Sepsis – why is it so complex?

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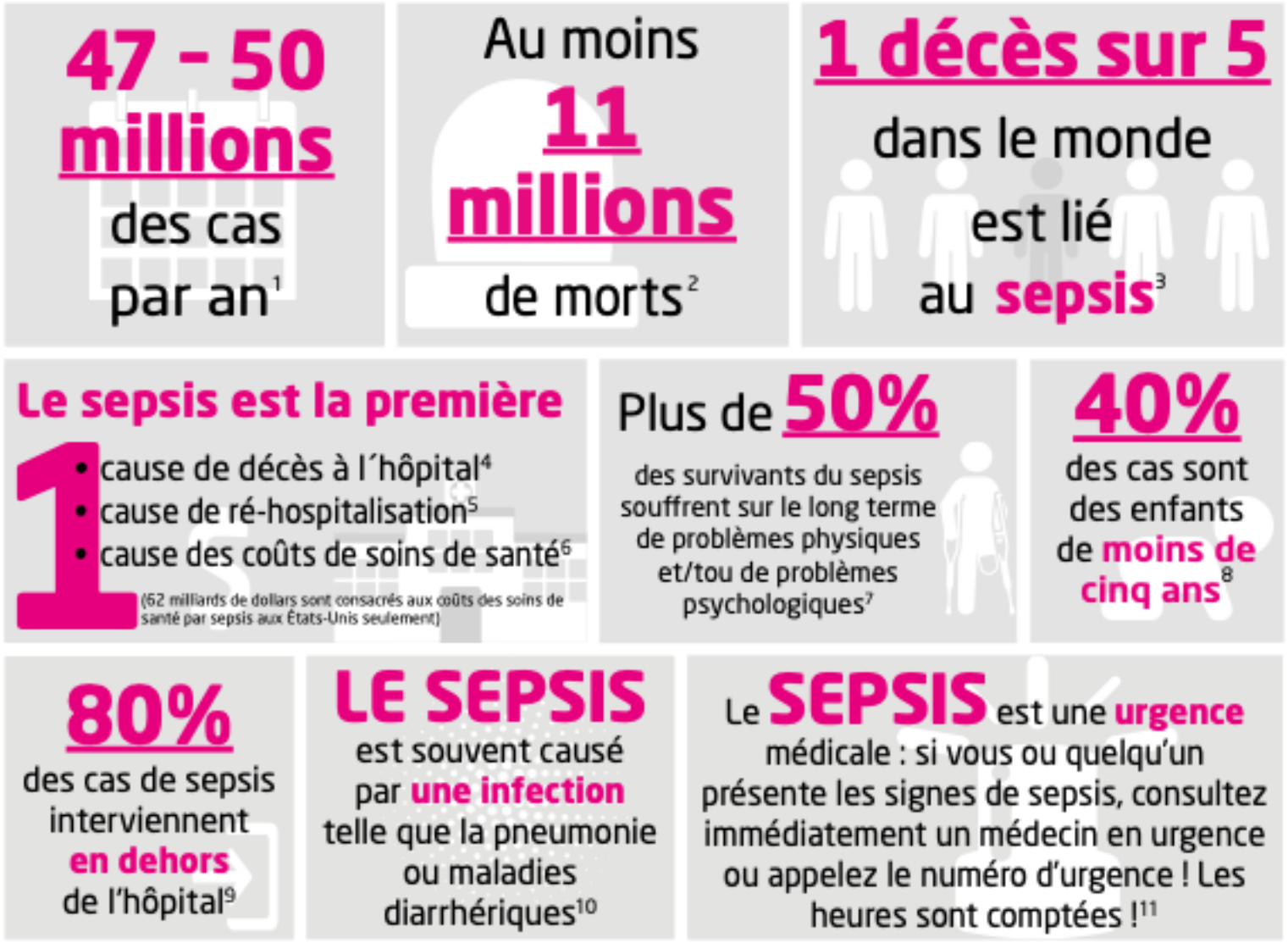
Conflicts of interest

