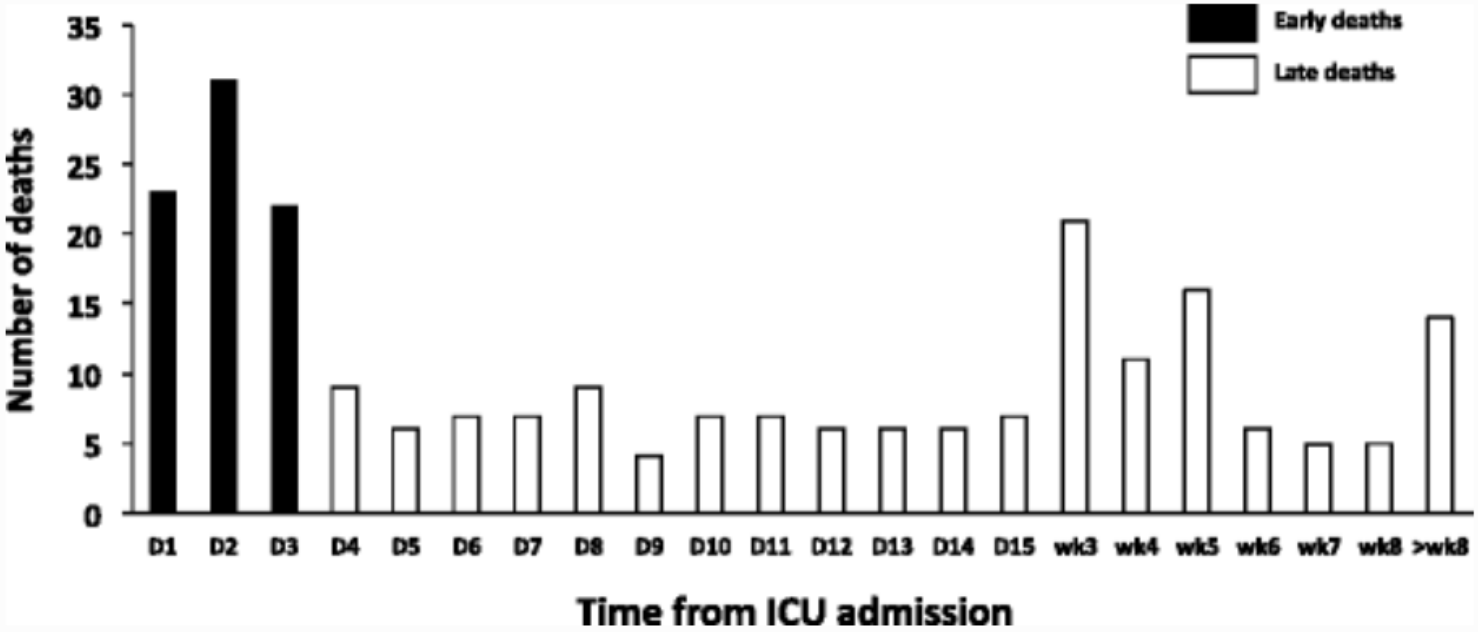
Timing and causes of death in septic shock

Fabrice Daviaud, David Grimaldi, Agnès Dechartres, Julien Charpentier, Guillaume Geri, Nathalie Marin, Jean-Daniel Chiche, Alain Cariou, Jean-Paul Mira & Frédéric Pène

