Sepsa in genski polimorfizem

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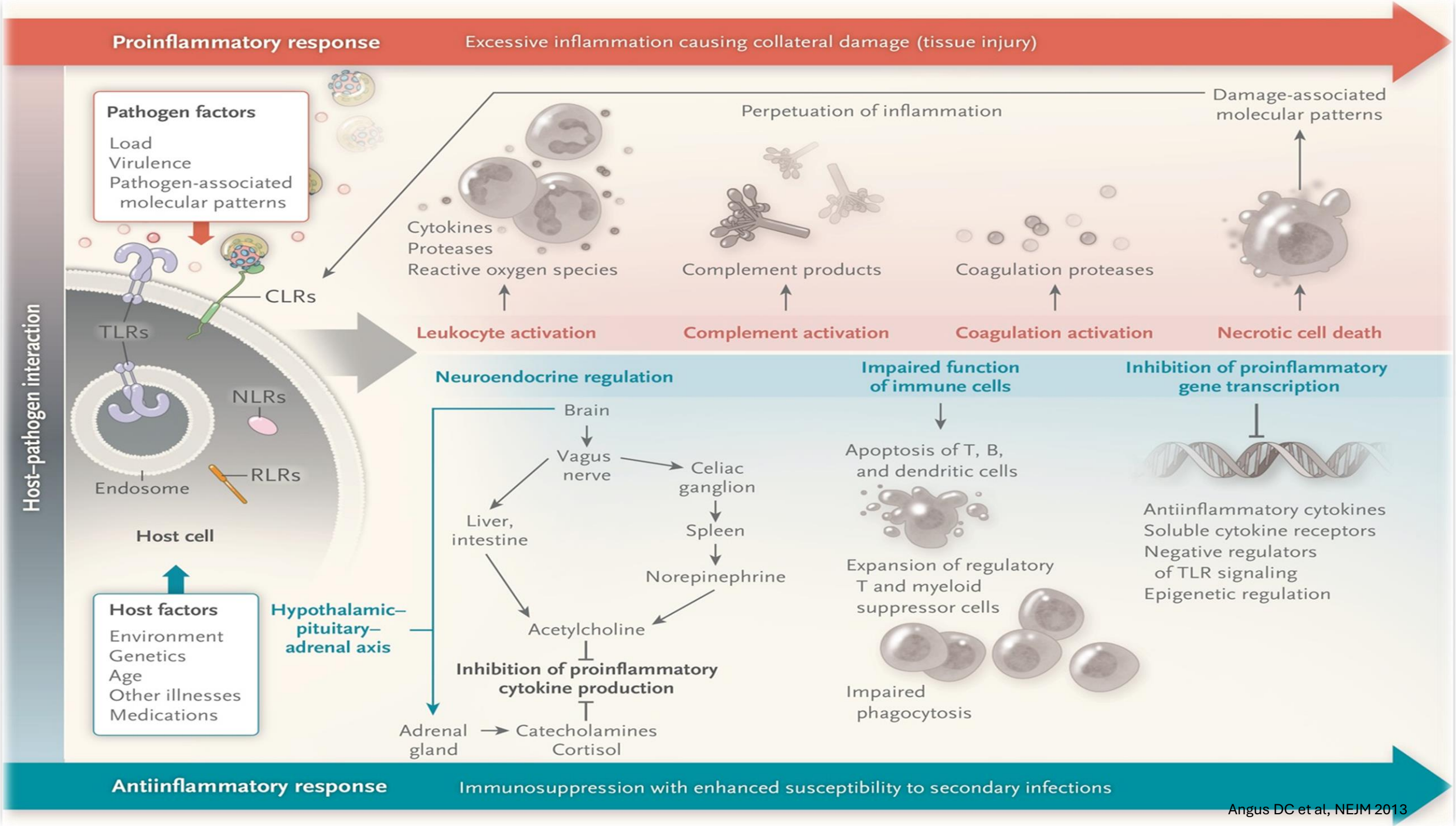
Razkritje

“Midva ne žwiva od tega”

Genski polimorfizem

- genski polimorfizem = prisotnost večih alelov za določen gen v populaciji, pri čemer so različne različice gena prisotne pri vsaj 1 % populacije
- alel = ena od različic istega gena na genskem lokusu, ki so prisotne v populaciji osebkov iste vrste
- število alelov in njihova porazdelitev v populaciji = eno od meril genetske raznolikosti



Angus DC et al, NEJM 2013

Ali ima bolnik sepso?

Bakterija, virus ali kaj drugega?

Kateri antibiotik?

Adjuvantno zdravljenje?

Kako se bo bolnik odzval na zdravljenje?

Kakšna je prognoza bolezni?

World Sepsis Day Infographics

stop sepsis save lives

These Symptoms Might Indicate Sepsis

Slurred Speech
or Confusion

Extreme Shivering
or Muscle Pain/Fever

Passing No Urine
All Day

Severe
Breathlessness

It Feels Like
You're Going to Die

Skin Mottled
or Discolored

Infographic 4/21

Experiencing any of these symptoms? Contact your local hospital or physician immediately.