- **Advisory Board**: OCEAN Dx

- **Conférences, Symposiums:** MSD, Pfizer, Novartis, Baxter, Cytosorb

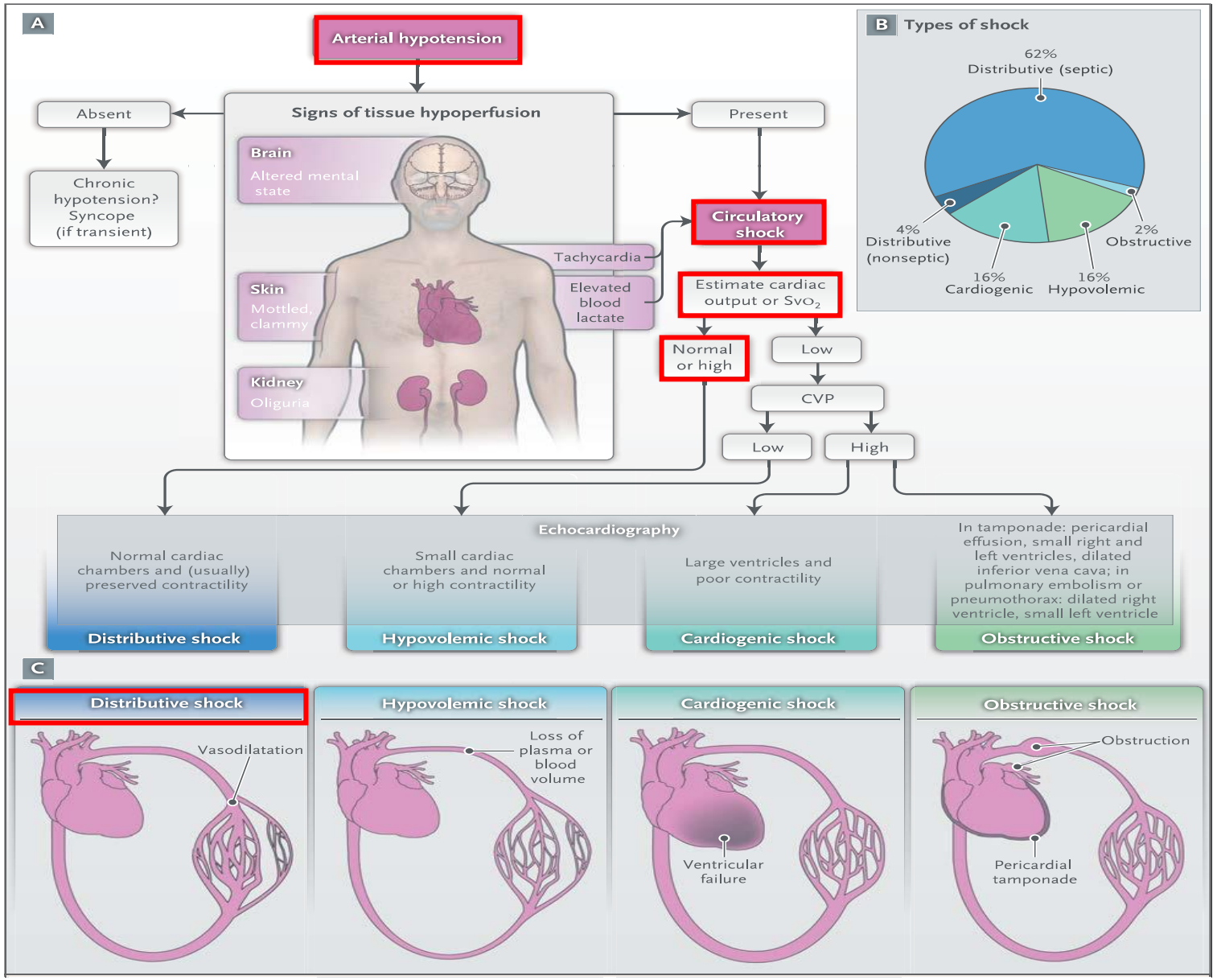
