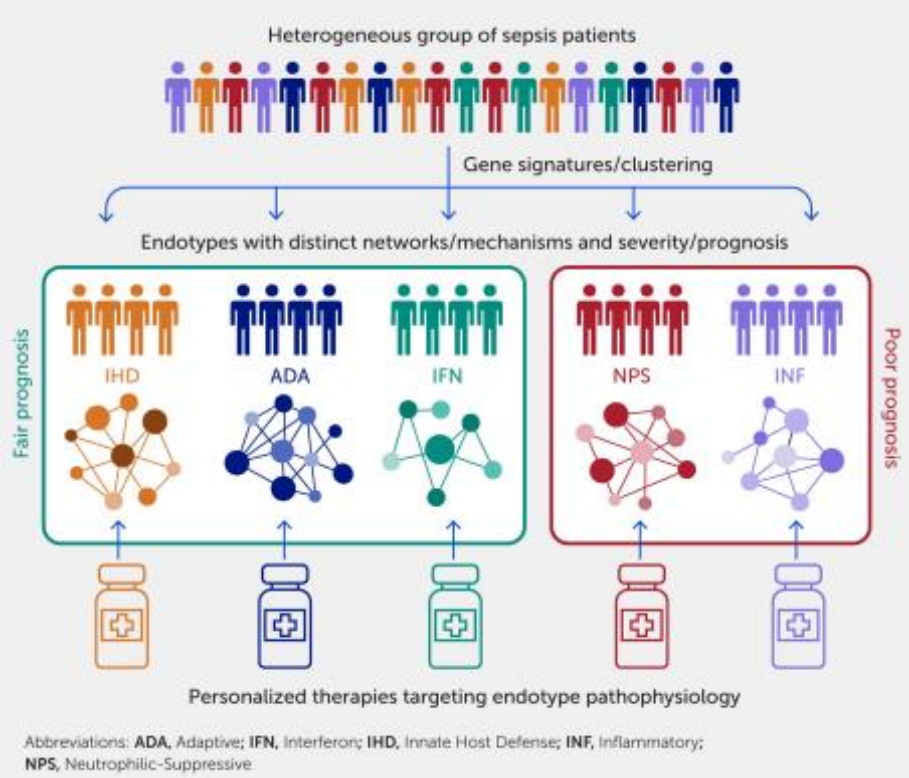
ENDOTIPI IN SEPSA



Matej Mavrič, dr. med.

KLINIKA ZA INFEKCIJSKE BOLEZNI IN VROČINSKA STANJA, ODDELEK ZA INTENZIVNO TERAPIJO

UNIVERZITETNI KLINIČNI CENTER LJUBLJANA

Strokovno srečanje ob svetovnem dnevu sepse, 11.9.2025, Ljubljana

Sepsis-3: ***…Sepsa je življenje ogrožajoče stanje z okvaro organov kot posledica disreguliranega imunskega odgovora na okužbo …***

…Sepsa je življenje ogrožajoče stanje z okvaro organov…

INTENZIVNO PODPORNO ZDRAVLJENJE

…kot posledica disreguliranega imunskega odgovora…

USMERJENO (?) ZDRAVLJENJE Z VPLIVOM NA IMUNSKI SISTEM

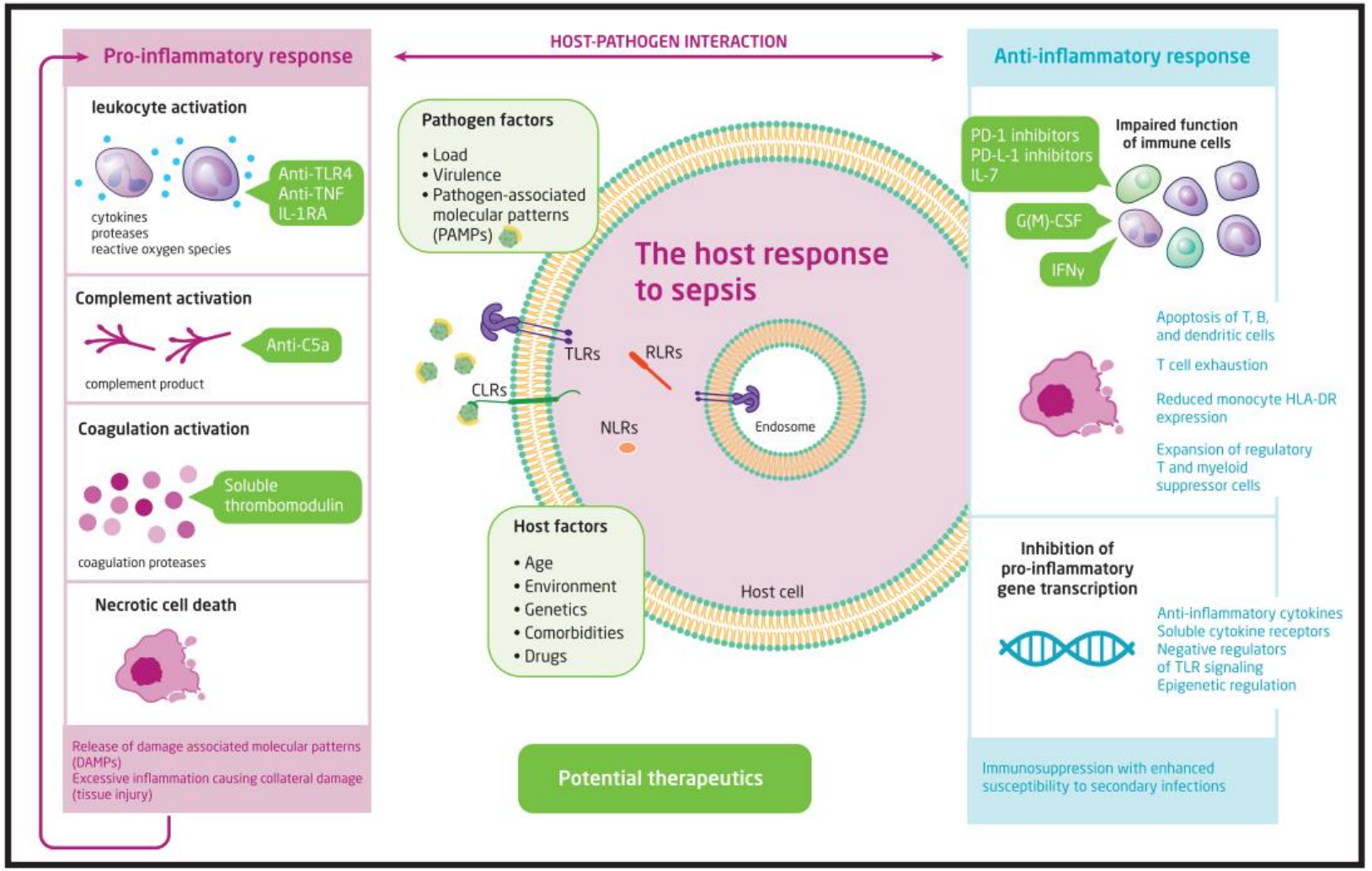
…na okužbo.