Global Sepsis Alliance

worldsepsisday.org

globalsepsisalliance.org

September 13 2024 | World Sepsis Day

Table 1 Different roles of the biomarkers in sepsis

Biomarker	Function	References
Acute-phase proteins		
CRP, hsCRP	Response to infection and other inflammatory stimuli	[4, 69, 70]
	Predictive for increased 28-day mortality in patients with sepsis	
	Hyperinflammatory phenotype	
Complement	Prognosis of disease severity	[25, 71]
Proteins	C5a can be predictive for DIC	
PTX-3	Discrimination of sepsis and septic shock	[72, 73]
	Diagnosis of sepsis and septic shock during the first week in the ICU	
	Prediction of septic shock	
Cytokines and chemokines		
IL-10	Hypoinflammatory phenotype	[22, 71]
MCP-1	It differentiates patients with septic shock from patients with sepsis	[73, 74]
	Mortality prognosis at 30 days and six months	
TNF-α, IL-1β, IL-6	IL-6 all-cause mortality prognosis at 30 days and six months	[27, 74]
	IL-1β and IL-6 acute phase of sepsis	
	It was increased in the hyperinflammatory phenotype	
	Organ dysfunction prognosis	
DAMPs		
Calprotectin	PCT to distinguish between patients with sepsis and patients without sepsis in the ICU	[28]
	Predictive for 30-day mortality	
HMGB-1	Worst prognosis and higher 28-day mortality	[75, 76]
Endothelial cells and BBB markers		
Syndecan-1	Increase related to sepsis severity	[34]
	Discriminative power for DIC and subsequent mortality	
VLA-3 (α3β1)	Indicative of sepsis	[77, 78]
	Discrimination of sepsis and SIRS	
Ang-1	It stabilizes the endothelium and inhibits vascular leakage by constitutively activating the Tie-2 receptor	[79]
	Ang-2/Ang-1, Ang-1/Tie-2 ratio has a prognosis for 90-day mortality in sepsis and septic shock in the ICU higher than the PCT and SOFA score	
	Independent and effective predictors of SOFA score changes	
Ang-2	It can disrupt microvascular integrity by blocking the Tie-2 receptor, which results in vascular leakage	[73, 79]
	Individuals with septic shock had higher levels of Ang-2 than those with sepsis	
CLDN-5	The absence of CLDN-5 may indicate damage to endothelial cells during sepsis	[31]
OCLN	Increase related to sepsis severity and positive correlation with SOFA scores	[31, 32]
	Predictive of mortality	
	The absence of OCLN in the cerebral microvascular endothelium was related to more severe disease and intense inflammatory response	
PAI-1	Sepsis severity prognosis	[33, 34]
	Predictor of mortality	
	An increase may indicate DIC	
sICAM-1	Sepsis severity prognosis	[33, 79]
	Prognosis of 90-day mortality in patients with sepsis and septic shock in the ICU	
S100B	It is associated with delirium in septic shock	[36, 37, 80]
	Prognosis of severe organ dysfunction	
	Shortest survival in 180 days	
	Diagnosis of sepsis-associated encephalopathy	
E-selectin	Sepsis severity prognosis	[33]
	Predicts mortality	

Original Article

The real-world impact of the BioFire FilmArray blood culture identification 2 panel on antimicrobial stewardship among patients with bloodstream infections in intensive care units with a high burden of drug-resistant pathogens

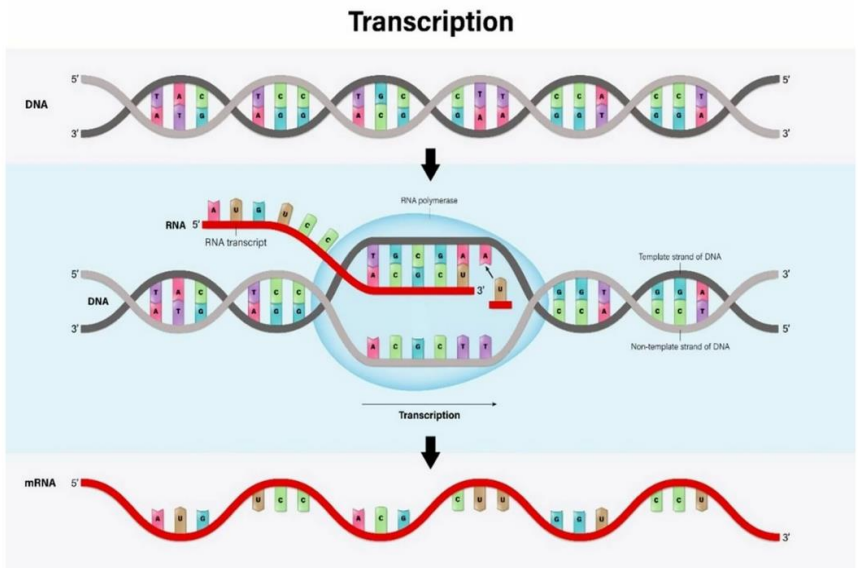
Hsu-Yuan Chen [a 1], How-Yang Tseng [a 1], Chieh-Lung Chen [a], Yu-Chao Lin [a b], Shinn-Jye Liang [a], Chih-Yen Tu [a b], Wei-Cheng Chen [a b c] ✉, Po-Ren Hsueh [d e f] ✉


Glukokortikoidi?
Izventelesno odstranjevanje citokinov?
Anakinra?
Imunoglobulini?
Tocilizumab?
Nič od naštetega?