Annals of Intensive Care **5**, Article number: 16 (2015) | Cite this article

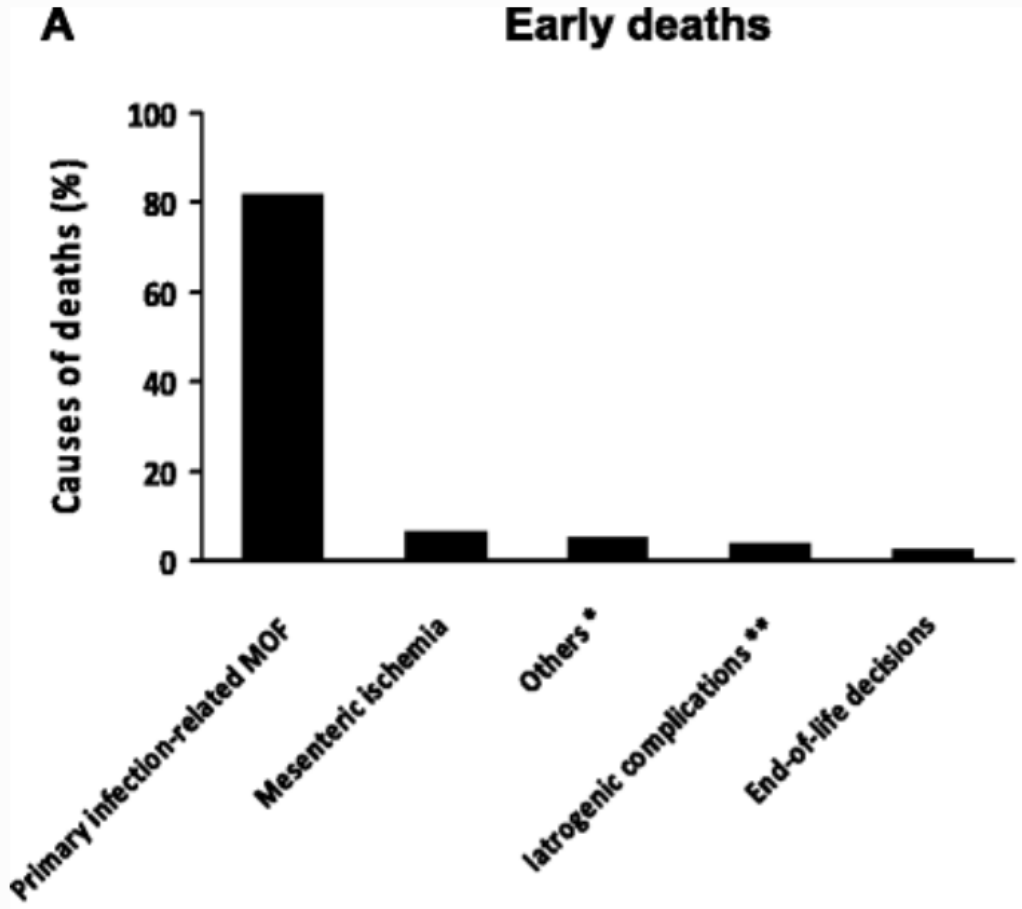
V závislosti na „rizikovosti“ pacienta ……..komorbidity , imunosuprese, biologická léčba