- **Grant support:** MSDavenir

Epidemiology



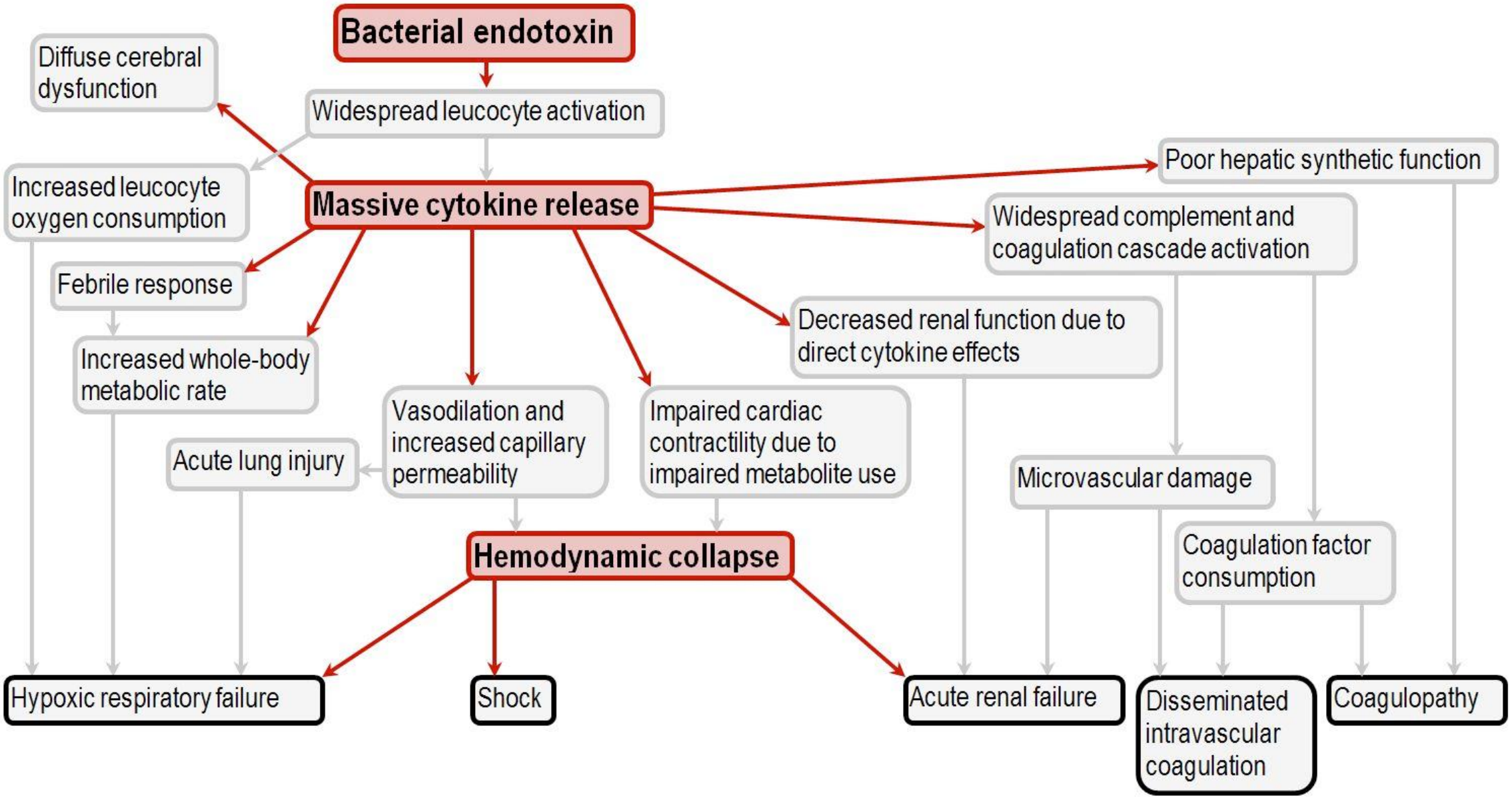
1. Because it is a complex syndrome with a recent definition

