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MUNI MED

Imunoterapie Sepse

Martin HELÁN

26.4.2022

Colours of Sepsis, Ostrava

Lecture content

- Background - Surviving sepsis campaign – additional therapies
- Failure of clinical studies

- Pharmacological options
  - Immuno-stimulating
  - Immuno-suppressive
  - Immuno-modulating

- Non-pharmacological treatment options

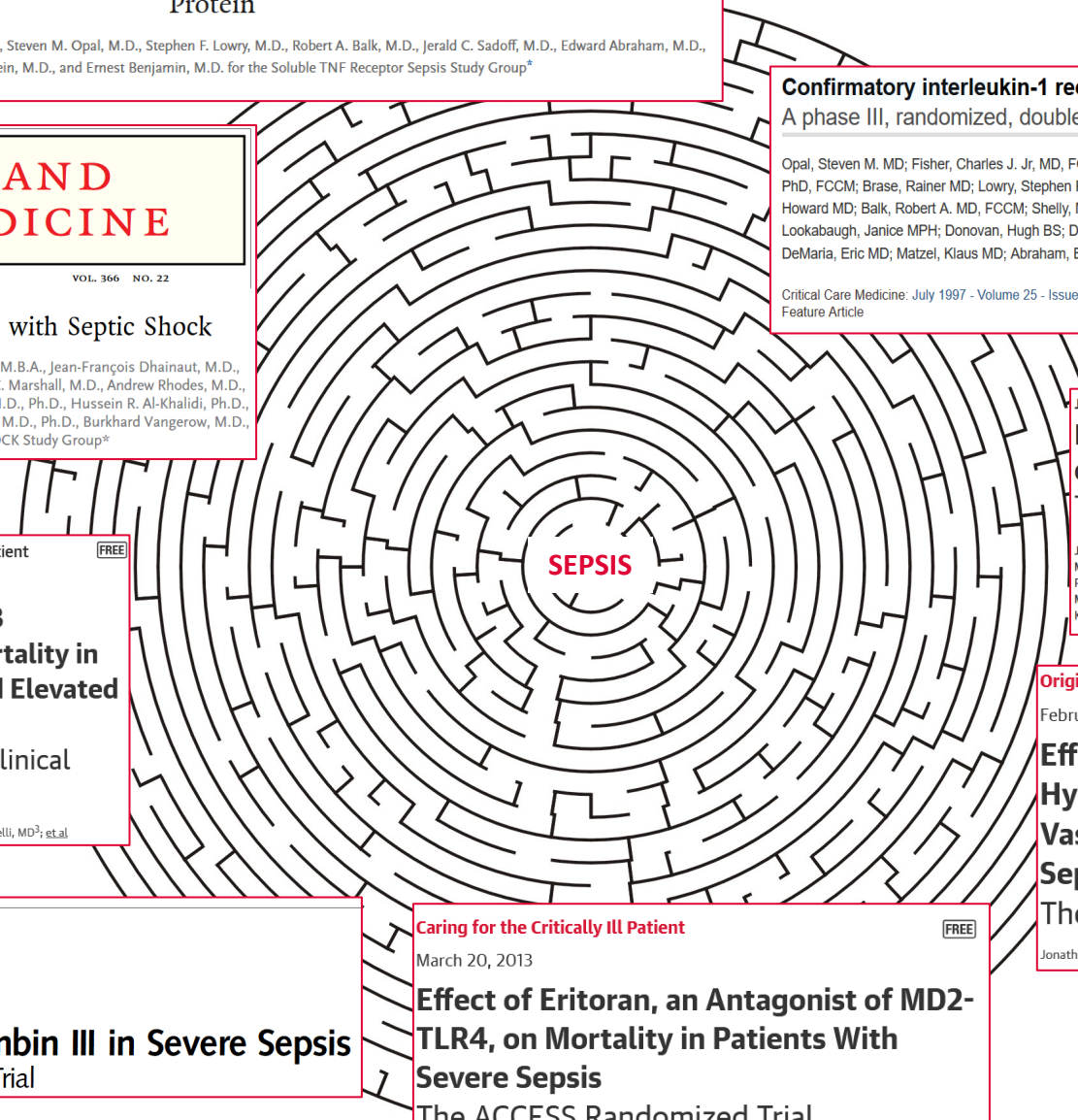
- Reasons for RCTs failure and future strategies

- Post-sepsis syndrom?

- Conclusions

- No conflict of interest to declare!

Exploring blind alleys



ORIGINAL ARTICLE

Treatment of Septic Shock with the Tumor Necrosis Factor Receptor:Fc Fusion Protein

Charles J. Fisher, Jr., M.D., Jan M. Agosti, M.D., Steven M. Opal, M.D., Stephen F. Lowry, M.D., Robert A. Balk, M.D., Jerald C. Sadoff, M.D., Edward Abraham, M.D., Roland M.H. Schein, M.D., and Ernest Benjamin, M.D. for the Soluble TNF Receptor Sepsis Study Group*

Confirmatory interleukin-1 receptor antagonist trial in severe sepsis

A phase III, randomized, doubleblind, placebo-controlled, multicenter trial

Opal, Steven M. MD; Fisher, Charles J. Jr, MD, FCCM; Dhainaut, Jean-Francois A. MD, PhD; Vincent, Jean-Louis MD, PhD, FCCM; Brase, Rainer MD; Lowry, Stephen F. MD; Sadoff, Jerald C. MD; Slotman, Gus J. MD, FCCM; Levy, Howard MD; Balk, Robert A. MD, FCCM; Shelly, Maire P. FRCA; Pribble, John P. PharmD; LaBrecque, John F. PhD; Lookabaugh, Janice MPH; Donovan, Hugh BS; Dubin, Howard MD, FCCM; Baughman, Robert MD; Norman, James MD; DeMaria, Eric MD; Matzel, Klaus MD; Abraham, Edward MD, FCCM; Seneff, Michael MD

Anakinra

Critical Care Medicine: July 1997 - Volume 25 - Issue 7 - p 1115-1124
Feature Article

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 31, 2012 VOL. 366 NO. 22

Drotrecogin Alfa (Activated) in Adults with Septic Shock

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*

Xigris, activated protein C

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy

The SCARLET Randomized Clinical Trial

Jean-Louis Vincent, MD, PhD; Bruno Francois, MD; Igor Zabolotskikh, MD, PhD; Mradul Kumar Daga, MD; Jean-Baptiste Lascarrou, MD; Mikhail Y. Kirov, MD; Ville Pettilä, MD; Xavier Wittebole, MD; Ferhat Meziani, MD, PhD; Emmanuelle Mercier, MD; Suzana M. Lobo, MD, PhD; Philip S. Barie, MD, MBA; Mark Crowther, MD; Charles T. Esmon, PhD; Jawed Fareed, PhD; Satoshi Gando, MD, PhD; Kenneth J. Gorelick, MD, PhD; Marcel Levi, MD, PhD; Jean-Paul Mira, MD, PhD; Steven M. Opal, MD; Joseph Parrillo, MD, PhD; James A. Russell, MD; Hidehiko Saito, MD, PhD; Kazuhisa Tsuruta, PhD; Takumi Sakai; David Fineberg, MD; for the SCARLET Trial Group