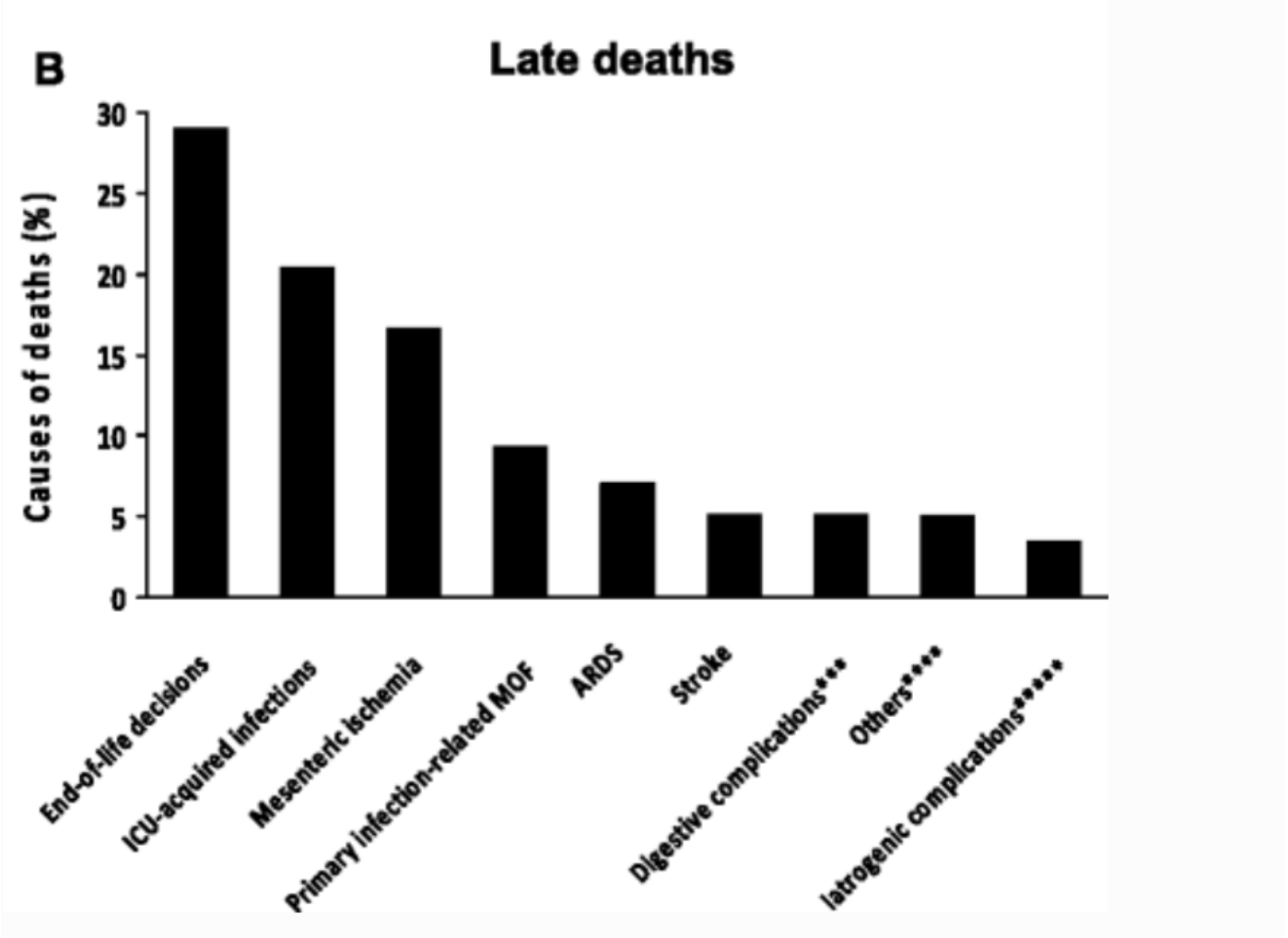
Fig. 2



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

Fig. 3


A
Early deaths
Causes of deaths (%)
100
80
60
40
20
0
Primary infection-related MOF
Mesenteric ischemia
Others *
Iatrogenic complications **
End-of-life decisions


B
Late deaths
Causes of deaths (%)
30
25
20
15
10
5
0
End-of-life decisions
ICU-acquired infections
Mesenteric ischemia
Primary infection-related MOF
ARDS
Stroke
Digestive complications***
Others****
Iatrogenic complications*****

J Infect. 2014 Mar;68(3):297-9. doi: 10.1016/j.jinf.2013.11.003. Epub 2013 Nov 15.

Presence of hypogammaglobulinemia in patients with severe sepsis, septic shock, and SIRS is associated with increased mortality

M Prucha [1], R Zazula [2], I Herold [3], M Dostal [4], T Hyanek [5], G Bellingan [6]

Affiliations + expand

PMID: 24239873 DOI: 10.1016/j.jinf.2013.11.003

Table 1 – Baseline characteristics of the patients

Diagnosis	Sex		Age (years)	PCT (med) (ng/ml)	CRP (mg/ml)	Apache II	Mortality (%)
	M	F					
SIRS (211)	143	68	62.3 ± 17	0.71	85	15 ± 6	9
Severe sepsis (452)	290	162	65.8 ± 14	2.83	126.1	21 ± 7	37.8
Septic shock (45)	29	16	67.3 ± 12	12.3	172.3	25 ± 10	42.8

PCT – procalcitonin; CRP – C-reactive protein; Apache II – acute physiology and chronic health evaluation II