Clinical presentation of sepsis



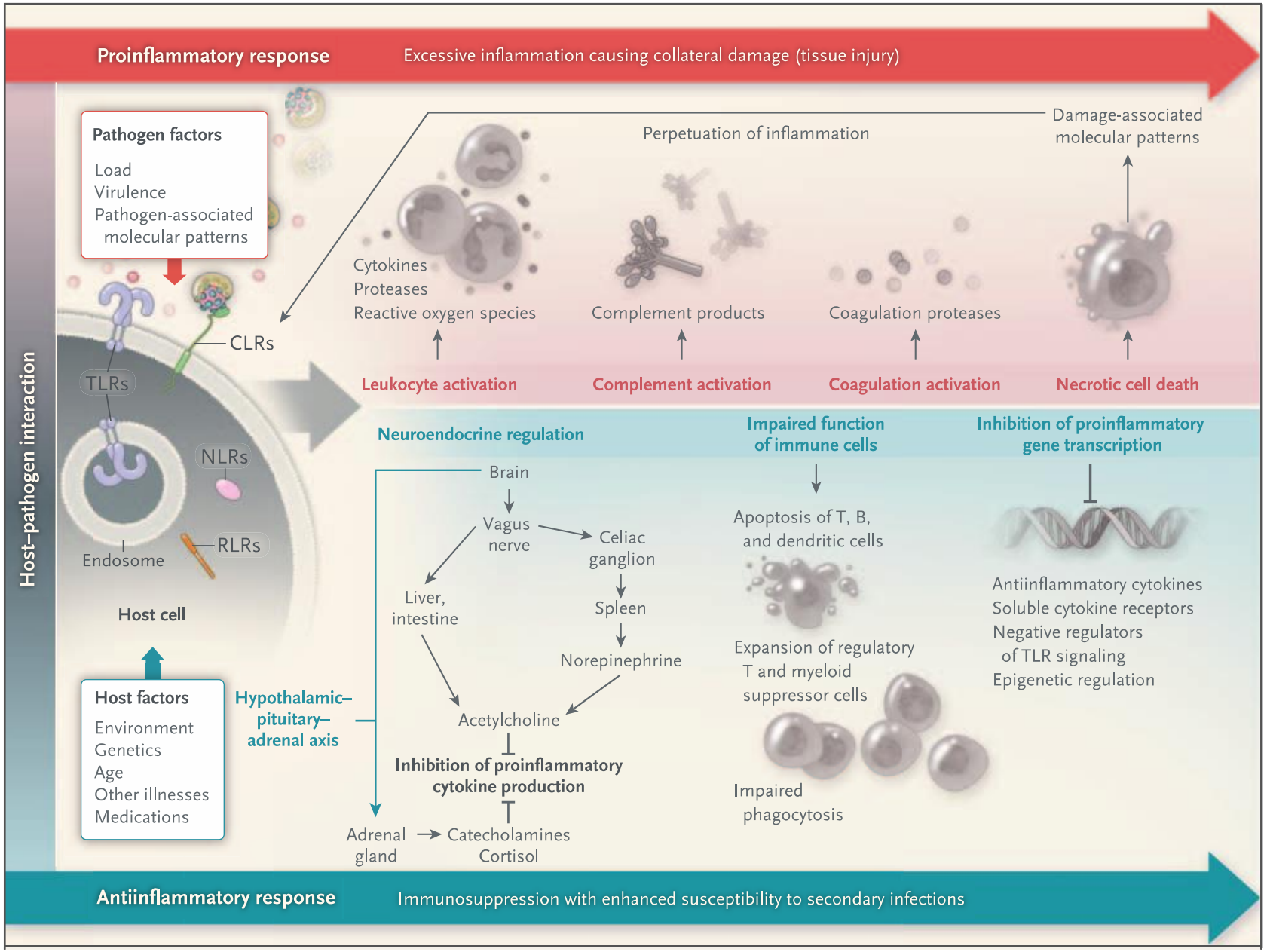
N Engl J Med 2013;369:1726-34.