ZGODNJA ANTIBIOTIČNA TERAPIJA
+
ODSTRANITEV VSEH VNETIH ŽARIŠČ
(„source-control“)

Imunopatogeneza sepse

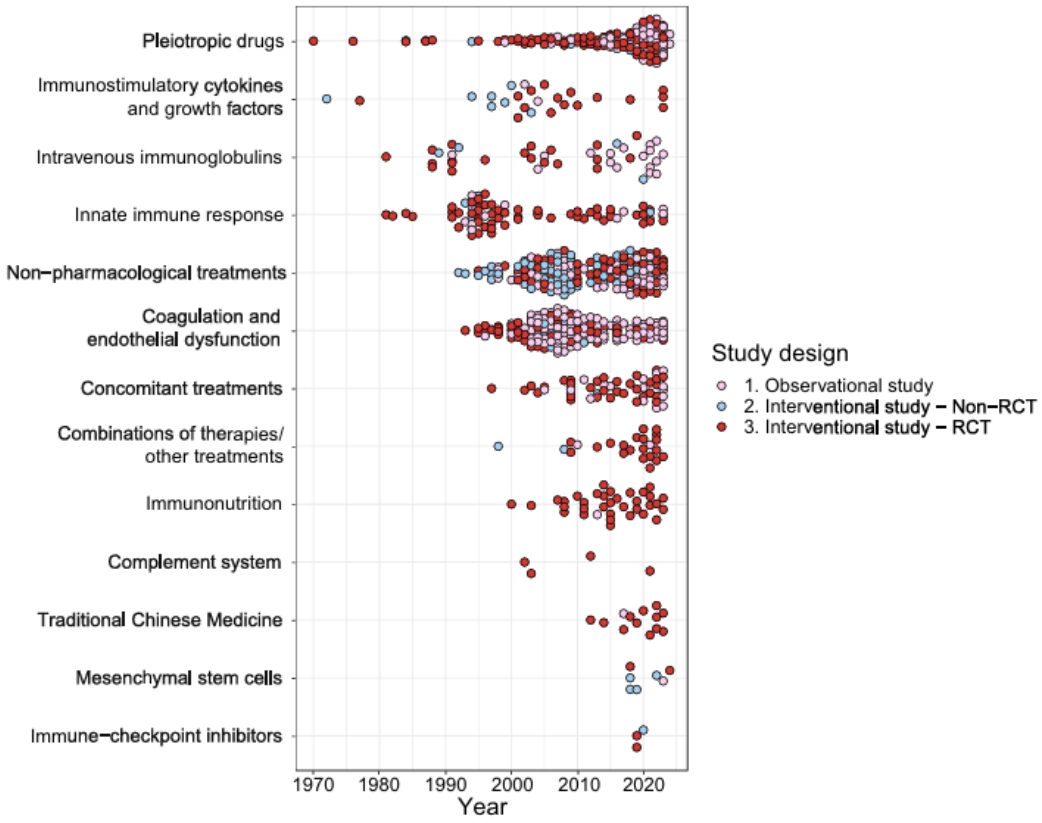
Klinični potek sepse je odvisen od ravnotežja med pro-vnetnim in proti-vnetnim odzivom, ki se razlikuje med posamezniki.

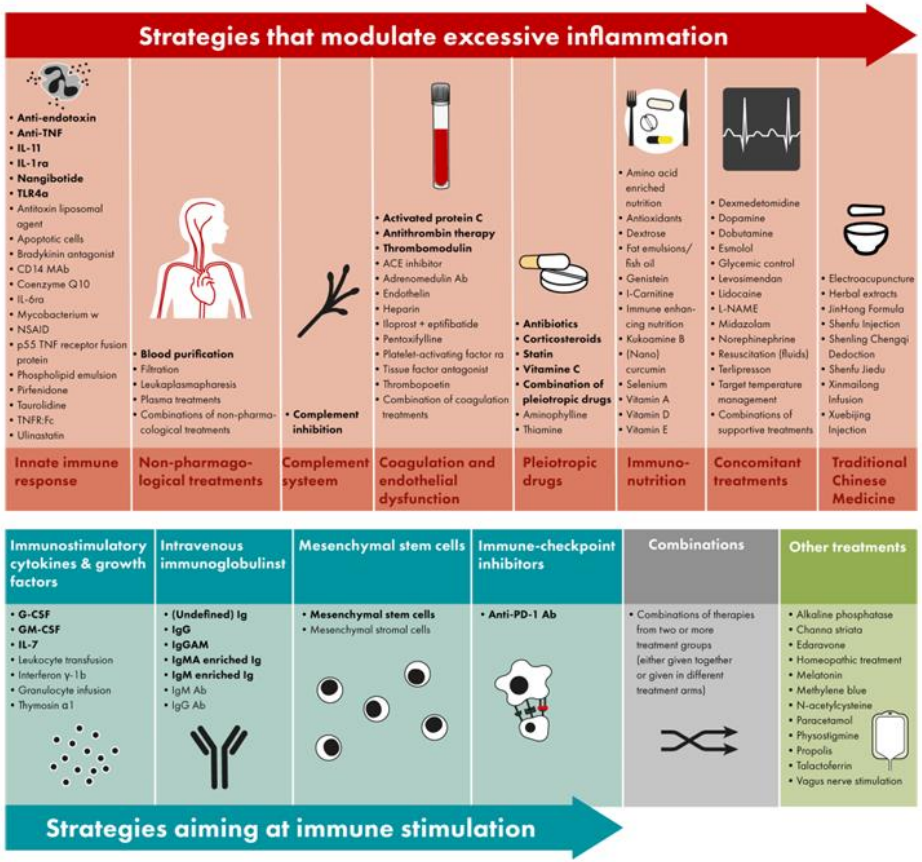
Obseg imunskega odziva posameznika je povezan z interakcijo med dejavniki na strani povzročitelja in gostitelja.



van der Poll T, et al. Immunity, 2021. PMID: 34758337.

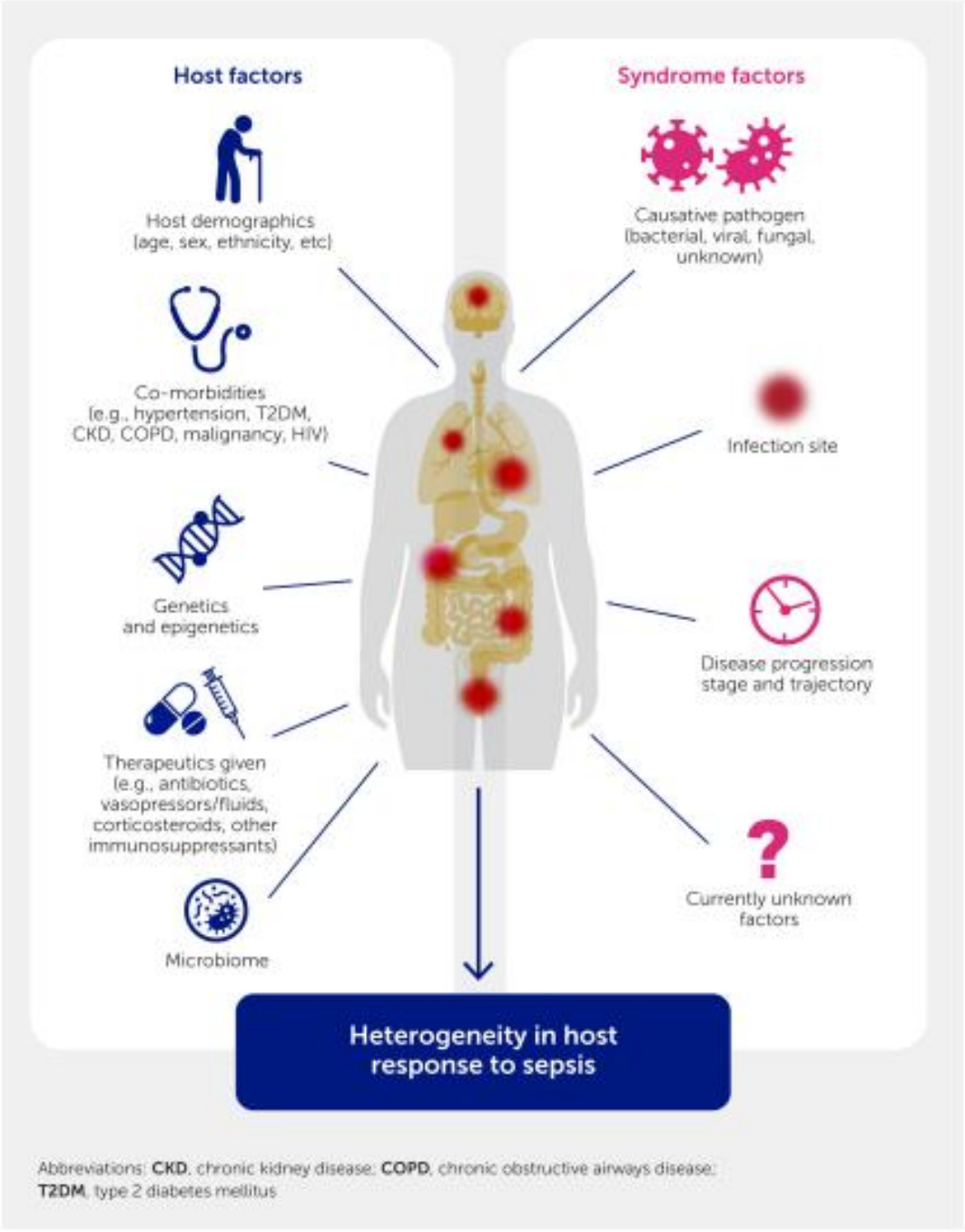
Zakaj sepse ne zdravimo z zdravili, ki vplivajo na imunski odziv posameznika?