RNK podpis (RNA signature)

= genski podpis/podpis genskega izražanja

- edinstven vzorec izražanja gena v celici
- vpogled v bolezenske odzive na molekularnem nivoju

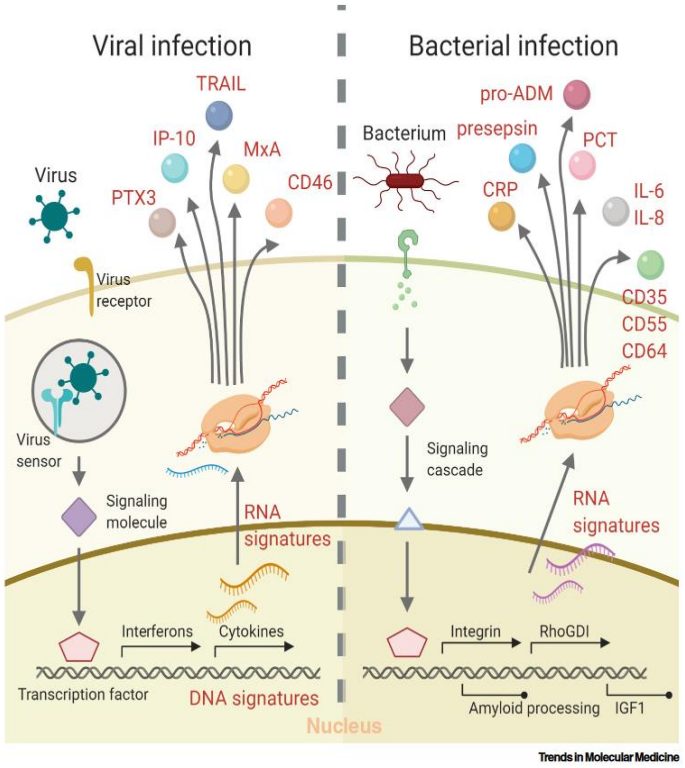


- mRNK transkript = rezultat izražanja gena ob določenem (fiziološkem/patološkem) procesu
- mRNK transkriptom = vsi transkripti v celici = vsi geni, ki se aktivno izražajo v celici v določenem trenutku
- mRNK podpis = specifična skupina mRNA transkriptov, ki so značilni za neko (bolezensko) stanje

https://www.quantumdx.com/blog/an-introduction-to-mrna-signatures/

RNK sekvenciranje

- tehnika, ki uporablja sekvenciranje naslednje generacije za oceno prisotnosti in količine RNK molekul v biološkem vzorcu
- analiza transkriptoma z oceno aktivacije/supresije genov, ugotavljanje mutacij....



Tsao YT et al. Trends Mol Med. 2020;26(12):1118-1132.

Diagnosing sepsis in the ICU: Comparison of a gene expression signature to pre-existing biomarkers

- 91 bolnikov, SIRS + okužba + antibiotik
- hemokulture in kri za analizo: CRP, PCR, NT-proBNP,

RNK za Septicyte LAB (4 RNK transkripti) in analizo

- odvzem v 24h po aplikaciji antibiotika
- izključeni bolniki, ki so prejemali atb v zadnjih 7d

in imunokompromitirani

Table 1
Comparison of individuals assessed as having blood culture (BC) positive sepsis, BC negative sepsis, and aseptic inflammation.A *P*-value <0.05 on post hoc test of multiple comparisons (compared with BC positive sepsis) was the threshold for statistical significance (bold).

	BC positive Sepsis (n = 31)	BC negative Sepsis (n = 38)	Aseptic Inflammation (n = 22)	P-value
Age (mean, SD)	57.90 (17.01)	56.13 (15.39)	54.50 (18.32)	0.762
Sex (male, %)	18 (58.1)	24 (63.2)	14 (63.6)	0.886
APACHE II score, mean (SD)	24.65 (8.10)	23.03 (8.73)	18.27 (8.03)	**0.024**
SOFA score, mean (SD)	9.65 (3.73)	8.63 (3.04)	6.68 (3.36)	**0.008**
ICU LOS, mean (SD)	11.39 (9.80)	10.42 (7.81)	9.14 (8.89)	0.657
Hospital LOS, median (IQR)	35.00 [17.00, 48.50]	22.50 [16.00, 35.00]	16.50 [11.25, 27.00]	**0.036**
ICU Mortality (n, %)	2 (6.5)	0 (0.0)	3 (13.6)	0.079
Hospital Mortality (n, %)	3 (9.7)	2 (5.3)	3 (13.6)	0.531
qSOFA criteria met (n, %)	19 (61.3)	20 (52.6)	9 (40.9)	0.342
Lactate mmol/L median (IQR)	3.50 [2.00, 6.20]	2.40 [1.33, 4.40]	1.70 [0.92, 2.65]	**0.006**
Leucocyte count, median 10^9/L (SD)	11.91 (8.84)	15.46 (7.27)	15.20 (5.91)	0.124
Neutrophil count, median 10^9/L (SD)	9.81 (8.01)	12.68 (6.72)	12.32 (5.23)	0.201
Procalcitonin mcg/L median [IQR]	33.00 [16.10, 64.80]	6.70 [1.22, 25.50]	0.70 [0.20, 1.85]	**<0.001**
C-reactive protein mg/L [IQR]	231.00 [123.00, 300.00]	208.50 [138.25, 303.75]	96.00 [60.75, 192.75]	**0.019**
NT-ProBNP median [IQR]	4943.00 [1793.00, 26,575.50]	1738.50 [569.75, 6166.00]	333.50 [192.25, 2256.25]	**<0.001**

Denny et al. J Crit Care 2023; 76: 154286
https://septicyte.com/septicyte-technology/

Comparison	CRP aROC (95% CI)	PCT aROC (95% CI)	NT-ProBNP aROC (95% CI)	Septicyte™ LAB aROC (95% CI)
BC+ sepsis vs. Aseptic inflammation	0.72 (0.57-0.87)	0.96 (0.9-1)	0.84 (0.73-0.96)	0.80 (0.68-0.93)
BC+ and BC- sepsis vs. Aseptic inflammation	0.74 (0.61-0.87)	0.86 (0.77-0.95)	0.76 (0.63-0.88)	0.79 (0.68-0.90)
BC+ vs. BC- sepsis	0.52 (0.37-0.67)	0.80 (0.69-0.90)	0.71 (0.59-0.84)	0.64 (0.51-0.77)

Fig. 1. Diagnostic accuracy of previously identified biomarkers in patients identified as having blood culture positive (BC+) sepsis (n = 31), blood culture negative (BC-) sepsis (n = 38) and aseptic inflammation (n = 22). aROC = area under the receiver operator characteristic curve; CRP: C-reactive protein; PCT: Procalcitonin; NT-ProBNP: NT- Pro B-type natriuretic peptide.