Clinical presentation of sepsis



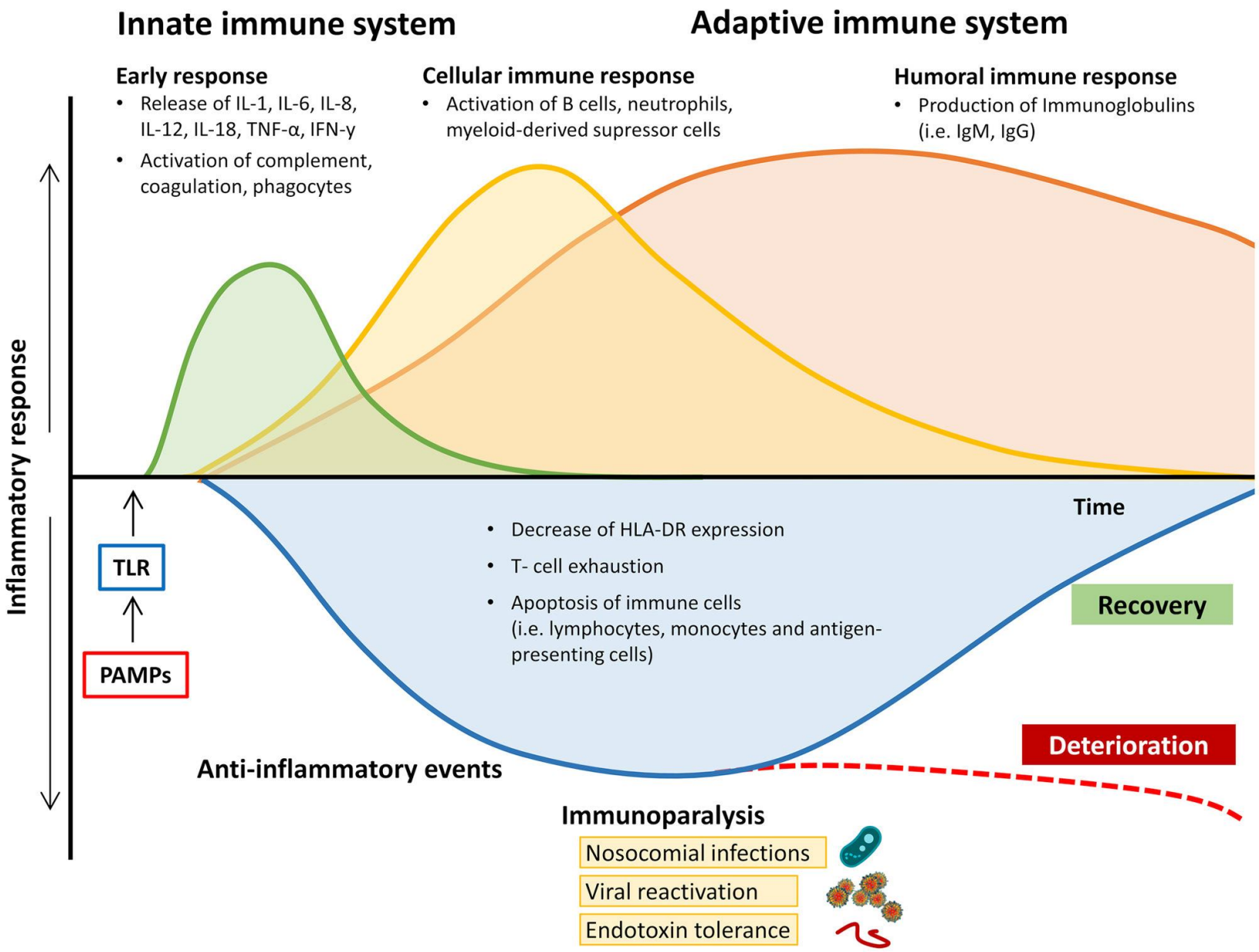
Anti-infectious immune response: from homeostasis to deregulation of the inflammatory response