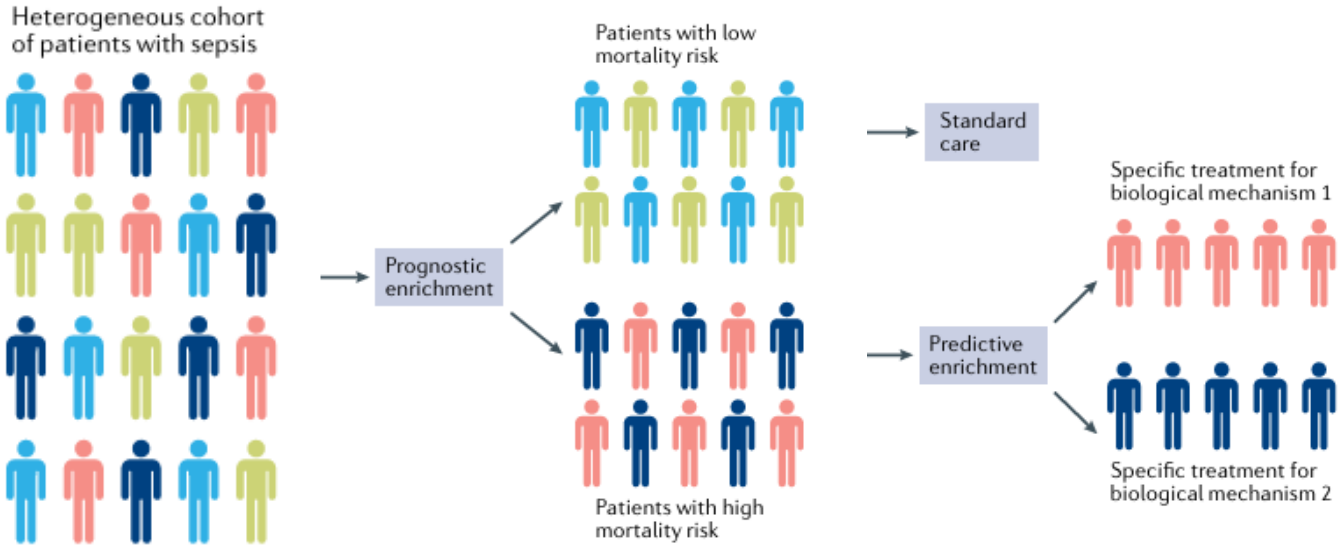
ZAKLJUČEK: rezultati nasprotujoči (pozitivni izidi v opazovalnih raziskavah, ki jih ni moč potrditi z intervencijskimi raziskavami), ob uporabi personaliziranega pristopa se kaže trend koristi posameznih terapij.

Slim MA, et al. Crit Care, 2024. PMID: 38807151.



Problem dosedanjih raziskav: SEPSA = HETEROGENA BOLEZEN

Kako premagati problem heterogenosti?



Stanski NL, Wong HR, Nat Rev Nephrol, 2020. PMID: 31511662

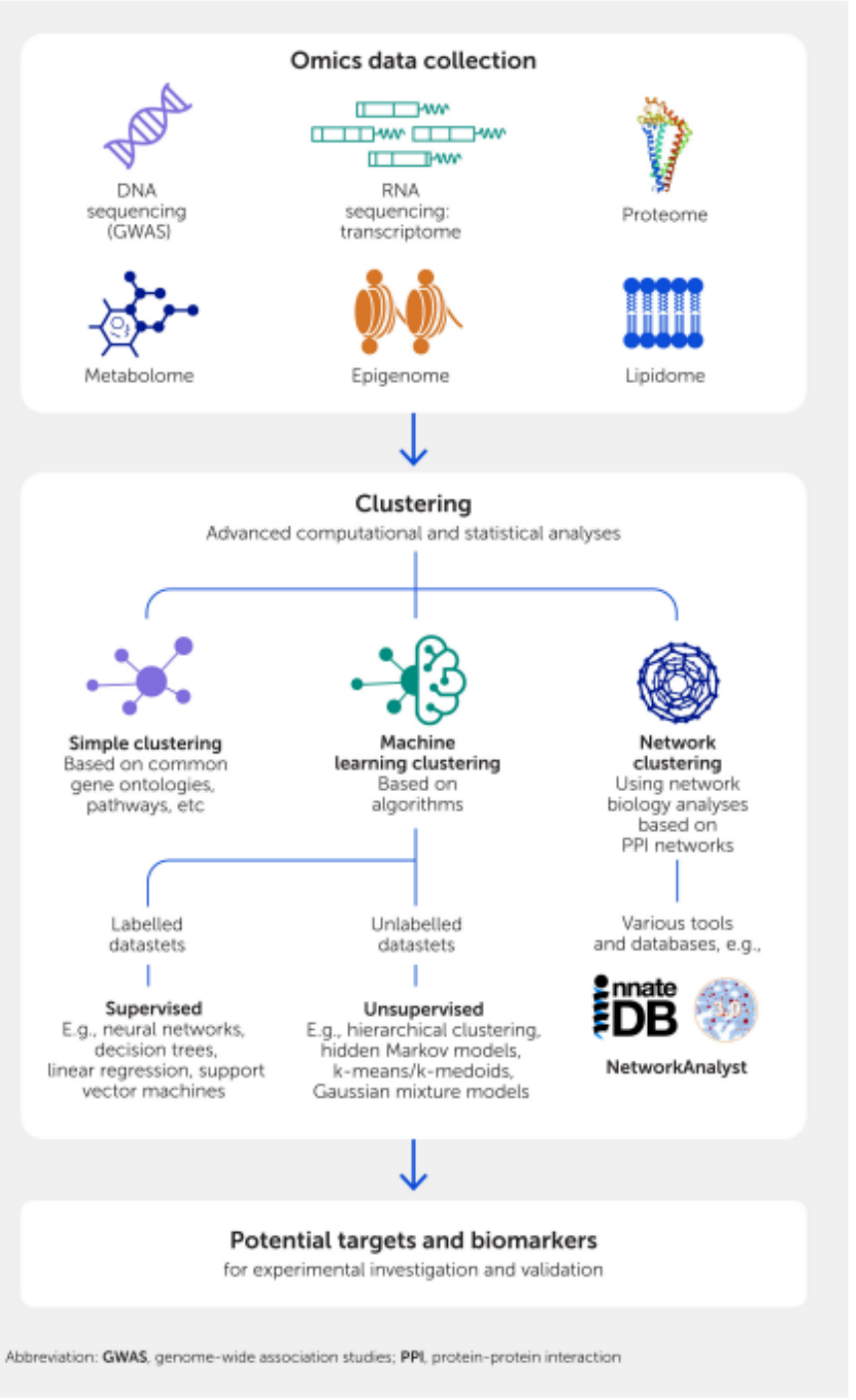
DOI:10.3389/fsci.2024.1469417

Kako to doseči?