Table 2 – Site of infection

Source of infection	n
Lung	233
Abdomen	138
Urinary	85
CNS	12
Catheter	29

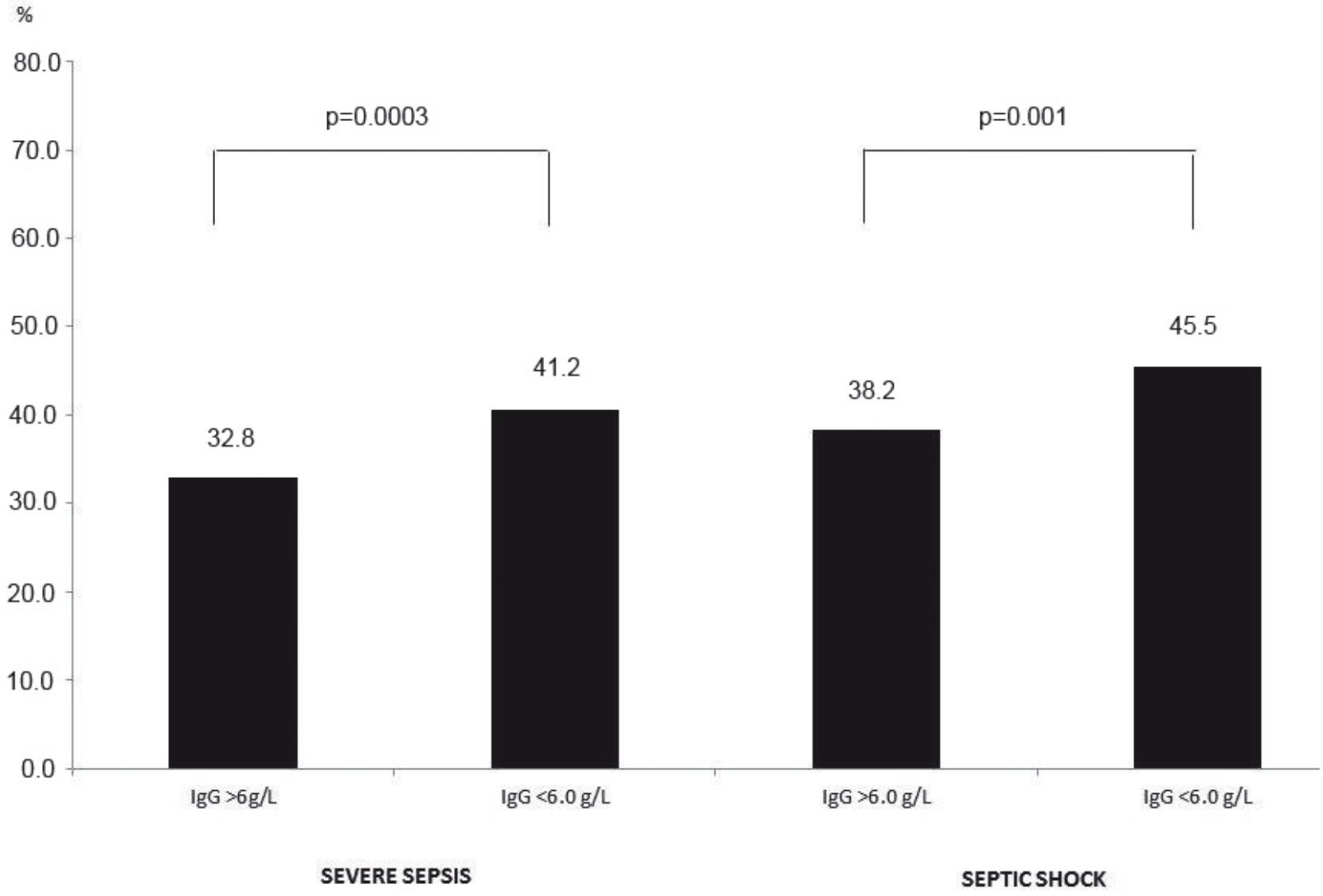


Figure 1 – Mortality of patients with hypogammaglobulinemia IgG.