Original Investigation | Caring for the Critically Ill Patient FREE

October 9, 2018

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level

The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, MD, MSc[1]; Sean M. Bagshaw, MD, MSc[2]; Massimo Antonelli, MD[3]; et al

Original Investigation | Caring for the Critically Ill Patient FREE

February 23, 2021

Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis

The VICTAS Randomized Clinical Trial

Jonathan E. Sevransky, MD, MHS[1,2]; Richard E. Rothman, MD, PhD[3]; David N. Hager, MD, PhD[4]; et al

CARING FOR THE CRITICALLY ILL PATIENT

High-Dose Antithrombin III in Severe Sepsis

A Randomized Controlled Trial

Caring for the Critically Ill Patient FREE

March 20, 2013

Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis

The ACCESS Randomized Trial

Steven M. Opal, MD; Pierre-Francois Laterre, MD; Bruno Francois, MD; et al

Surviving sepsis campaign – additional therapies

Corticosteroids: For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids.

- **Weak** recommendation; moderate quality of evidence

Blood purification: For adults with sepsis or septic shock, we suggest **against** using polymyxin B haemoperfusion.

- Weak recommendation; low quality of evidence

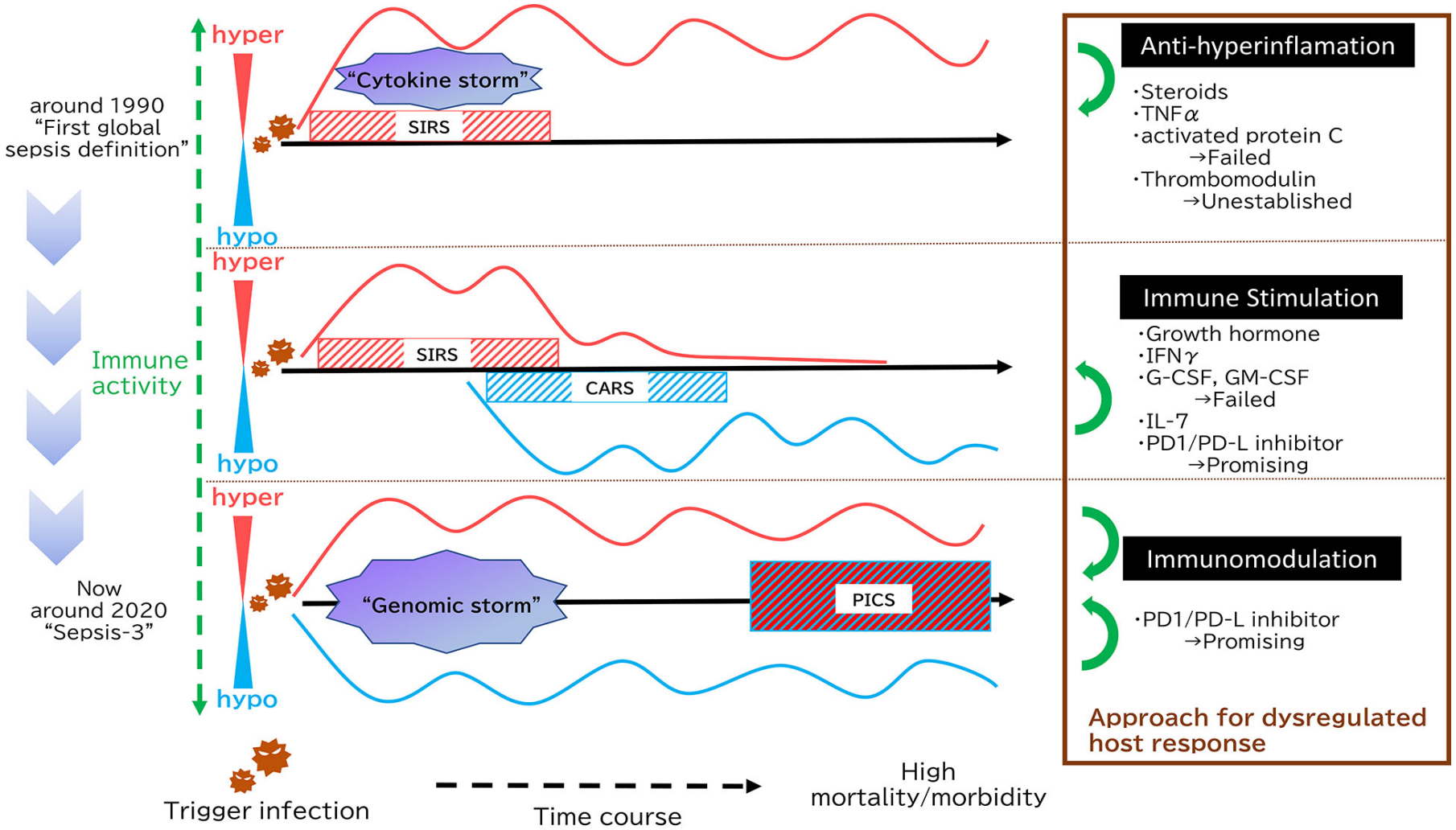
IVIG: For adults with sepsis or septic shock, we suggest **against** using intravenous immunoglobulins

- Weak recommendation, low quality of evidence

Vitamin C: For adults with sepsis or septic shock, we suggest **against** using IV vitamin C

- Weak recommendation, low quality of evidence.