→ **Stratifikacija bolnikov s sepso v homogene podskupine s pomočjo novih tehnologij (umetna inteligenca) in obdelavo velikih zbirk podatkov, pridobljenih s preučevanjem skupin bioloških molekul (t. i. omika, angl. „*omics*“).**

1. **Združevanje glede na sorodne klinične in laboratorijske značilnosti = (klinični) subfenotipi (angl. „*subphenotypes*“)**

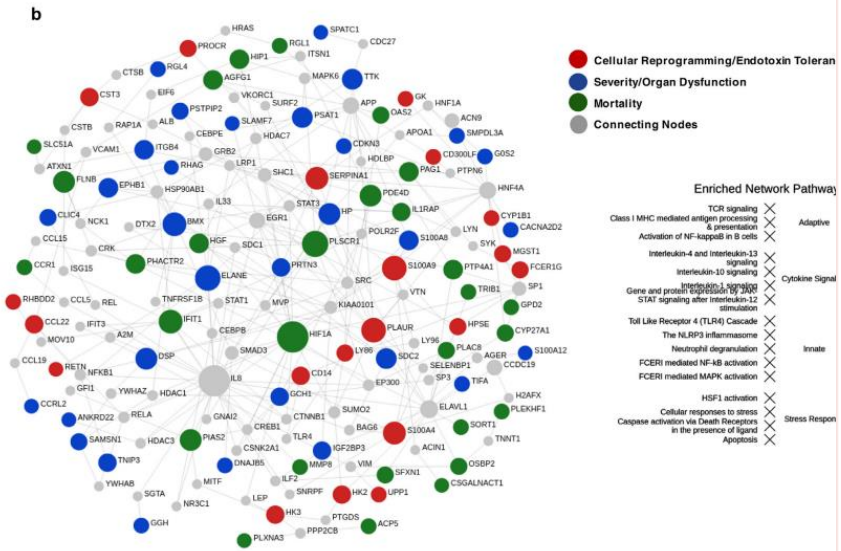
2. **Združevanje glede na pato-biološki mehanizem, odgovoren za določeno klinično sliko = endotipi (angl. „*endotypes*“)**



DOI:10.3389/fsci.2024.1469417

Predicting sepsis severity at first clinical presentation
The role of endotypes and mechanistic signatures

*Arjun Baghela,[a,b] Olga M. Pena,[a] Amy H. Lee,[c] Beverlie Baquir,[a] Reza Falsafi,[a] Andy An,[a] Susan W. Farmer,[a] Andrew Hurlburt,[d] Alvaro Mondragon-Cardona,[e,f] Juan Diego Rivera,[e,f] Andrew Baker,[g] Uriel Trahtemberg,[g] Maryam Shojaei,[h] Carlos Eduardo Jimenez-Canizales,[e,f] Claudia C. dos Santos,[g] Benjamin Tang,[h] Hjalmar R. Bouma,[i,j] Gabriela V. Cohen Freue,[k] Robert E.W. Hancock[a]**



Comparison	Gene Sets	Cross Validation (%) AUC ≡ Accuracy	Sensitivity	Specificity
Severity[a]				
High vs. Low Severity	Severity Signature	80	72	73
	Reduced Severity Signature[c]	80	76	70
	CR Signature	75	70	68
	Reduced CR Signature[d]	77	73	73
High + Intermediate vs. Low Severity	Severity Signature	71	72	60
	Reduced Severity Signature[c]	69	64	63
	CR Signature	68	64	62
	Reduced CR Signature[d]	73	67	67
Survived vs Died	Mortality	75	68	70
	Reduced Mortality Signature[e]	67	62	62
	CR Signature	60	57	61
	Reduced CR Signature[c]	62	60	61
Endotypes[b]				
Multinomial Model	40 gene set	96	81	95
NPS vs. all others	MLLT1/NSUN7	97	93	91
INF vs. all others	SPTA1/GLRX5	95	90	85
IHD vs. all others	MAP7/PLCB1	90	85	79
IFN vs. all others	PLEKHO1/EPSTI1	86	83	76
ADA vs. all others	CENPF/PDIA4	97	87	91

Table 3: Model performance statistics for endotype predictions and outcome measures predicting impending severity. **The AUC (≡ Accuracy), sensitivity, and specificity of the models, expressed as percent is provided. The performance of the 40 gene signature and the top 5/148 performing gene pairs is shown. For the severity comparisons, comparisons are based on patient groups with SOFA scores measured 24 H post ER/ICU admission: High (≥ 5), Intermediate (≥ 2 and < 5), and Low (< 2). The cellular reprogramming/endotoxin tolerance (CR) Signature is as per Pena et al.[23] The severity and mortality signatures were further reduced by filtering the genes input to LASSO using a more stringent fold change cut off (top 25% highest fold changes).**

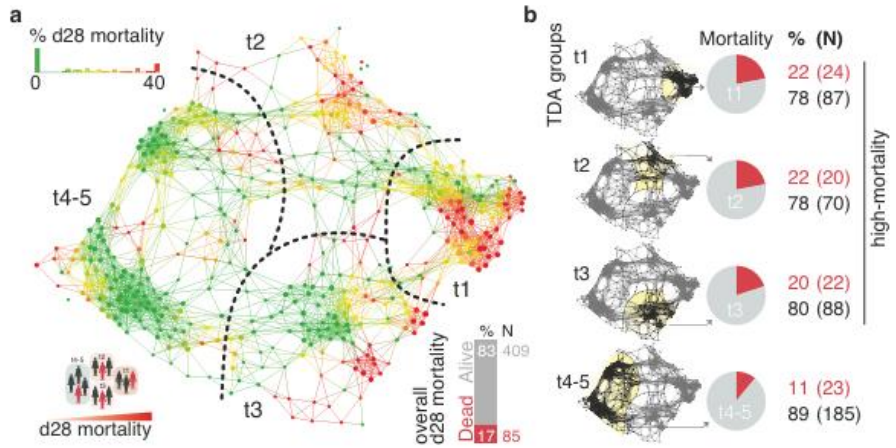
Baghela A, et al. EBioMedicine, 2022.PMID: 35027333.