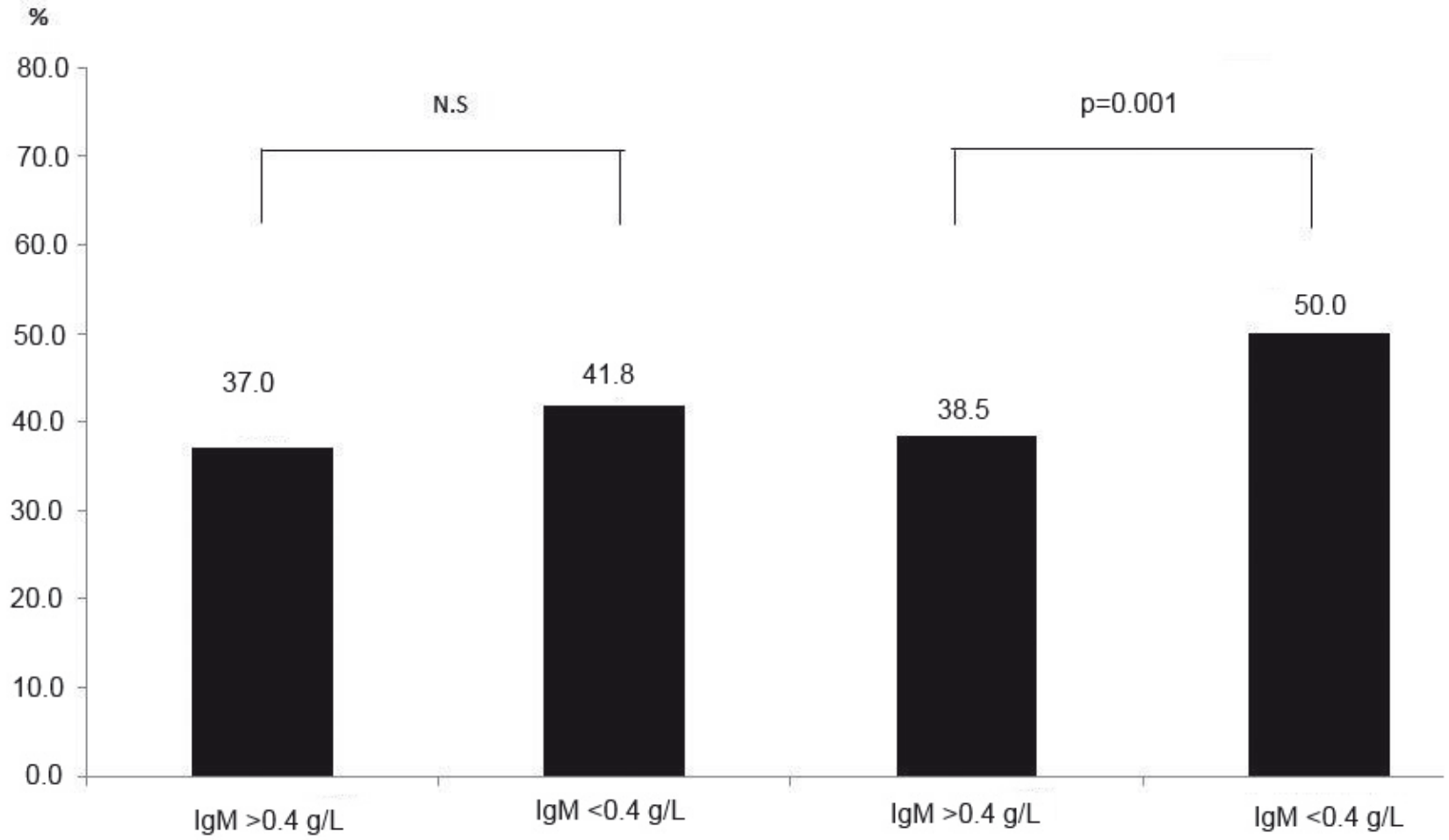


Figure 2 – Mortality of patients with hypogammaglobulinemia IgM.

Research | Open Access | Published: 06 February 2019

The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis

Jie Cui, Xuxia Wei, Haijin Lv, Yuntao Li, Ping Li, Zhen Chen ✉ & Genglong Liu ✉

Annals of Intensive Care **9**, Article number: 27 (2019) | Cite this article

Results

Nineteen studies comprising 1530 patients were included in this meta-analysis. Pooled analyses showed that the use of IVIgGM reduced the mortality risk of septic patients (relative risk 0.60; 95% confidence interval [CI] 0.52–0.69, I^2 = 0%). TSA showed that IVIgGM had a significant effect on mortality. Additionally, the meta-analysis suggested that use of IVIgGM shortened length of mechanical ventilation (mean difference – 3.16 days; 95% CI – 5.71 to – 0.61 days) and did not shorten length of stay in the intensive care unit (mean difference – 0.38 days; 95% CI – 3.55 to 2.80 days). The GRADE scale showed that the certainty of the body of evidence was low for both benefits and IVIgGM.

Conclusion

Administration of IVIgGM to adult septic patients may be associated with reduced mortality. Treatment effects tended to be smaller or less consistent when including only those studies deemed adequate for each indicator. The available evidence is not clearly sufficient to support the widespread use of IVIgGM in the treatment of sepsis.