Surviving Sepsis Campaign®



Anti-hyperinflamation

- Steroids
- TNFα
- activated protein C
  →Failed
- Thrombomodulin
  →Unestablished

Immune Stimulation

- Growth hormone
- IFNγ
- G-CSF, GM-CSF
  →Failed
- IL-7
- PD1/PD-L inhibitor
  →Promising

Immunomodulation

- PD1/PD-L inhibitor
  →Promising

Approach for dysregulated host response

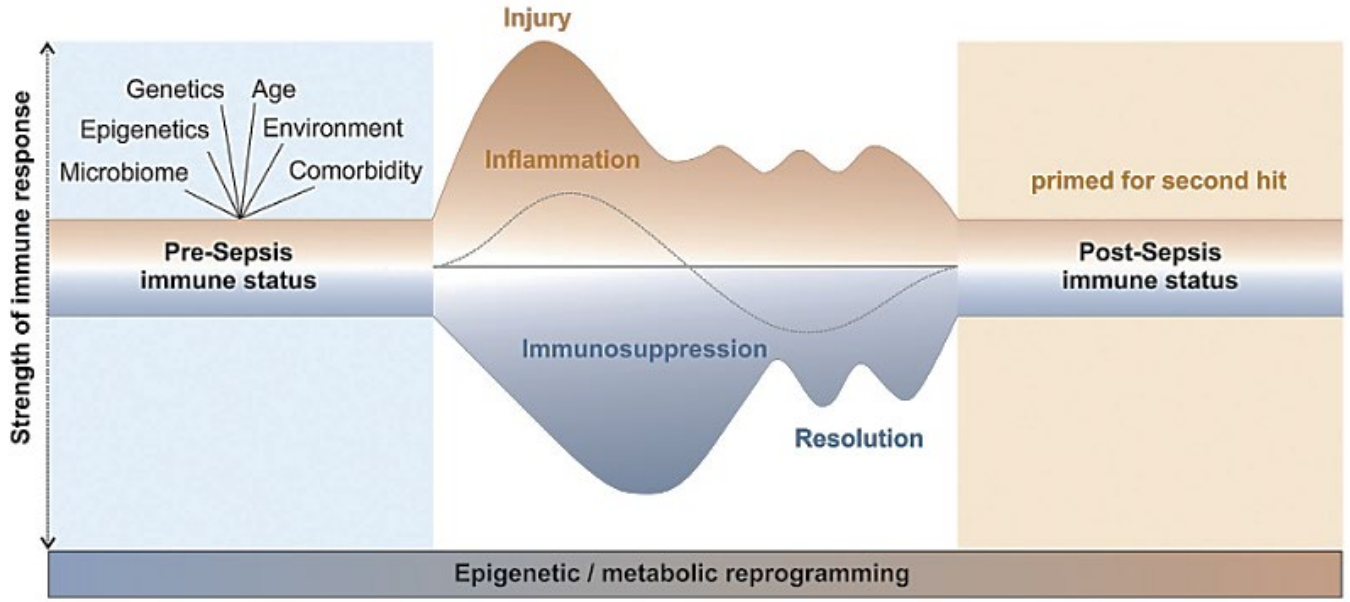
Conventional Basic Treatment

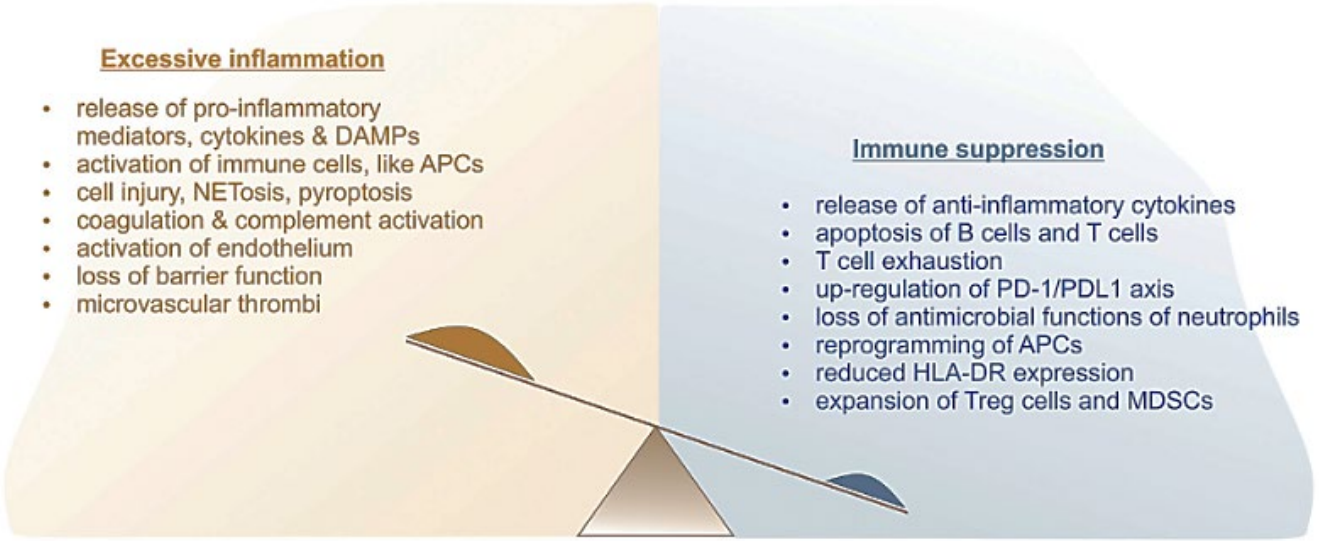
Initial resuscitation

Antibiotics/ Source control

Supportive Care (Ventilation, Nutrition, Rehabilitation, etc.)