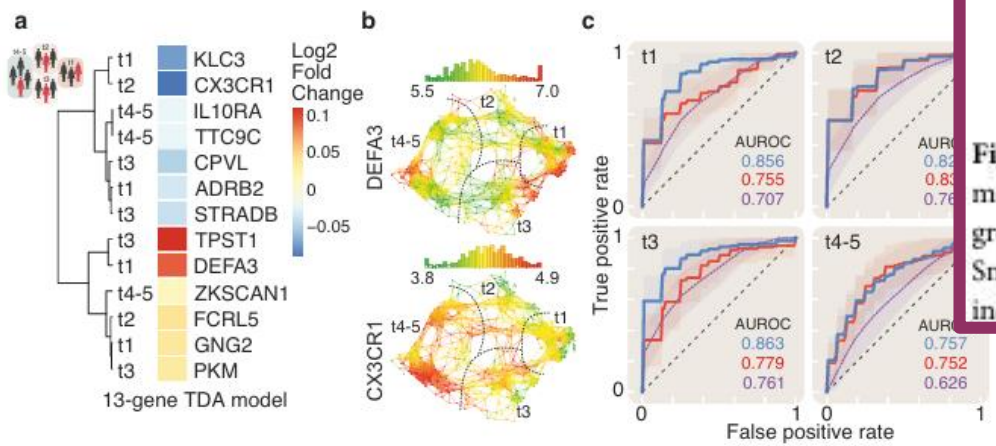
https://doi.org/10.1038/s43856-024-00542-7

Sepsis endotypes identified by host gene expression across global cohorts

Check for updates

Josh G. Chenoweth[1], Joost Brandsma[1], Deborah A. Striegel[1], Pavol Genzor[1], Elizabeth Chiyka[1], Paul W. Blair[1], Subramaniam Krishnan[1], Elliot Dogbe[2], Isaac Boakye[3], Gary B. Fogel[4], Ephraim L. Tsalik[5,12], Christopher W. Woods[5], Alex Owusu-Ofori[2,6], Chris Oppong[7], George Oduro[7], Te Vantha[8], Andrew G. Letizia[9], Charmagne G. Beckett[10], Kevin L. Schully[11] & Danielle V. Clark[1]





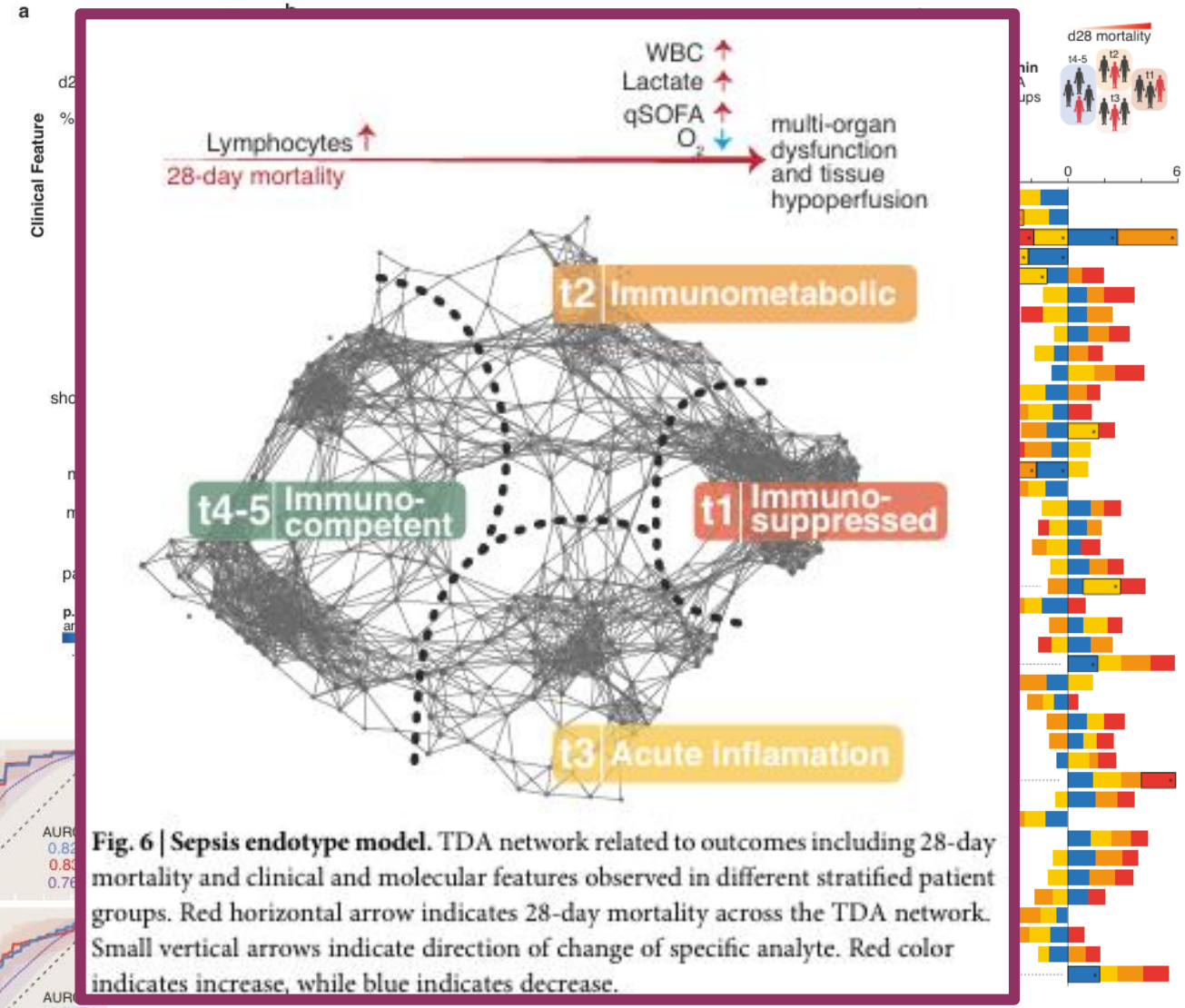


Fig. 6 | Sepsis endotype model. TDA network related to outcomes including 28-day mortality and clinical and molecular features observed in different stratified patient groups. Red horizontal arrow indicates 28-day mortality across the TDA network. Small vertical arrows indicate direction of change of specific analyte. Red color indicates increase, while blue indicates decrease.

Chenoweth JG, et al., Commun Med (Lond), 2024. PMID: 38890515.

Mekata *et al. Journal of Intensive Care* (2025) 13:30
https://doi.org/10.1186/s40560-025-00802-1

Journal of Intensive Care

RESEARCH Open Access

Molecular endotypes in sepsis: integration of multicohort transcriptomics based on RNA sequencing

Kengo Mekata[1†], Michihito Kyo[1,2*†], Modong Tan[3], Nobuaki Shime[2] and Nobuyuki Hirohashi[1]