Table 2

Differentially expressed genes (DEGs) identified in patients with blood culture positive (BC+) sepsis (n = 31), blood culture negative (BC-) sepsis (n = 38) and aseptic inflammation (n = 22). aROC = area under the receiver operator characteristic curve; n/a: not-applicable.

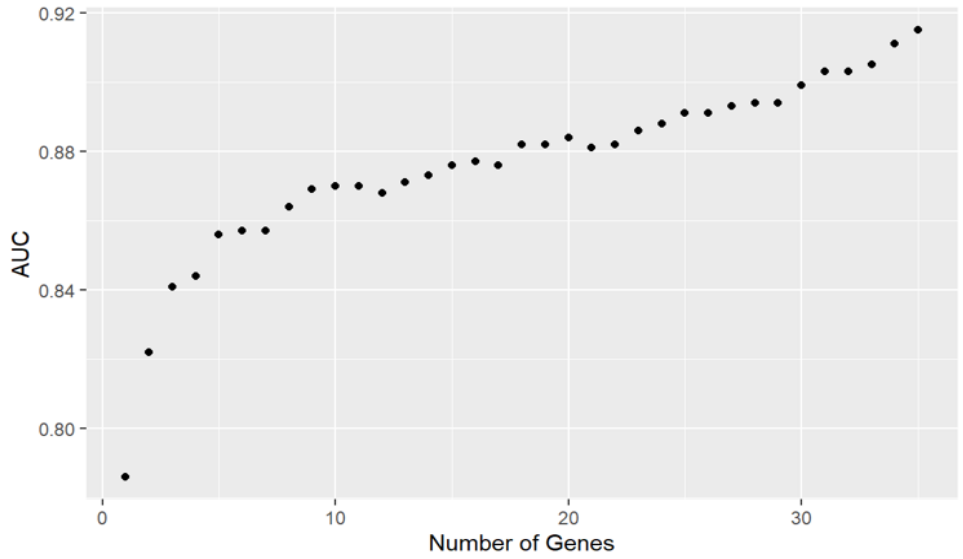
Comparison	DEGs	
	Number	aROC (95% CI)
BC+ sepsis vs. Aseptic inflammation	53	0.97 (0.95–0.99)
BC+ sepsis and BC- sepsis vs. Aseptic inflammation	210	0.91 (0.9–0.92)
BC+ vs. BC- sepsis	0	n/a

GO terms	Description
GO:0071621	granulocyte chemotaxis
GO:0006468	protein phosphorylation
GO:0097530	granulocyte migration
GO:0010942	positive regulation of cell death
GO:0031394	positive regulation of prostaglandin biosynthetic process
GO:0097352	autophagosome maturation
GO:0031622	positive regulation of fever generation
GO:0022407	regulation of cell-cell adhesion
GO:2001280	positive regulation of unsaturated fatty acid biosynthetic process
GO:0007292	female gamete generation
GO:0043065	positive regulation of apoptotic process
GO:0031620	regulation of fever generation
GO:0030593	neutrophil chemotaxis
GO:0043278	response to morphine
GO:0008333	endosome to lysosome transport
GO:0014072	response to isoquinoline alkaloid
GO:0043068	positive regulation of programmed cell death
GO:0045429	positive regulation of nitric oxide biosynthetic process
GO:0042098	T cell proliferation
GO:0031652	positive regulation of heat generation
GO:0051451	myoblast migration
GO:1904407	positive regulation of nitric oxide metabolic process
GO:0071622	regulation of granulocyte chemotaxis
GO:0031392	regulation of prostaglandin biosynthetic process
GO:0097529	myeloid leukocyte migration
GO:0030595	leukocyte chemotaxis
GO:0001660	fever generation
GO:1903039	positive regulation of leukocyte cell-cell adhesion
GO:0042110	T cell activation
GO:1990266	neutrophil migration

Validacijska kohorta:

– 536 bolnikov z bakterijsko sepso, 319 bolnikov s SIRS/neinfekcijsko vnetje

- izraženih 36 od 53 RNK transkriptov iz prve kohorte



Supplementary Figure 1 Change in classification accuracy area under the receiving operator curve (AUC) by increasing number of differentially expressed genes. The AUC decreases as genes are removed, indicating that each gene contributed to the performance of the model.

Conclusions

A gene expression signature was identified that accurately discriminates between sepsis and aseptic inflammation in patients given antibiotics in the intensive care unit.