The Host Response in Sepsis: pro and anti-inflammatory responses



N Engl J Med 2013; 369:840-851 DOI: 10.1056/NEJMra1208623

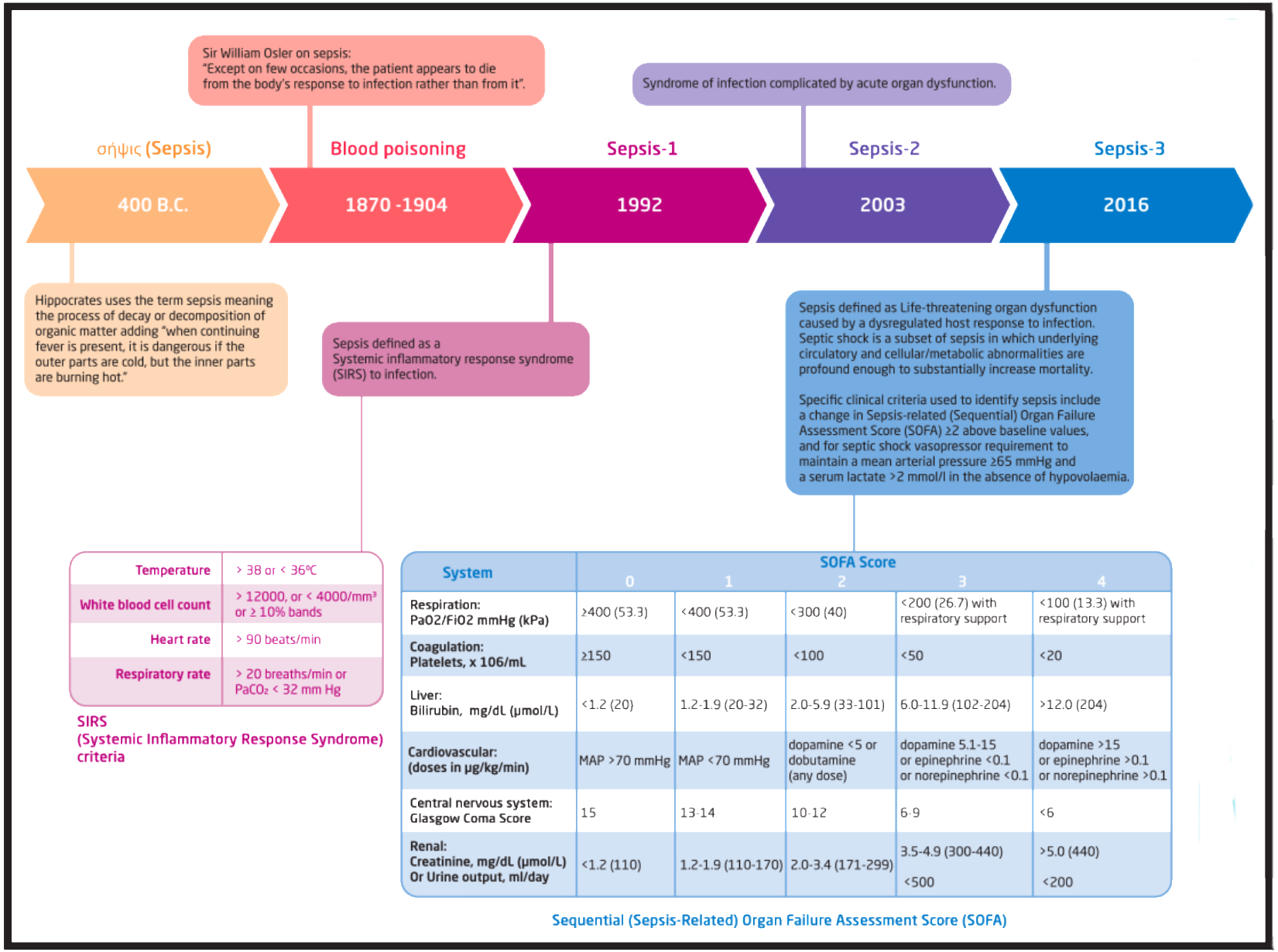
Anti-infectious immune response: from homeostasis to deregulation of the inflammatory response



Front. Med. 8:628302. doi: 10.3389/fmed.2021.628302

Anti-infectious immune response: from homeostasis to deregulation of the inflammatory response

Sepsis definition



Immunity. 2021 Nov 9;54(11):2450-2464. doi: 10.1016/j.immuni.2021.10.012.

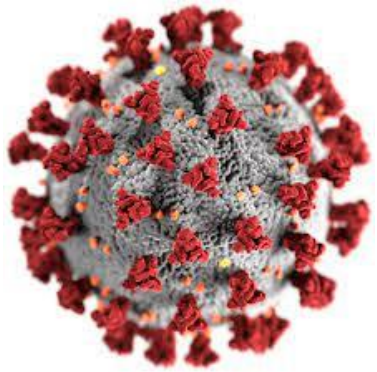
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

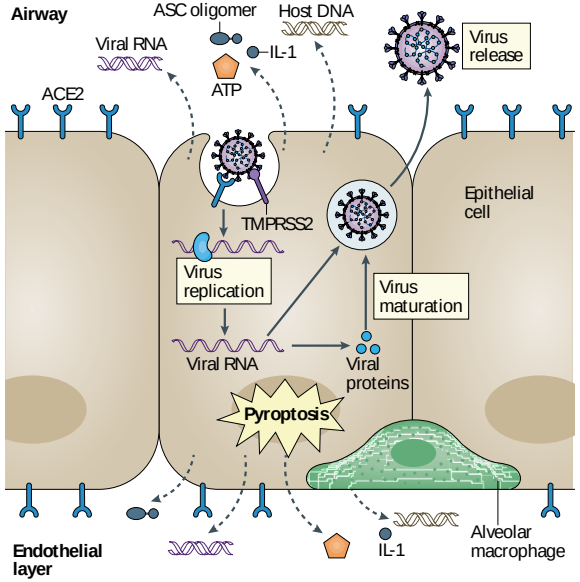
Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