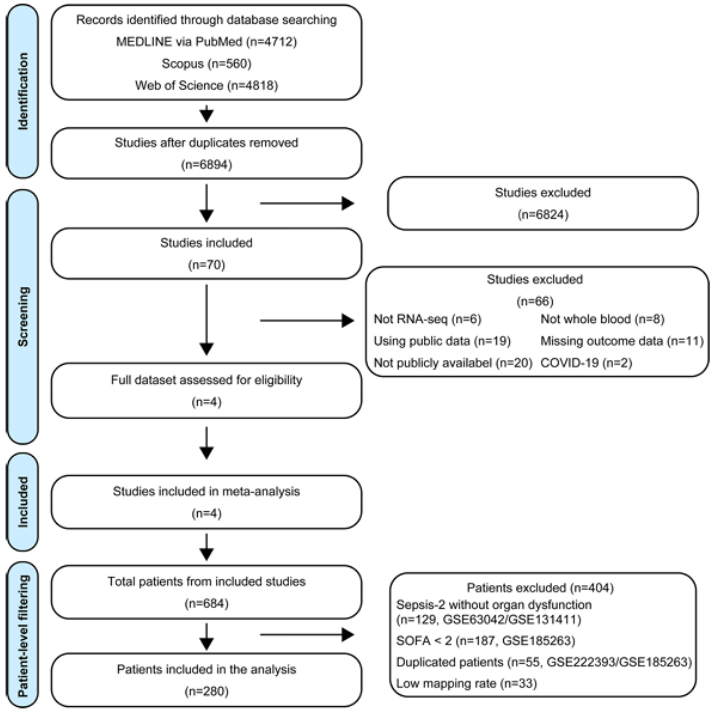
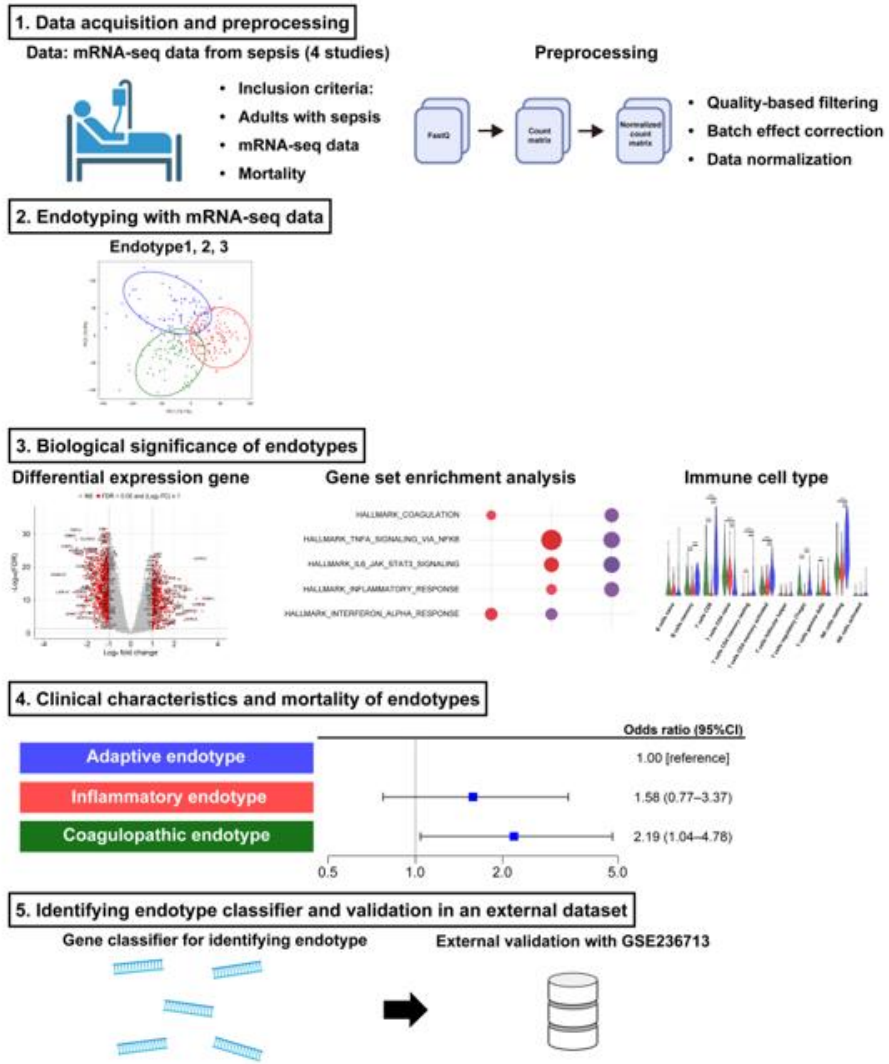


Fig. 1 Flowchart of study and patient selection. To acquire mRNA-seq data from patients with sepsis, we systematically searched MEDLINE, Scopus, and Web of Science databases. We initially identified 6,894 studies after removing duplicates. Title and abstract screening resulted in the selection of 70 studies for full-text and metadata assessment. Of these, four studies met all eligibility criteria and were included in the meta-analysis. At the patient level, we finally included 280 patients in this analysis after excluding 404 patients

Figure S1. Study design and analytical workflow for sepsis endotyping



Mekata K, et al. J Intensive Care, 2025. PMID: 40448231.

Cell Reports Medicine

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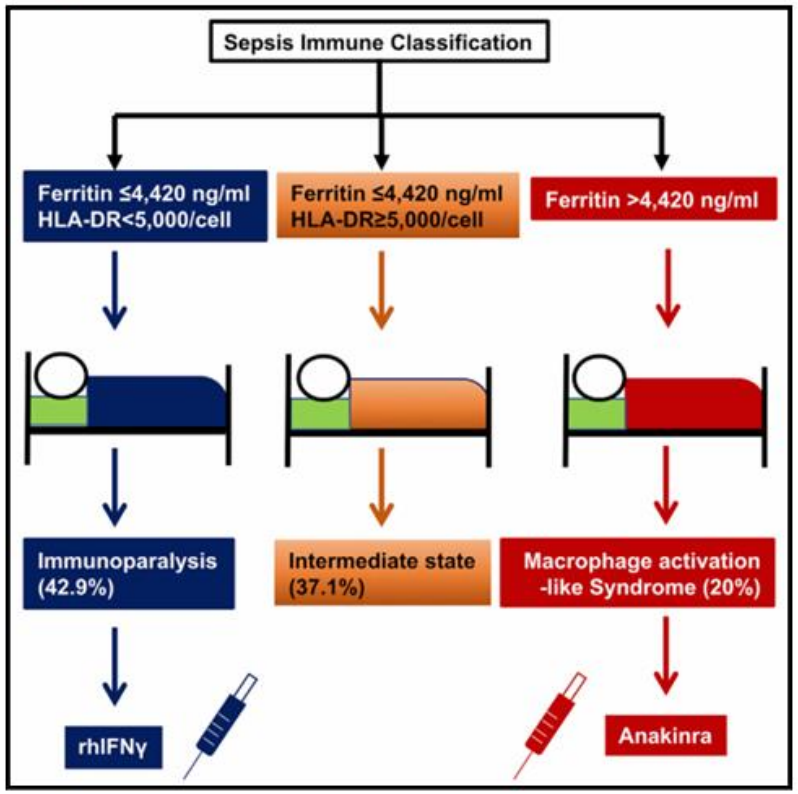
Article

Toward personalized immunotherapy in sepsis: The PROVIDE randomized clinical trial

Konstantinos Leventogiannis,[1,17] Evdoxia Kyriazopoulou,[1,17] Nikolaos Antonakos,[1,17] Antigone Kotsaki,[1,17] Iraklis Tsangaris,[2] Dimitra Markopoulou,[3] Inge Grondman,[4] Nikoleta Rovina,[5] Vassiliki Theodorou,[6] Eleni Antoniadou,[7] Ioannis Koutsodimitropoulos,[8] George Dalekos,[9] Glykeria Vlachogianni,[10] Karolina Akinosoglou,[11] Vassileios Koulouras,[12] Apostolos Komnos,[13] Theano Kontopoulou,[14] Athanassios Prekates,[15] Antonia Koutsoukou,[5] Jos W.M. van der Meer,[4] George Dimopoulos,[5] Miltiades Kyprianou,[1] Mihai G. Netea,[4,16] and Evangelos J. Giamarellos-Bourboulis[1,18,*]