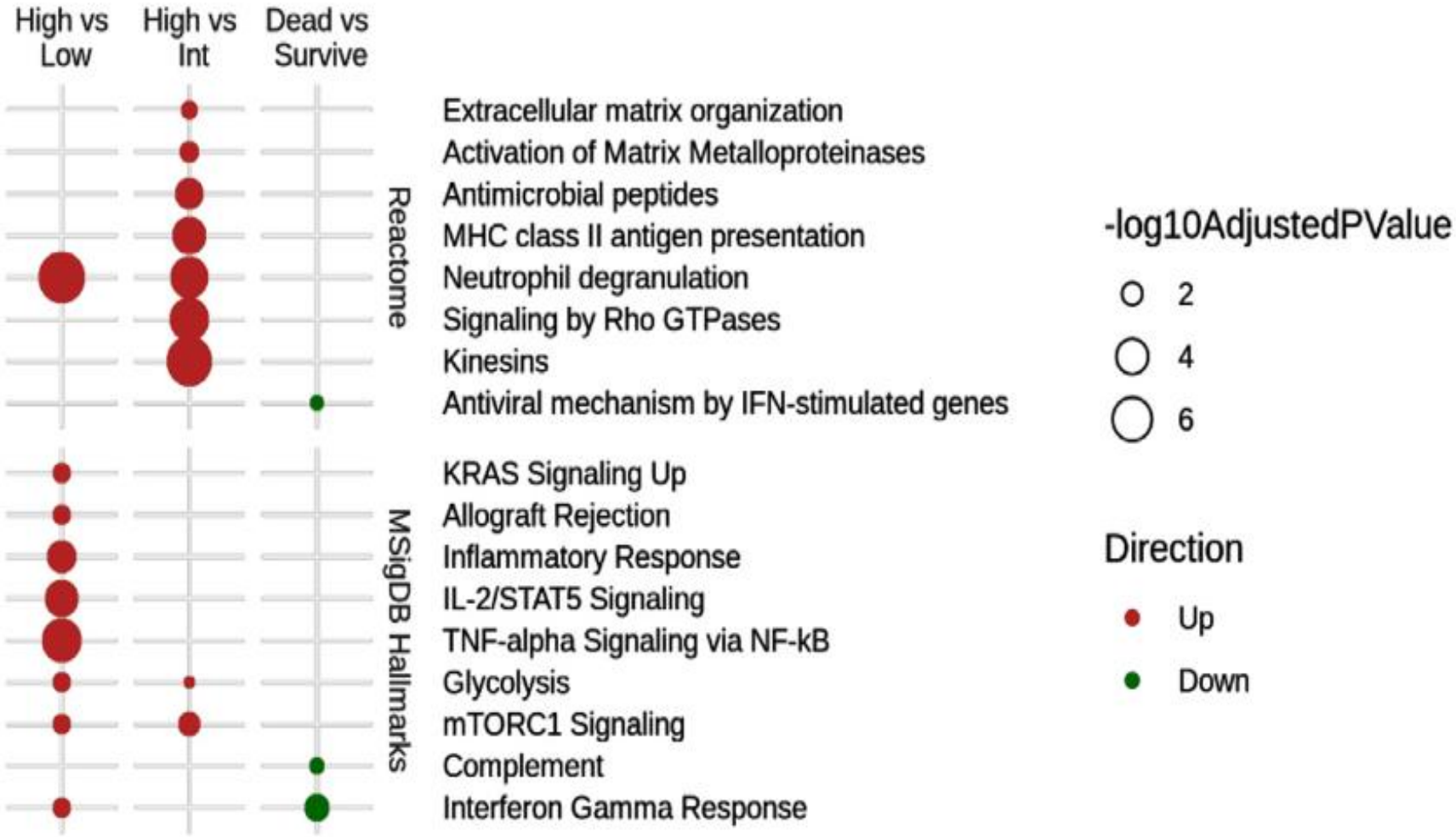
Denny et al. J Crit Care 2023; 76: 154286

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

- ugotoviti označevalce/zgodnje molekularne odzive, s katerimi bi bilo možno napovedati potek sepse
- zbrali so klinične podatke in podatke RNA sekvenciranja bolnikov ob sprejemu na urgenco/EIT
  - odrasli s sumom na sepso v 2h po sprejemu,
  - 5 kohort bolnikov (Nizozemska, Kolumbija, Kanada, Avstralija) + kontrola
  - brez imunosupresije/NSAI pred odvzemom
- identificirali so klinično relevantne RNK podpise, ki kažejo na resnost bolezni, disfunkcijo organov, smrtnost in specifične endotipe