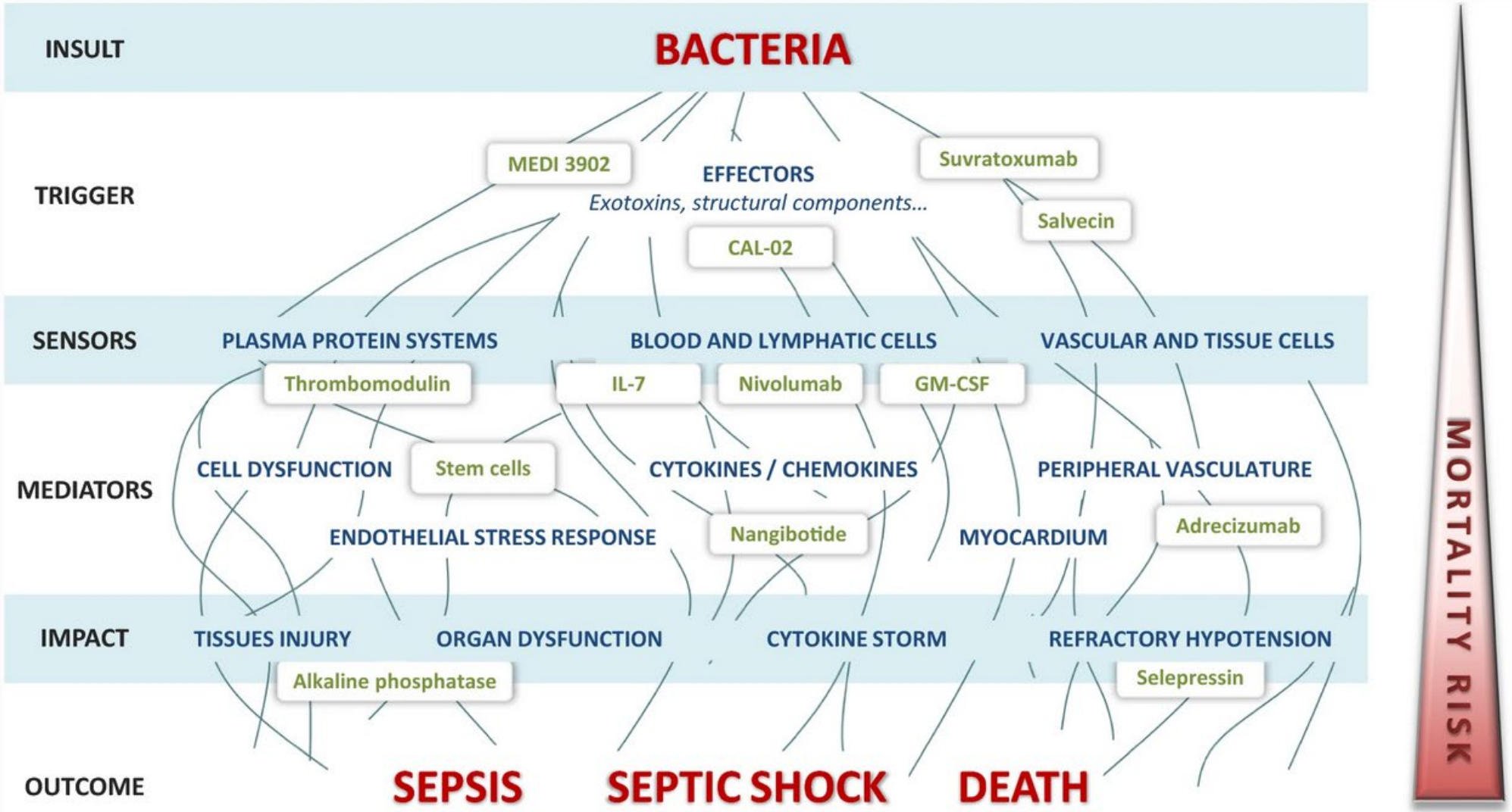
Nakamori Y et al.: Immune Deregulation in Sepsis and Septic Shock: Reversing Immune Paralysis by Targeting PD-1/PD-L1 Pathway. 2021





📖 *Steinhagen F et al.: Immunotherapy in sepsis - brake or accelerate? Pharmacol Ther. 2020.*

From: New Agents in Development for Sepsis: Any Reason for Hope?



Adapted from Azeredo da Silveira S, Shorr AF. Critical parameters for the development of novel therapies for severe and resistant infections-A case study on CAL02, a non-traditional broad-spectrum anti-virulence drug. Antibiotics (Basel). 2020;9(2):94

Inhibition of excessive inflammation

- Blocking TLR-4 receptor (Eritoran) – mortality not reduced (n=1961) – widrawn from further clinical testing
  - Anti-TLR4 monoclonal Ab – phase I testing
- Blocking TNFα (neutralising fusion protein) – didn't reduce mortality (1996)
  - Afelimomab (anti-TNF Ab) – significant reduction in mortality in subgroup of patients (IL-6 > 1000pg/ml) (2004)
- Blocking IL-1 receptor (rh IL-1RA, Anakinra) – non-significant (2-5%) reduction in mortality
  - Retrospective subgroup analysis – significant mortality reduction (45,4 vs. 34,3%) in subgroup of patients with baseline (IL-1RA > 2071pg/ml)

📖 Meyer NJ et al.: Mortality Benefit of Recombinant Human Interleukin-1 Receptor Antagonist for Sepsis Varies by Initial Interleukin-1 Receptor Antagonist Plasma Concentration. Crit Care Med. 2018

- Targeting immuno-thrombosis (activated protein C, drotrecogin alpha) – anti-inflammatory, anti-apoptotic effects – did not reduced mortality.

Non-pharmacological strategies

- Polymyxin B hemoperfusion – neutralize LPS, failed to improve survival
- CytoSorb – removing PAMPs, DAMPs, cytokines, …, failed to remove IL-6, organ dysfunction
- Plasma Exchange – running RCT (EXCHANGE) -reduces cytokines, improved hemodynamics.

Inhibition of excessive inflammation

Current clinical studies that aim hyperinflammation in sepsis.

Treatment	Target molecule and main action	Clinicaltrials.gov identifier	Primary outcome	Comment
Anakinra	Recombinant human IL-1 receptor antagonist	NCT03332225	28-day mortality	Another study arm receives IFNγ in immunosupressive state
Adrecizumab	ADM binding Ab	NCT03085758	safety over a 90-days	Only patients with ADM serum levels >70 pg/mL are recruited (Geven et al., 2019)
Ascorbic acid	- Inhibition of NF-kB activation	NCT02106975	Change in SOFA score at 96 hours	Terminated: no differences in SOFA score (Fowler et al., 2019)
	- Inhibition of HMGB1 release	NCT03680274	28-day mortality and organ failure	None
	- Enhancement of chemotaxis and phagocytosis	NCT03835286	Vasopressor consumption	None
Hydrocortisone, ascorbic acid and thiamine	- Pleiotropic immuno-modulatory effects e.g.:	NCT03509350	Vasopressor and ventilator-free days	Study protocol also published (Hager et al., 2019)
	- Inhibition of NF-kB and AP-1 activation	NCT03333278	Time alive and free of vasopressors at day 7	study protocol also published (Fujii et al., 2019)
		NCT03380507	60-day mortality	None
	- Inhibition of endothelial and neutrophil activation	NCT03540628	2-year mortality	None
		NCT03828929	30-day mortality	None
		NCT03258684	14-day mortality	None
Clarithromycin	Inhibition of NF-kB and IRF3 activation	NCT03345992	28-day mortality	None
Polymyxin B hemoperfusion	Neutralizes LPS by binding lipid A	NCT01046669	28-day mortality	Terminated: no differences in mortality rate (Dellinger et al., 2018)
		NCT01222663	28-day mortality	Terminated: no differences in mortality rate (Payen et al., 2015)
CytoSorb	Elimination of PAMPs, DAMPS and cytokines	NCT29084247	IL-6-serum concentrations	Terminated: no differences in IL-6 levels (Schädler et al., 2017)
Therapeutic plasma exchange	Elimination of pro-inflammatory and replacement of protective molecules	NCT03065751	28-day mortality	Improved hemodynamics in preliminary study (Knaup et al., 2018)

Immune augmentation

- Granulocyte-macrophage colony-stimulating factor (GM-CSF) – restores HLA-DR expression, cytokine production – so far not associated with survival benefit
  - Running RCT (GRID) – HLA-DR guided GM-CSF therapy (effect on secondary infections)
- Interferon gamma IFNγ – promissing clinical results, running RCT
- Mesenchymal stem cells – reduces organ injury and mortality in animal models, 2 phase II RCTs running
- Intravenous immunoglobulin (IVIG) - results are in-consistent. Meta-analyses of these studies failed to show an overall benefit
  - IgM-enriched immunoglobulin (IVIgM) - meta-analysis of nineteen studies showed reduced mortality risk, -RCT is ongoing (monitoring HLA-DR, cytokines, immunoglobulins to sort patients based on therapy effect).
- Immune checkpoint inhibitors - Immune checkpoint receptors activate inhibitory pathways that are essential for self-tolerance. → apoptosis, senescence death.
  - PD-1/PD-L1 – programmed cell death receptor/ligand. Monoclonal anti-PD-1 Ab - nivolumab

Immune augmentation

Current clinical studies that aim immunosuppression in sepsis.