Graphical abstract



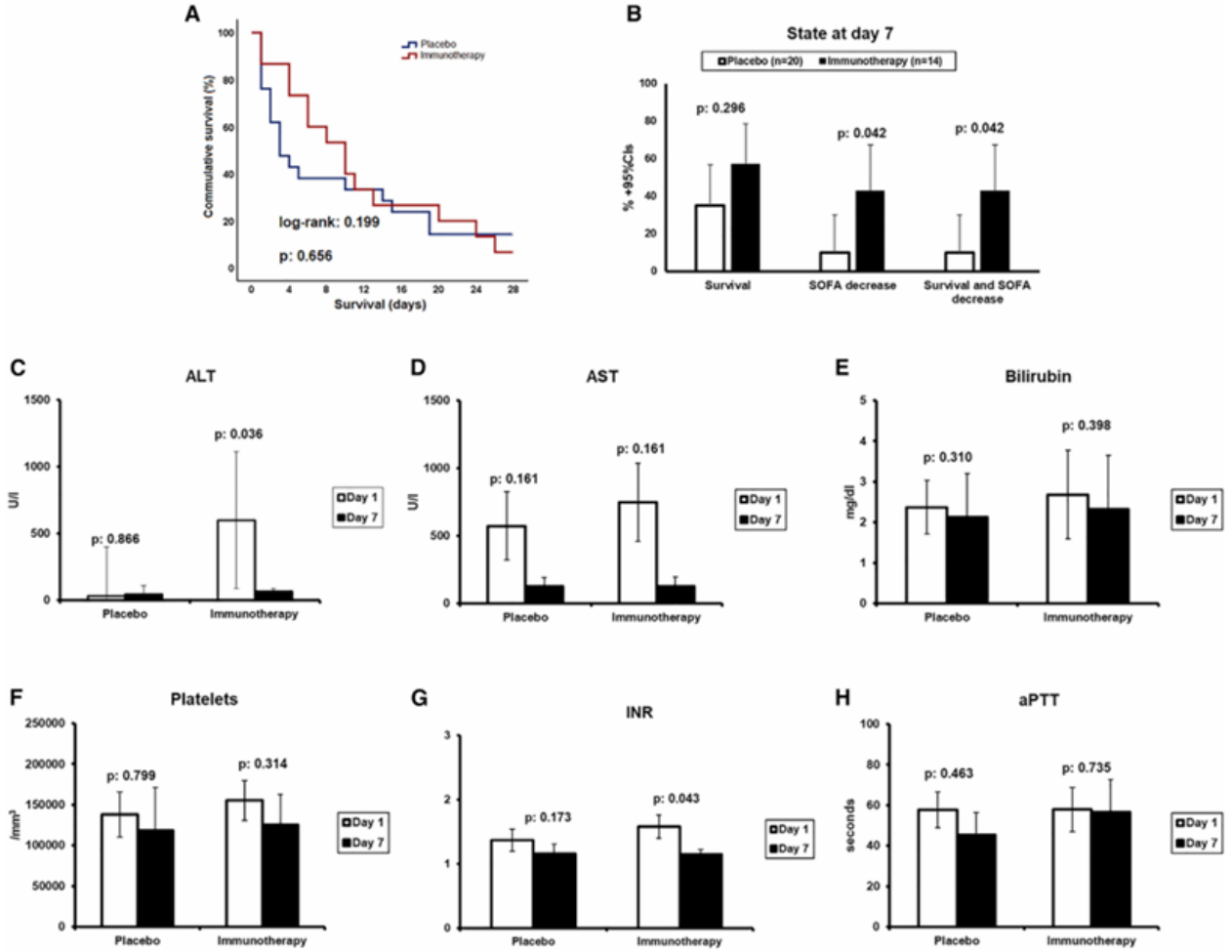


Figure 4. Effect of personalized immunotherapy

(A) Survival curves of both treatment arms. Log rank value and p value are presented.

(B) State of patients at day 7; patients are presented according to the survival status, decrease of SOFA score from baseline, or both.

(C–H) Comparison of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, absolute platelet count, international normalized ratio (INR), and activated partial thromboplastin time (aPTT) between days 1 and 7 for each treatment arms; p values of indicated statistical comparison are presented. CI, confidence interval; SOFA, sequential organ failure assessment.

Leventogiannis K, et al. Cell Rep Med, 2022. PMID: 36384100.

Omejitve

1. **Dostopnost metod** za uporabo v vsakodnevni klinični praksi (stroški, zapletenost za izvedbo, ponovljivost…).

2. Ni konsenza glede „zlatega standarda“ za **opredelitev podskupin sepse** (heterogenost med različnimi raziskavami, kar otežuje oblikovanje enotnih diagnostičnih in terapevtskih orodij).

3. Skopi podatki o **dinamiki podskupin** bolnikov s sepso v poteku bolezni (večinoma gre za enkratne meritve ali retrospektivne podatke).

4. Heterogenost pri kriterijih za opredelitev kliničnih entitet (sepsa, okužba okvara organov).

Table 2. Overview of endotypes

Endotype (prevalence)	Main characteristics	Mortality (%)	Ref
Sepsis Response Signatures (SRS) [a]			33,35
Unsupervised hierarchical cluster analysis for the top 10% most variable probes			
SRS1 (41%)	Immunosuppression, endotoxin tolerance, T-cell exhaustion, and metabolic derangement	22%[a]	
SRS2 (59%)	Immunocompetent, reference endotype	10%[a]	
Molecular Diagnosis and Risk Stratification of Sepsis (MARS) endotypes[a]			37
Unsupervised consensus cluster analysis			
MARS1 (29.4%)	Enhanced heme biosynthesis with impaired pattern recognition, cytokine and lymphocyte signaling, and antigen presentation	39%[b]	
MARS2 (34.3%)	Enhanced pattern recognition and cytokine signaling with increased NF-κB and IL-6 signaling	22%[b]	
MARS3 (23.2%)	Enhanced adaptive immune functions (T-cell pathways)	23%[b]	
MARS4 (13.1%)	Enhanced pattern recognition and cytokine signaling with increased interferon signaling	33%[b]	
Sweeney endotypes[a]			36
Unsupervised unified cluster analysis			
Inflammopathic (25%)	Innate immune activation	30%[c]	
Adaptive (31%)	Adaptive immune activation	8%[c]	
Coagulopathic (15%)	Clinical and molecular evidence of coagulopathy	25%[c]	
Calfee endotypes[b]			40
Latent class analysis			
Hypoinflammatory (70.5%)	Lower inflammatory biomarkers	16.5%[b]	
Hyperinflammatory (29.5%)	Higher plasma pro-inflammatory cytokines, lower protein C, more vasopressor use, more bacteremia	42.6%[b]	
Early sepsis endotypes[a]			38
Machine learning and data mining			
Neutrophilic suppressive/NPS (31%)	Immunosuppressed; poorer prognosis, elevated neutrophil proportions, downregulation of inflammatory markers and adaptive signaling pathways	46%[b]	
Inflammatory/INF (17%)	Severe trajectory; upregulation of multiple inflammatory pathways	26%[b]	
Innate host defense/IHD (21%)	Innate host defenses, moderate upregulation of interleukin signaling	0%[b]	
Interferon/IFN (22%)	High expression of interferon-α, -β, and -γ signaling	0%[b]	
Adaptive/ADE (9%)	Mild progression; upregulation of adaptive immune pathways, more abundant lymphocytes	–	

Table summarizes only studies that examined adult patients Mortality at day 14[a], 28[b], or 30[c] [a]Endotypes based on blood transcriptomes [b]Endotypes based on clinical parameters and plasma protein biomarkers

Kolodyazhna A, et al. Burns Trauma, 2025. PMID: 39759543.