Baghela A et al. Ebiomedicine 2022; 75: 103776

SOFA: ≥ 5 (visoka vrednost), 2-5 (srednja vrednost), ≤ nizka vrednost



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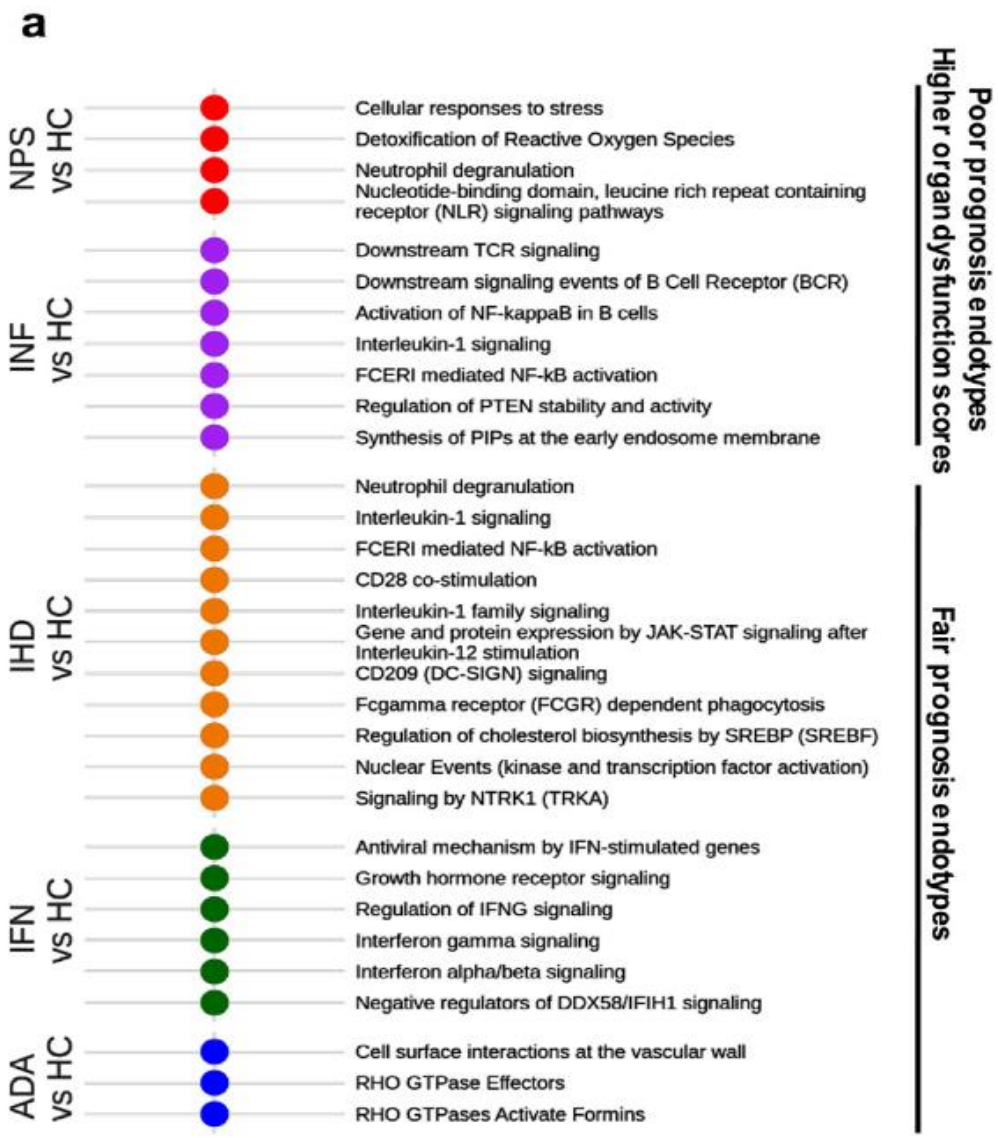

Endotipi na osnovi profilov različno izraženih genov – 200 genskih podpisov za vsak endotip v primerjavi z zdravimi kontrolami

NPS = neutrophilic suppressive:
- ↑degranulacija nevtrofilcev, ↓ pridobljena imunost, od interferona odvisne signalne poti

INF = inflammatory:
- podoben NPS, izrazitejša aktivacija vnetnega odziva

IHD = innate host defence
- ↑ prirojena imunost

IFN = interferon
- ↑ aktivacija od interferona odvisnih signalnih poti

ADA = adaptive
- ↑ pridobljena imunost, prisotnost limoficitov

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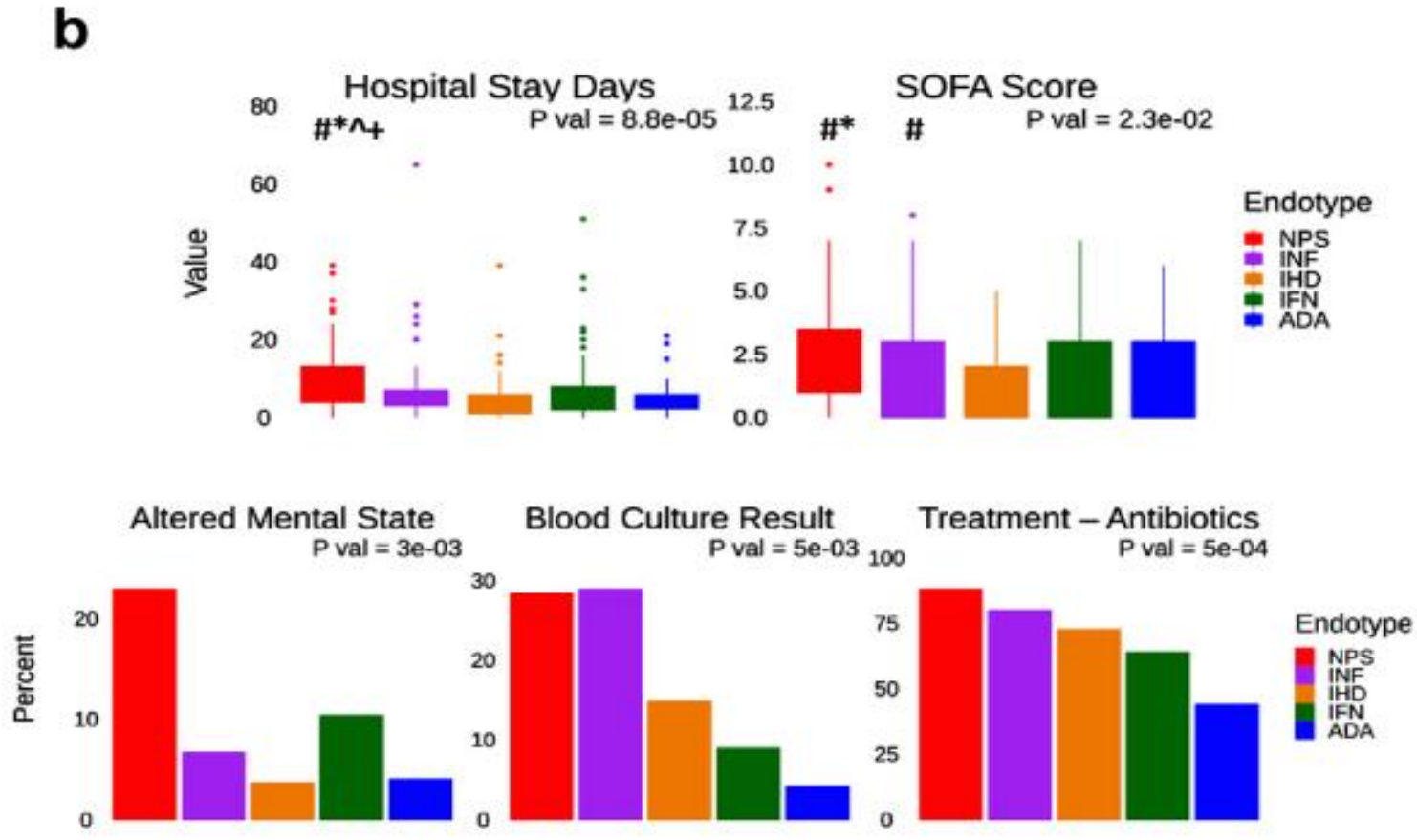