Treatment	Target molecule and main action	ClinicalTrials.gov Identifier	Primary Outcome	Immune Biomarker used to initiate therapy	Comment
GM-CSF	Increases production and activity on neutrophils, macrophages and monocytes	NCT02361528	ICU-acquired infection at D28 or ICU discharge	reduced monocytes HLA-DR levels (< 8000 monoclonal Abs per cell)	
IFNγ	Increases activity of leucocytes	NCT01649921	TNF secretion by LPS-stimulated leukocytes	none	
		NCT03332225	28-day mortality	HLA-DR expression on CD14-monocytes <30%	another study arm receives anakinra in hyperinflam-matory state
IL-7	Promotes lymphocyte proliferation and survival	NCT02640807	Safety and immune reconstitution	≤ 900 lymphocytes/μl	Terminated: well tolerated and >3-fold increase in lymphocyte count (Francois et al., 2018)
IgGAM	Improves pathogen recognition and anti-apoptotic effects	NCT03334006	Improvement of the mean MOF score on day 7	IL-6 levels >1000 pg/ml	
Mesenchymal stem cells	- augmenting bacterial clearance	NCT02421484	Safety and cytokine response	none	Terminated: safe and no exacerbation of elevated cytokine levels (Schlosser et al., 2019)
	- limiting apoptosis	NCT03369275	reduction in days on mechanical ventilation, or renal replacement therapy, or vasopressors	none	
	- enhancing injury repair	NCT02883803	SOFA score on day 7	none	
anti-PD-L1	Reduces apoptosis and promotes T-cell responses	NCT02576457	Safety and 90-day mortality	≤ 1100 lymphocytes/μl	Terminated: safe and no drug-induced cytokine release syndrome (Hotchkiss et al., 2019)

Immune augmentation

- Potentially adjunctive treatment for refractory/resistant fungal infections?

A case report:

- Immunocompetent host, woman, 30 yo, severe pelvic trauma
  Refractory mycotic infection despite surgery source control (splenectomy, gastrectomy) and convetional therapy.
- Low absolute lymphocyte count, low monocyte HLA-DR expression, and increased expression of programmed death-1 (PD-1) on T-cells
- Immunoadjuvant therapy with interferon-γ (100 µg X3/wk for 5 doses) starting on D28, followed by a single 250 mg dose of nivolumab on D30.
- Subsequent immunological examinations showed increases in absolute lymphocyte count, monocyte HLA-DR expression, and CD8 T-cells, and decreased T-cell PD-1 expression
- Pt improved slowly, and repeat CT scans showed no residual infection,
- D80 – discharged from ICU

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)	
	Points
• Infection by HIV or long term immunosuppressive treatment e.g., cyclosporine, glucocorticoids, azathioprine	18
• Core temperature	
<38.4°C	0
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

HBD	
Presence of at least 2 of the following:	
• Serum bilirubin > 2.5 mg/dl • Aspartate aminotransferase ≥2 × upper normal limit • International normalized ratio (INR) >1.5	
DIC score (more than 5 points are needed)	
	Points
• Platelet count (/mm^3)	
<100,000	1
<50,000	2
• D-dimers	
No increase	0
Moderate increase	2
Strong increase	3
• Prothrombin time	
<3 s	0
3–6 s	1
>6 s	2
• Fibrinogen (g/l)	
>1	0
<1	1

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

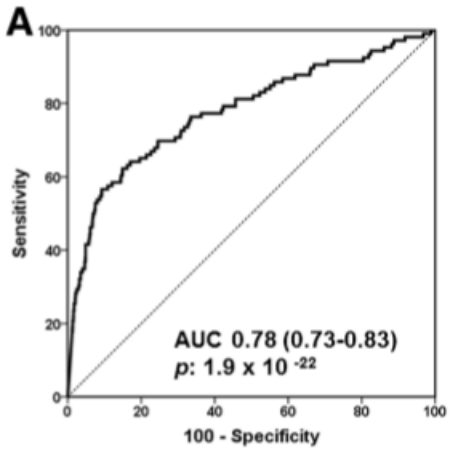
Macrophage activation-like syndrom - MALS

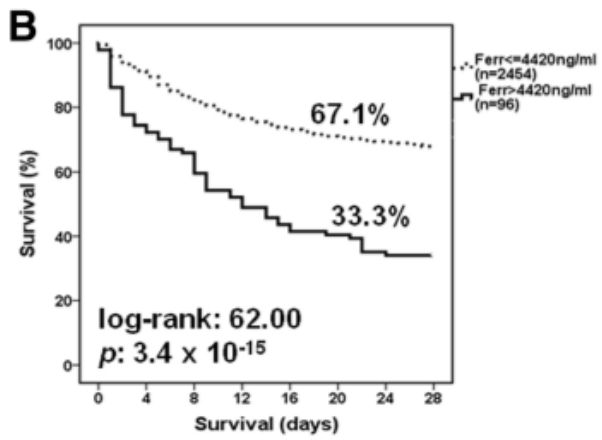
- Ferritin levels above 4420 ng/ml
- The frequency of MALS was 3.7% and 4.3%
- MALS was an independent risk factor for 10-day mortality
- less than 15% decrease of ferritin on day 3 was associated with more than 90% sensitivity for unfavorable outcome