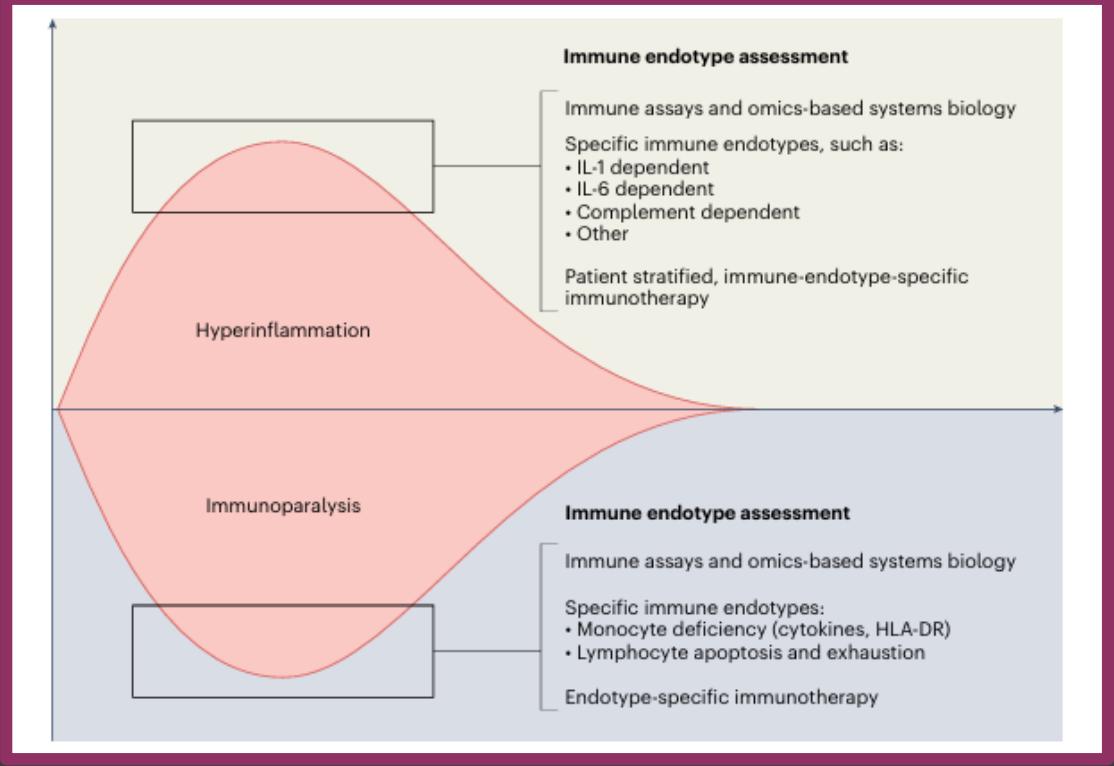
Zaključki

1. Heterogena narava sepse nam omogoča uporabo **personaliziranega pristopa** v diagnostiki in zdravljenju.

2. Pri tem je ključen koncept t. i. **obogatitve** (tako v napovedovanju (slabšega) izida bolezni, angl. „***prognostic enrichment***“, kot tudi mehanizmov, ki so odgovorni za različen potek bolezni, angl. „***predictive enrichment***“).

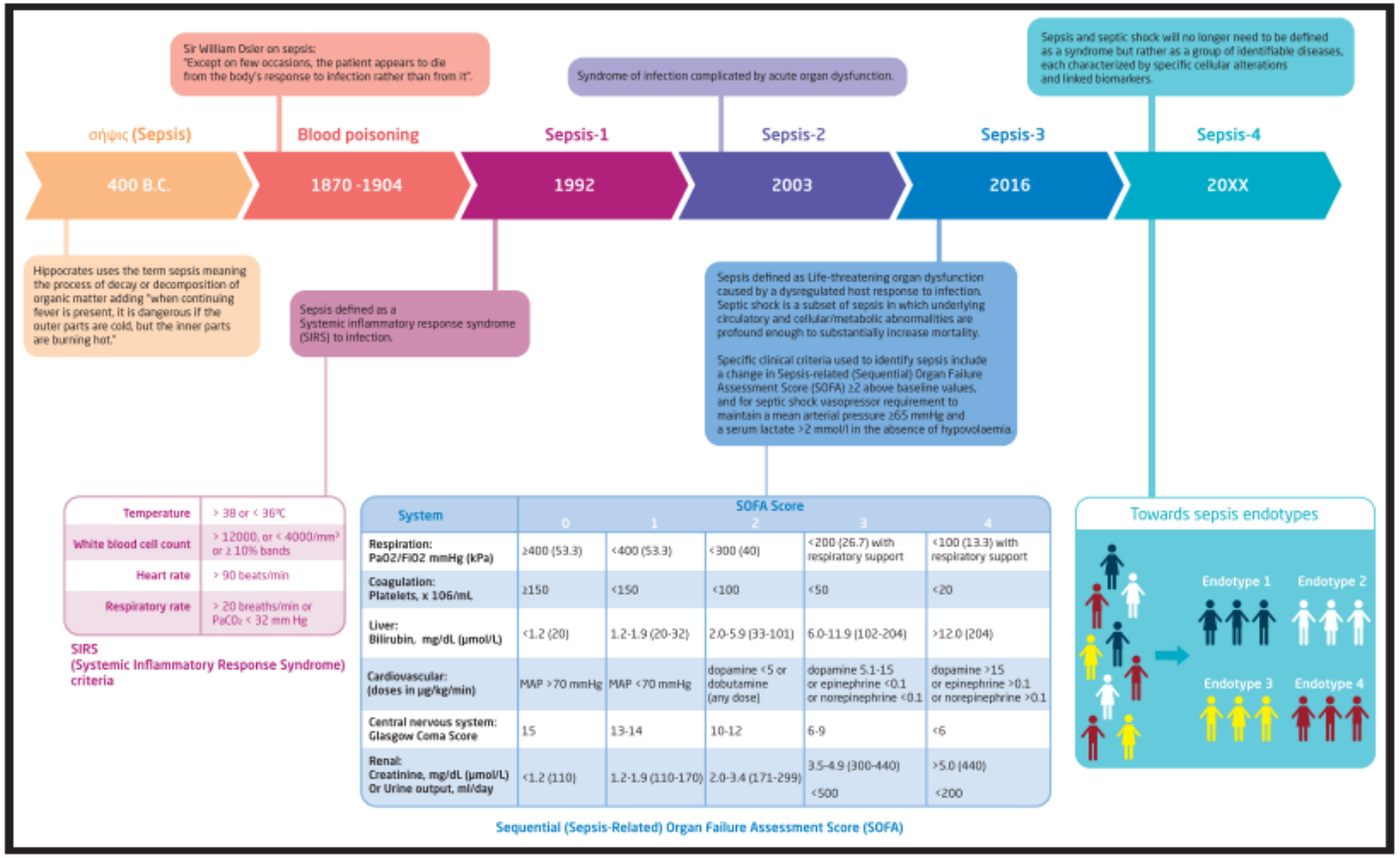
3. Idealen pristop bi vključeval uporabo obogatitvenih strategij za razvoj orodij („**biomarkerji**“), ki bi jih lahko uporabljali pri vsakdanjem delu, in sicer preko poenotenih modelov, ki bi bili ustrezno validirani v kliničnih raziskavah.

4. Končni cilj je posamezniku prilagojeno usmerjeno zdravljenje disreguliranega imunskega odziva (angl. „**right therapy, right patient, right time**“.)



Giamarellos-Bourboulis EJ, et al. Nat Immunol, 2024.PMID: 38168953.

ENDOTIPI IN SEPSA



Hvala za pozornost!

PMID: 34758337