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	Mechanistic Endotypes				
Parameter	**NPH (*N* = 36)**	**INF (*N* = 33)**	**IHD (*N* = 6)**	**IFN (*N* = 7)**	***P* Val**
Covid-19 PCR Positivity	16·7% (6/36)	39·4% (13/33)	16·7% (1/6)	100% (7/7)	0·00050
Mortality within 28 Days	45·7% (16/35)	25·9% (7/27)	0% (0/5)	0% (0/6)	0·025
SOFA 24H post ICU admission	7·6 ± 0·9 (34)	8·2 ± 0·78 (32)	3·5 ± 1·34 (6)	3·7 ± 1·49 (7)	0·033
ICU Mortality	38·9% (14/36)	18·2% (6/33)	0% (0/6)	0% (0/5)	0·034
ICU Stay Days	10·4 ± 1·29 (36)	15·2 ± 1·63 (33)	6·8 ± 2·7 (6)	9·7 ± 3·43 (7)	0·050
SOFA 48H post admission	7·5 ± 0·98 (31)	8·4 ± 0·75 (30)	3·5 ± 0·87 (4)	4·1 ± 1·7 (7)	0·079
SOFA at ICU admission	8·4 ± 0·9 (36)	7·9 ± 0·64 (33)	4·2 ± 1·7 (6)	5 ± 1·66 (7)	0·093

***Table 4*:** Severity and outcomes of the endotypes in the ICU cohort. **The mean value ± standard error is presented for numerical variables with the total available observations/ patient numbers recorded in brackets. Categorical variables are presented as percent positive (% total positive/total available observations). *P* values are derived from Kruskal-Wallis and Chi squared tests testing for significant differences between endotypes for numerical and categorical values, respectively.**

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Klinični pomen endotipov

- hitra diagnostika (PCR) v zelo zgodnji fazi bolezni
- pomoč pri triaži bolnikov
- priložnost za individualizirano zdravljenje
  - NPS – zgodnja aplikacija zdravil s podpornim delovanjem na imunski sistem (IFN γ, GM-CSF, IL7)
  - INF – zdravila s protivnetnim učinkom
  - IFN, IHD, ADA – monitoring, ocena potrebe po antibiotičnem zdravljenju