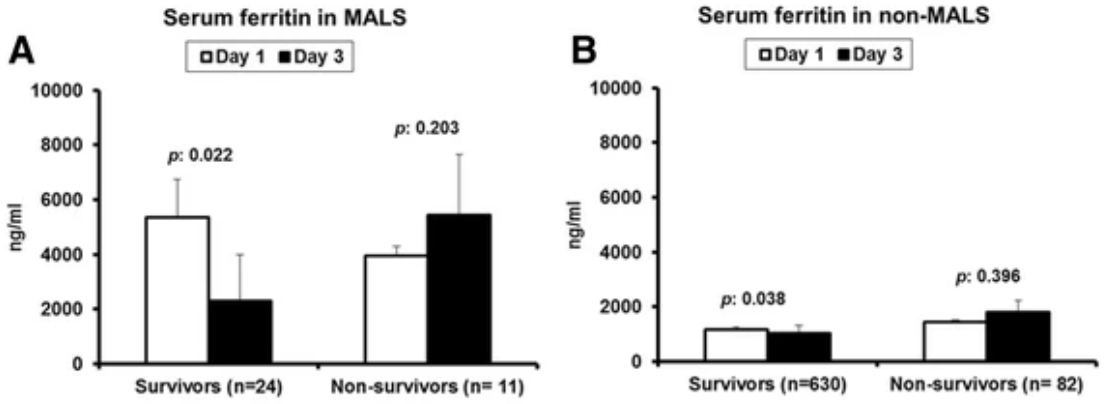
RESEARCH ARTICLE Open Access

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

Evdoxia Kyriazopoulou[1], Konstantinos Leventogiannis[1], Anna Norrby-Teglund[2], Georgios Dimopoulos[3], Aikaterini Pantazi[4], Stylianos E. Orfanos[3], Nikoletta Rovina[5], Iraklis Tsangaris[3], Theologia Gkavogianni[1], Elektra Botsa[1], Eleftheria Chassiou[6], Anastasia Kotanidou[7], Christina Kontouli[8], Panagiotis Chaloulis[9], Dimitrios Velissaris[10], Athina Savva[1], Jonas-Sundén Cullberg[2], Karolina Akinosoglou[10], Charalambos Gogos[10], Apostolos Armaganidis[3], Evangelos J. Giamarellos-Bourboulis[1*] on behalf of the Hellenic Sepsis Study Group

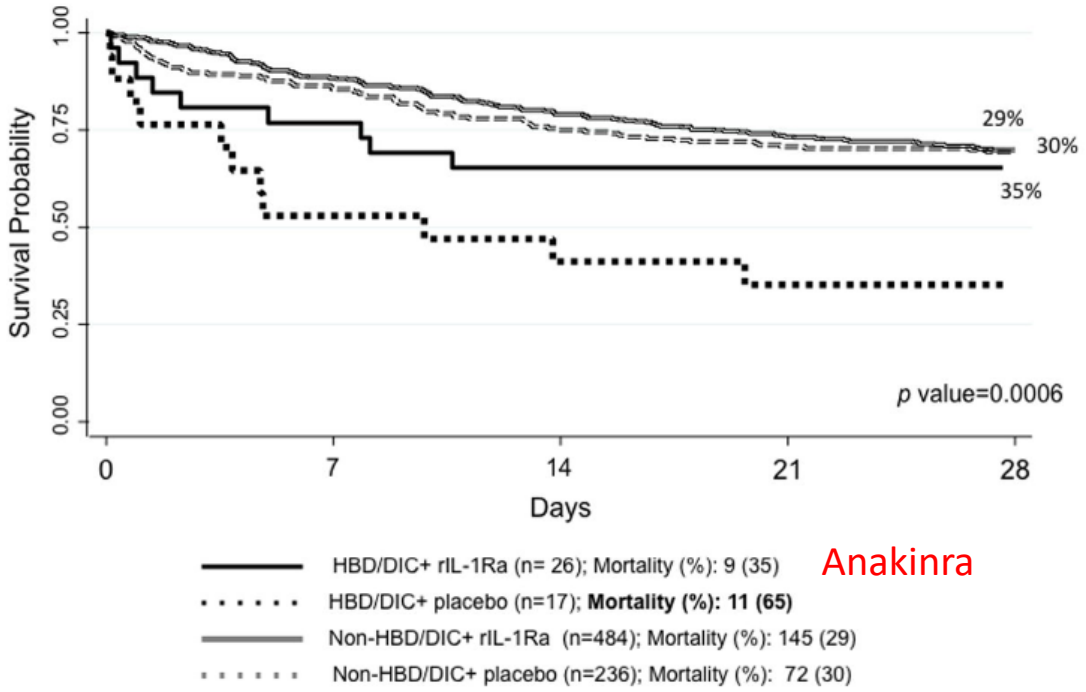






- *A Trial of Validation and Restoration of Immune Dysfunction in Severe Infections and Sepsis* (**PROVIDE**, NCT03332225) – Athens, Greece – recruitment completed, not yet published.
  - 3 arms (Anakinra, Recombinant human interferon-gamma, placebo)

Study Re-analysis



Anakinra

Critical care medicine
Author Manuscript
HHS Public Access

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

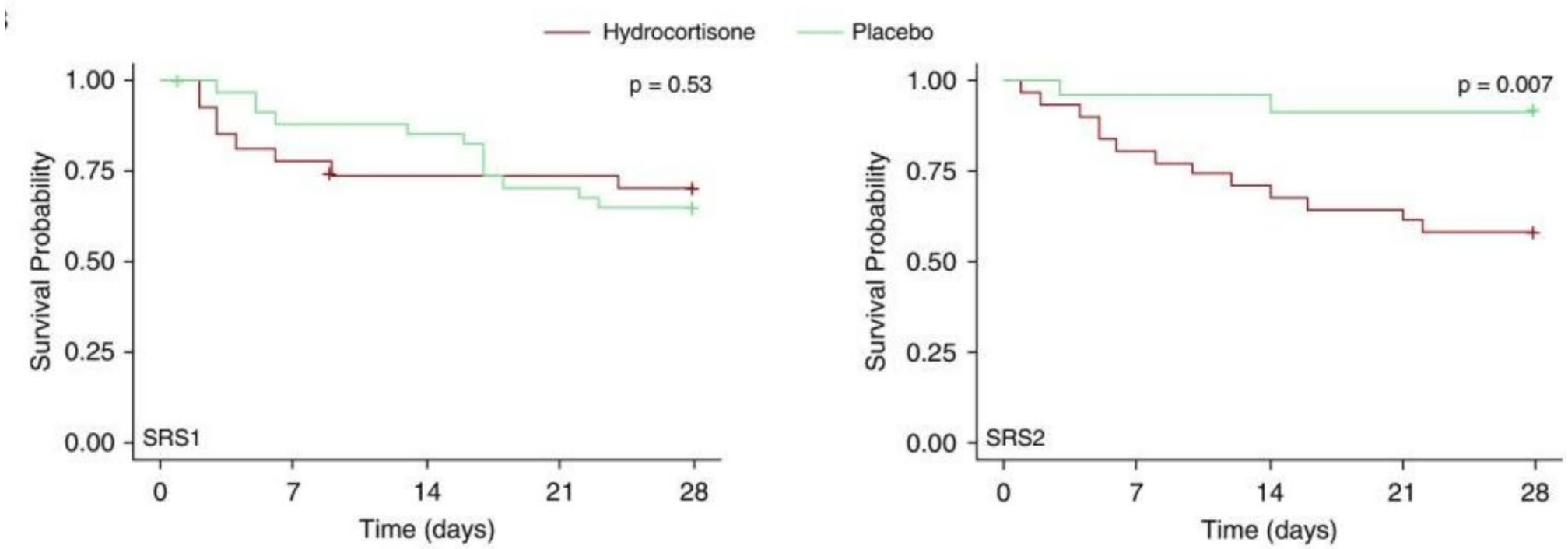
B. Shakoory, M.D., J.A. Carcillo, M.D., [...], and S.M. Opal, M.D.