Trial registration PROSPERO registration number: CRD42018084120. Registered on 11

frontiers in Medicine

REVIEW
published: 18 February 2021
doi: 10.3389/fmed.2021.616511

Adjunctive Immunotherapy With Polyclonal Ig-M Enriched Immunoglobulins for Septic Shock: From Bench to Bedside. The Rationale for a Personalized Treatment Protocol

Stefano Busani[1], Erika Roat[1], Martina Tosi[1], Emanuela Biagioni[1], Irene Coloretti[1], Marianna Meschiari[2], Roberta Gelmini[3], Lucio Brugioni[4], Sara De Biasi[5] and Massimo Girardis[1]

Nierhaus et al. Ann. Intensive Care (2020) 10:132
https://doi.org/10.1186/s13613-020-00740-1

Annals of Intensive Care

REVIEW Open Access

Best-practice IgM- and IgA-enriched immunoglobulin use in patients with sepsis

Axel Nierhaus[1,2*], Giorgio Berlot[3], Detlef Kindgen-Milles[4], Eckhard Müller[5] and Massimo Girardis[6]

Main text: Sepsis patients with hyperinflammation and patients with immunosuppression may benefit most from treatment with IgM- and IgA-enriched immunoglobulin (Pentaglobin). Patients with hyperinflammation present with phenotypes that manifest throughout the body, whilst the clinical characteristics of immunosuppression are less clear. Potential biomarkers for hyperinflammation include elevated procalcitonin, interleukin-6, endotoxin activity and C-reactive protein, although thresholds for these are not well-defined. Convenient biomarkers for identifying patients in a stage of immune-paralysis are still matter of debate, though human leukocyte antigen–antigen D related expression on monocytes, lymphocyte count and viral reactivation have been proposed. The timing of treatment is potentially more critical for treatment efficacy in patients with hyperinflammation compared with patients who are in an immunosuppressed stage. Due to the lack of evidence, definitive dosage recommendations for either population cannot be made, though we suggest that patients with hyperinflammation should receive an initial bolus at a rate of up to 0.6 mL (30 mg)/kg/h for 6 h followed by a continuous maintenance rate of 0.2 mL (10 mg)/kg/hour for ≥ 72 h (total dose ≥ 0.9 g/kg). For immunosuppressed patients, dosage is more conservative (0.2 mL [10 mg]/kg/h) for ≥ 72 h, without an initial bolus (total dose ≥ 0.72 g/kg).

Conclusions: Two distinct populations that may benefit most from Pentaglobin therapy are described in this review. However, further clinical evidence is required to strengthen support for the recommendations given here regarding timing, duration and dosage of treatment.

Keywords: Immunoglobulin, IgM- and IgA-enriched immunoglobulin, Sepsis, Pentaglobin, Hyperinflammation, Immunosuppression

Honore *et al. Ann. Intensive Care* (2019) 9:56
https://doi.org/10.1186/s13613-019-0530-y

Annals of Intensive Care

REVIEW Open Access

Cytokine removal in human septic shock: Where are we and where are we going?

Patrick M. Honore[1*], Eric Hoste[2], Zsolt Molnár[3], Rita Jacobs[4], Olivier Joannes-Boyau[5], Manu L. N. G. Malbrain[4,6] and Lui G. Forni[7,8]

Abstract

Although improving, the mortality from septic shock still remains high despite increased international awareness. As a consequence, much effort has focused on alternative treatment strategies in an effort to improve outcomes. The application of blood purification therapies to improve immune homeostasis has been suggested as one such method, but these approaches, such as high-volume continuous haemofiltration or cytokine and/or endotoxin removal, have enjoyed little success to date. More recently, the use of sorbent technologies has attracted much attention. These adsorbers are highly effective at removing inflammatory mediators, in particular, cytokines, from the bloodstream. This narrative review is the executive summary of meetings held throughout the 6th International Fluid Academy Days in Antwerp, Belgium (Nov 23–25, 2017), focusing on the current understanding regarding the use of such adsorbers in humans with septic shock. We followed a modified Delphi approach involving a combination of evidence appraisal together with expert opinion in order to achieve recommendations for practice and, importantly, future research.

Keywords: Blood purification, Cytokines, Sepsis, Septic shock, Haemoperfusion, Cytosorb, Sorbents, Cartridges, Immune modulation, DAMPS, PAMPS

BLÍZKÁ FUTUROLOGIE???