Table 2. Pathogenic genes and alleles

Reference	Pathogenic gene	Description	Pathogenic allele
Tang *et al.* [33], Küçükaycan *et al.* [34], Al-Amodi *et al.* [35]	TNF-α	Tumor necrosis factor α	TNF2, TNF-α-376 GA and TNF-α-376 AA
Holmes *et al.* [36]	TNF-β	Tumor necrosis factor β	TNF-β-252A and TNF-β-252AA
Behairy *et al.* [37]	TLR	Toll-like receptor	TLR2 Arg753Gln
Nakada *et al.* [38]	VPS13D	Vacuolar protein sorting-associated protein 13D, which is associated with increased IL-6 production *in vitro*	rs6685273 C and rs6685273 CC
Zhang *et al.* [39]	IL-10	Interleukin-10	IL-10-1082G
Nakada *et al.* [40]	IL-20	Interleukin-20	rs2981573 GG
He *et al.* [32]	IL-27	Interleukin-27	IL-27-964AA
Zapata-Tarrés *et al.* [41]	IL1RN	Interleukin-1-receptor antagonist	IL-1RN*2
Gibot *et al.* [42]	CD14	Cluster of differentiation 14	TT
Madách *et al.* [43]	PAI-1	Plasminogen-activator inhibitor 1	4G/4G and 4G/5G
Cogulu *et al.* [44]	ACE	Angiotensin-converting enzyme	I/I
Nakada *et al.* [45]	AGTRAP	Angiotensin II type 1 receptor-associated protein	rs11121816 GG
Nakada *et al.* [46]	ADRB2	Beta(2)-adrenergic receptor	rs1042717 AA
Graebin *et al.* [47]	HLA-G	Human leucocyte antigen G	Exon 8 at the 3′ UTR
Toubiana *et al.* [48]	IRAK1	Interleukin receptor-associated kinase 1	IRAK1 variant haplotype
Peng *et al.* [49]	TREM-1	Trigger receptor-1	AA
Pérez-García *et al.* [50]	CEACAM7	Carcinoembryonic antigen-related cell adhesion molecule 7	rs1001578, rs10409040 and rs889365
O'Dwyer *et al.* [51]	DDAH II	Dimethylarginine dimethylaminohydrolase II	G at position −449 in the DDAH II gene
Rosier *et al.* [52]	CISH	Cytokine-inducible SRC homology 2 (SH2) domain protein	rs143356980
Li *et al.* [53]	lincRNA-NR_024015	Long non-coding RNA lincRNA-NR_024015	rs8506 TT
Nakada *et al.* [54]	SVEP1	Sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1	c.2080A > C (p. Gln581His, rs10817033)
Sun *et al.* [55]	PECAM-1 Leu125Val	Platelet endothelial cell adhesion molecule-1 Leu125Val	CG and GG(rs668:C > G)
Paludo *et al.* [56]	SOD2	Superoxide dismutase 2	47C(rs4880)
Nakada *et al.* [57]	LNPEP	Leucyl/cystinyl aminopeptidase	rs4869317 TT
Vilander *et al.* [58]	SERPINA4	Serpin peptidase inhibitor, clade A, member 4	rs2093266
Vilander *et al.* [58]	SERPINA5	Serpin peptidase inhibitor, clade A, member 5	rs1955656
Cui *et al.* [59]	ADAM10	A disintegrin and metalloproteinase 10	rs653765 CC
Temple *et al.* [60]	HSPA1B	HSP70 gene	HSPA1B-179C > T
Clavier *et al.* [61]	PTPN1	Tyrosine-protein phosphatase non-receptor type 1	-
Clavier *et al.* [61]	ATF6	Activating transcription factor 6	-
Turrel-Davin *et al.* [62]	BID	BH3-interacting domain death agonist	-
Turrel-Davin *et al.* [62]	FAS	Fatty acid synthase	-
Hara *et al.* [63]	Mint3/Apba3	Munc18–1-interacting protein 3; human amyloid beta A4 precursor protein- binding family A member 3	-
Wang *et al.* [64]	NLRC4	NLR family CARD domain containing protein 4	-

TNF2 alel/TNFα polimorfizem:
- frekvenca večja pri bolnikih s krg okužbami v krg EIT kot v splošni populaciji
- višja smrtnost zaradi septičnega šoka

TNFα (376 G/A) SNPS:
- večja frekvenca pri bolnikih s sepso povzročeno akutno ledvično odpovedjo
- neodvisni napovedni dejavnik ALO

IL10-1082G:
- sign večja prevalence pri bolnikih s septičnim šokom kot pri bolnikih brez šoka
- ključna vloga pri dovzetnosti bolnikov z akutnim pankreatitisom za napredovanje v septični šok

Baghela A et al. Burns & Trauma 2024, 12: tkae006

Table 3. Protective genes and alleles

Reference	Protective gene	Description	Protective allele
Georgescu *et al.* [65]	TNF-α	Tumor necrosis factor α	489G/A SNP A
Ferwerda *et al.* [66]	TLR	Toll-like receptor	TIRAP 180 L
Cogulu *et al.* [44]	ACE	Angiotensin-converting enzyme	DD
Meyer *et al.* [67]	IL1RN	Interleukin-1-receptor antagonist	rs315952C
Pérez-García *et al.* [68]	OLFM4	Olfactomedin 4	rs17552047 A and rs1891944 TT
Xu *et al.* [69]	GRK5	G Protein-coupled receptor kinase 5	rs2230349A
Cohen *et al.* [70]	GLCCI1	Glucocorticoid-induced transcript protein 1	-

TIRAP 180 L
- ojačan odziv na TLR4 in TLR2 ligande – “okrepljena” nativna imunost
- povečana odpornost na okužbe

Z glukokortikoidi induciran transkript protein 1
- regulira odziv na hidrokortizon
- bolj izražen – boljši odziv na hidrokortizon

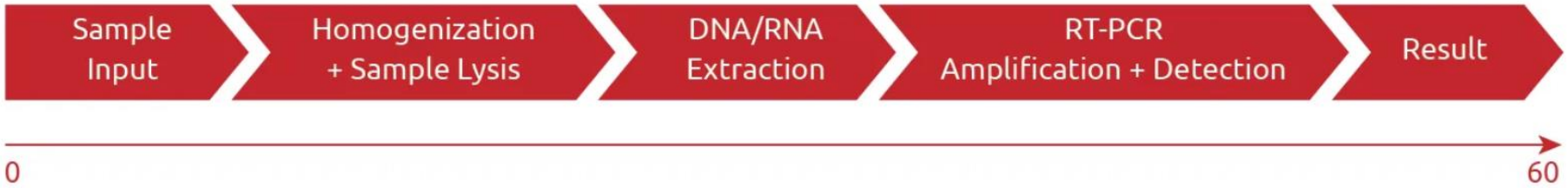
BHSD1
- bolj izražen – počasnejše izzvenevanje šokovnega stanja, če prejmejo hidrokortizon

Baghela A et al. Burns & Trauma 2024, 12: tkae006

Point-of-care testi

SeptiCyte® RAPID Workflow on the Idylla™ Platform

SeptiCyte® RAPID is designed for ease of use and rapid, accurate results in about an hour.



https://inflammatix.com/pipeline/#endotypes

https://septicyte.com/idylla-platform/labtestforsepsis/


Per aspera ad astra