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

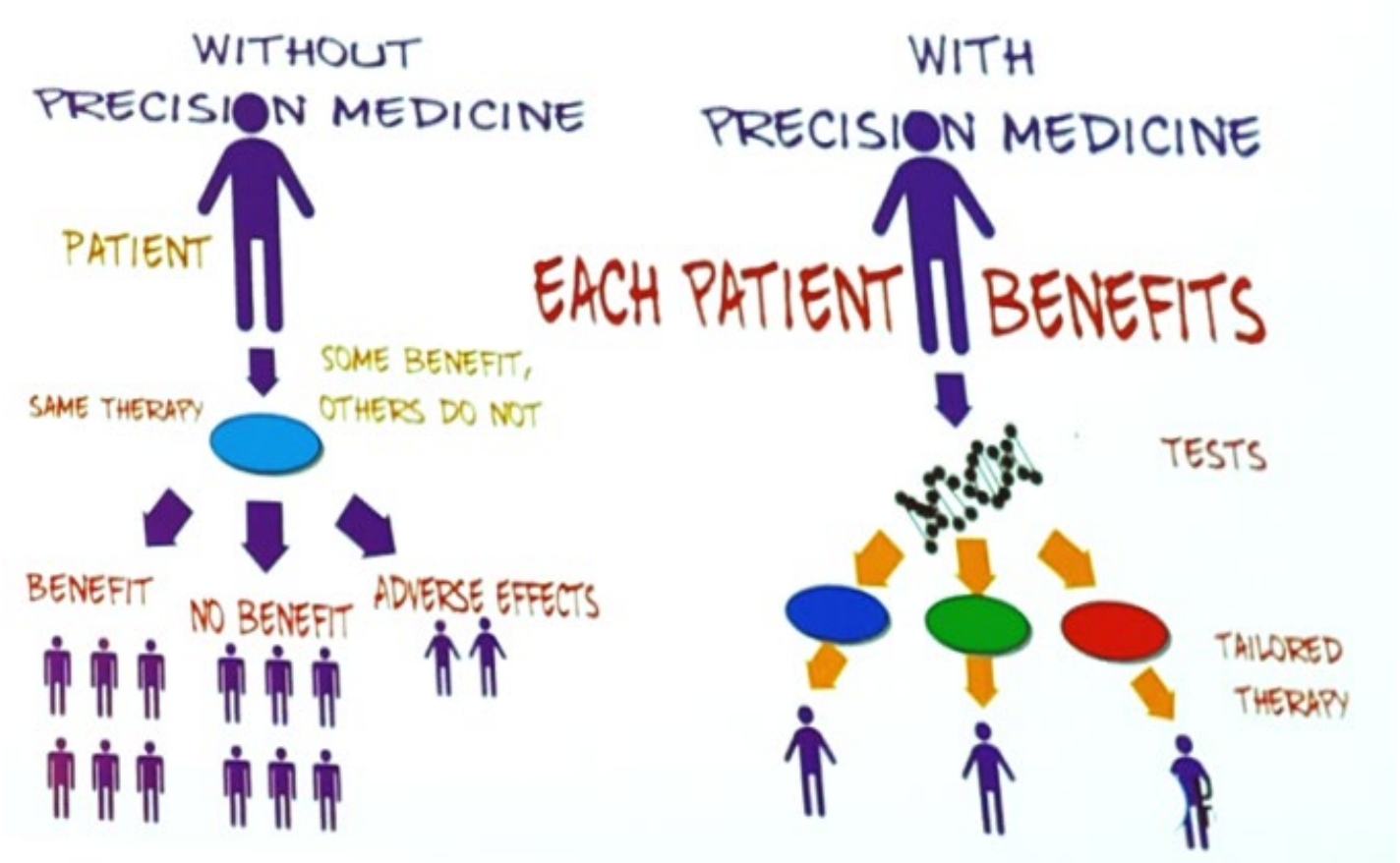
Vanish study re-analysis

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

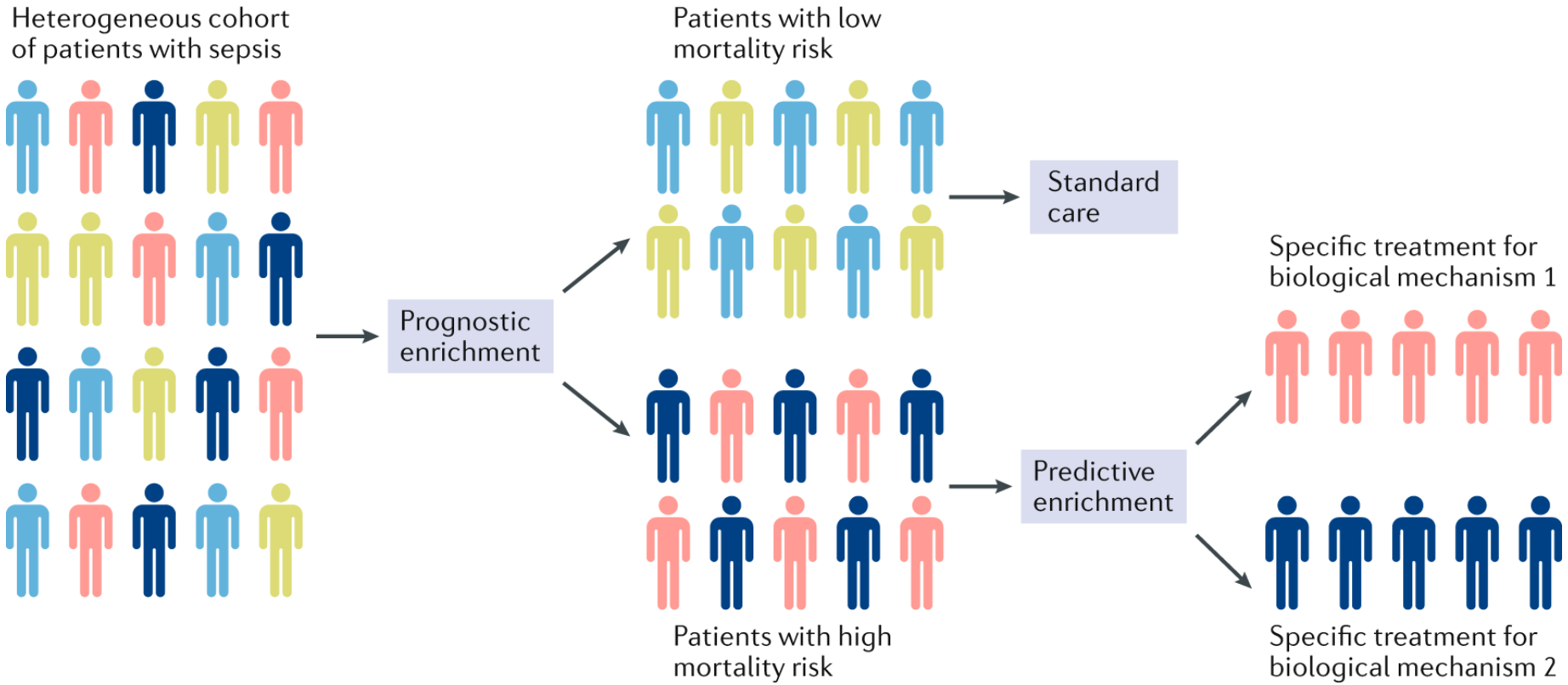


Precision medicine



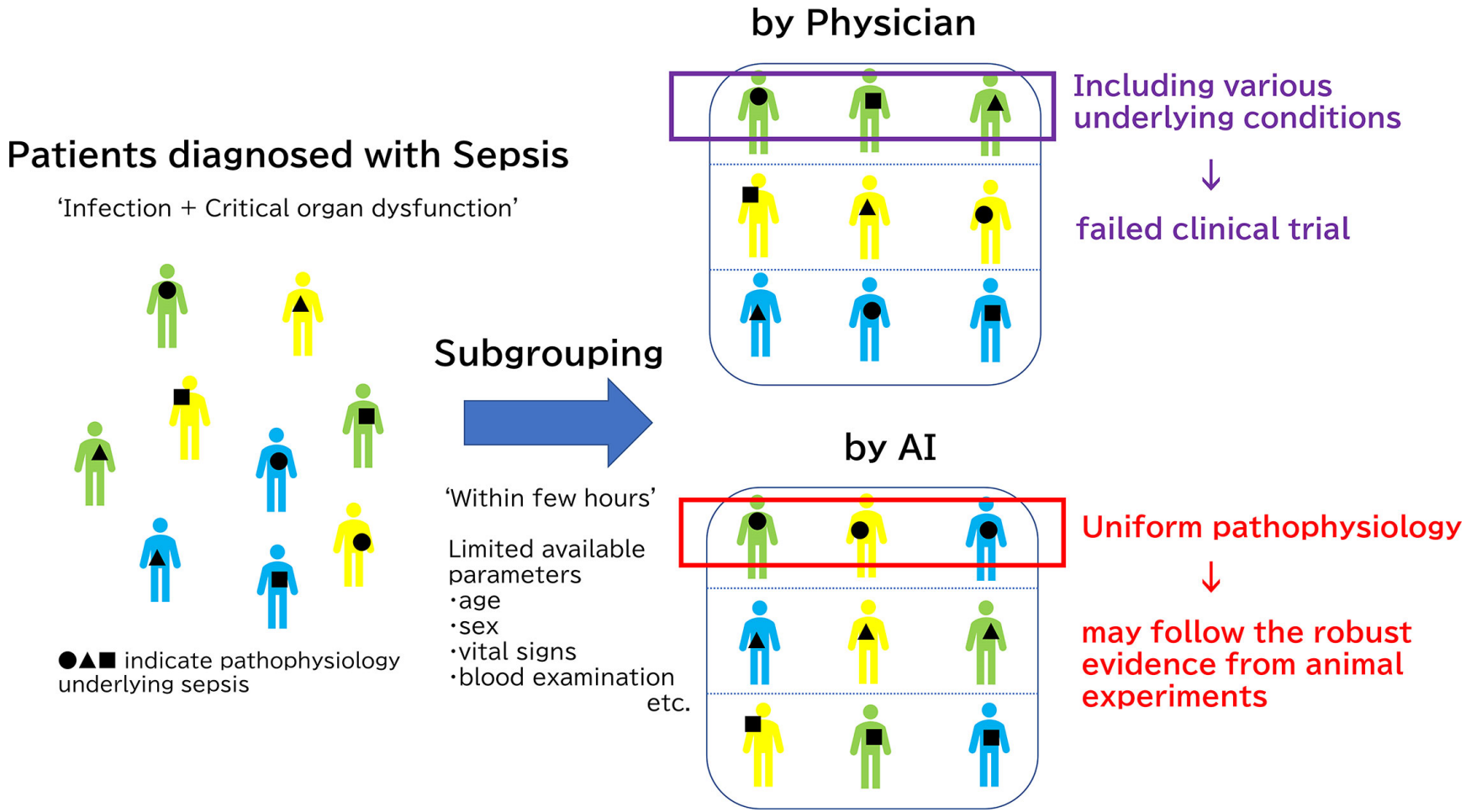
- *Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. Nat Rev Nephrol. 2019*

Prognostic/predictive enrichment



- *Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. Nat Rev Nephrol. 2019*

Artificial inteligence



📖 *Nakamori Y et al.: Immune Deregulation in Sepsis and Septic Shock: Reversing Immune Paralysis by Targeting PD-1/PD-L1 Pathway. 2021*

Thank you for your attention !

- Special thanks to my:
  - Mentors (Šrámek, Prakash, Pařenica)
  - Cooperators (Frič, Hortová Kohoutková, Vlková, De Zuani)
  - Students (Tomášková, Mýtniková)

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Editorial

Peace, not war in Ukraine or anywhere else, please

Jean-Yves Lefrant [a, b], Romain Pirracchio [c, d], Dan Benhamou [e, f], Marc-Olivier Fischer [f, g], Rosanna Njeim [h], Bernard Allaouchiche [i], Sophie Bastide [j], Matthieu Biais [k, l], Lionel Bouvet [m], Olivier Brissaud [n], Sorin J. Brull [o], Xavier Capdevila [p], Nicola Clausen [q], Philippe Cuvillon [r], Christophe Dadure [s], Jean-Stéphane David [t], Bin Du [u], Sharon Einav [v, w] ... Hervé Bouaziz [ay, az]