NEWS | 04 June 2021

A complete human genome sequence is close: how scientists filled in the gaps

Researchers added 200 million DNA base pairs and 115 protein-coding genes — but they've yet to entirely sequence the Y chromosome.

Now, researchers in the Telomere-to-Telomere (T2T) Consortium, an international collaboration that comprises around 30 institutions, have filled in those gaps. In a 27 May preprint[1] entitled 'The complete sequence of a human genome', genomics researcher Karen Miga at the University of California, Santa Cruz, and her colleagues report that they've sequenced the remainder, in the process discovering about 115 new genes that code for proteins, for a total of 19,969.

Data

- **Geny kódující proteiny tvoří cca 1% lidského genomu !!!**
- **1 gen kódující protein v průměru vede ke vzniku 3 proteinů – cca 70% genů**
- **U genetických polymorfismů se jedná až o 100 proteinů!**

Technical Specifications

Augment your study with the
world's most impactful protein assay

Largest Menu

7,000 Proteins

Highly Reproducible

~5% CV

Ultra High-Throughput

1000 Samples a day

High And Low Abundance Proteins

10-Log Range

International Journal of
Molecular Sciences

MDPI

Article

Genetic Predisposition to the Mortality in Septic Shock Patients: From GWAS to the Identification of a Regulatory Variant Modulating the Activity of a *CISH* Enhancer

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Abstract: The high mortality rate in septic shock patients is likely due to environmental and genetic factors, which influence the host response to infection. Two genome-wide association studies (GWAS) on 832 septic shock patients were performed. We used integrative bioinformatic approaches to annotate and prioritize the sepsis-associated single nucleotide polymorphisms (SNPs). An association of 139 SNPs with death based on a false discovery rate of 5% was detected. The most significant SNPs were within the *CISH* gene involved in cytokine regulation. Among the 139 SNPs associated with death and the 1311 SNPs in strong linkage disequilibrium with them, we investigated 1439 SNPs within non-coding regions to identify regulatory variants. The highest integrative weighted score (IW-score) was obtained for rs143356980, indicating that this SNP is a robust regulatory candidate. The rs143356980 region is located in a non-coding region close to the *CISH* gene. A CRISPR-Cas9-mediated deletion of this region and specific luciferase assays in K562 cells showed that rs143356980 modulates the enhancer activity in K562 cells. These analyses allowed us to identify several genes associated with death in patients with septic shock. They suggest that genetic variations in key genes, such as *CISH*, perturb relevant pathways, increasing the risk of death in sepsis patients.

Keywords: sepsis; GWAS; SNPs; non coding region; *CISH*; enhancer; CRISPR-Cas9; luciferase assay

832 pacientů se septickým šokem, asociace se SNP u zemřelých….u 139, nejsilnější u CISH genu (Cytokiny indukovatelný protein obsahující SH2), ve vazbě na něj dalších 1311 SNPs v nekódující oblasti. Vyšetřili celkem 1439 SNPs a největší významzjistili u rs143356980… použili editační nůžky CRISPr-Cas9, následně použili v in vitro pokusu na K562 bb a potvrdili biologickou účinnost!!

For survival between day 7 and day 28, the leader SNPs were rs359952, rs17442970, rs6692946, rs1509380, rs2239753, rs17072628, rs9856368, rs6852672, rs12654328, rs7726677, rs3797817, rs6910170, rs11987625, rs11994554, rs7840669, rs3005838, rs7096890, rs4575240, rs7953683, rs1882182, rs527603, rs7992136, rs4646220, rs1756650, rs7178141, rs2340518, rs1434590, rs7214197, rs1502522, rs4381690, rs17271418, and rs2232619**. The results show that individuals with four or more risk alleles have a death risk 123.35-fold higher than those with no risk alleles (adjusted OR = 123.35, 95% CI 23.64–2292**

Závěry

- Výběr a stratifikace pacientů – „conditio sine qua non“
- Klinický fenotyp – pacienti s imunosupresí, biologickou léčbou……..
- Fenotyp prozánětlivý a imunosuprimovaný
- Aktuálně monitorování vybraných parametrů – cytokiny, HLA-DR/CD14, Ig

Závěr

Monitorování imunitní odpovědi na infekci provádět individuálně na základě klinického vyhodnocení stavu pacienta, protože má praktický význam pro stratifikaci pacientů a imunomodulační terapii

Děkuji za pozornost