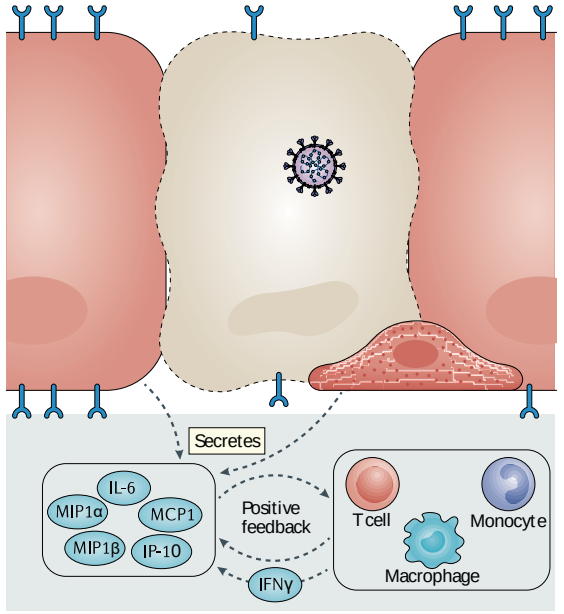
- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.

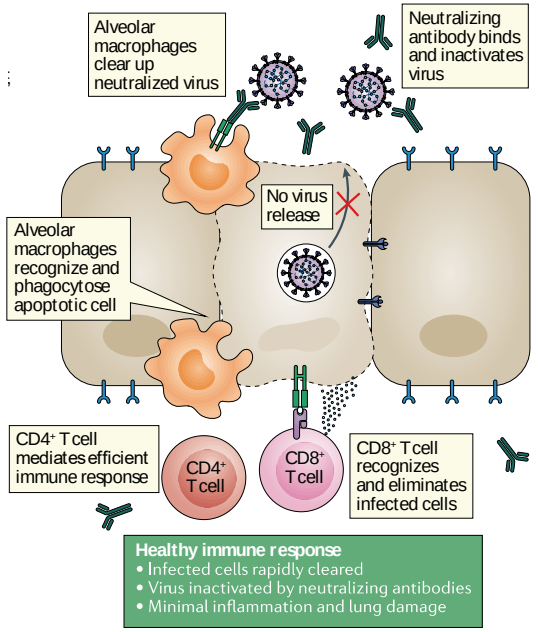
	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

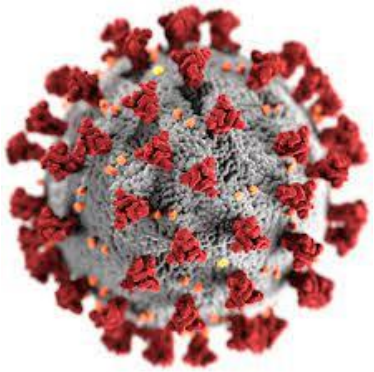


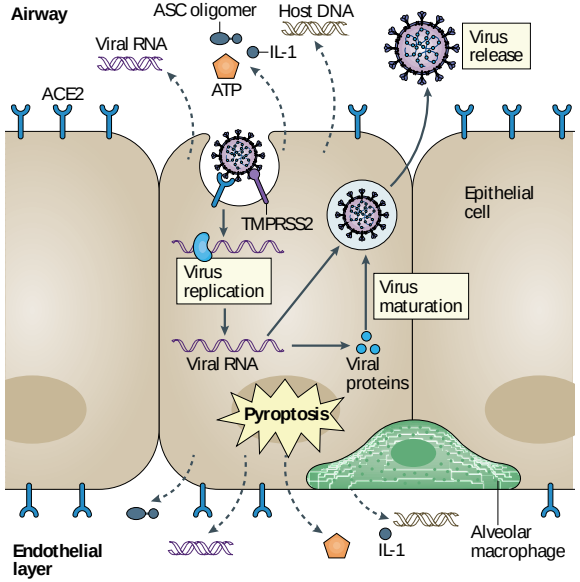


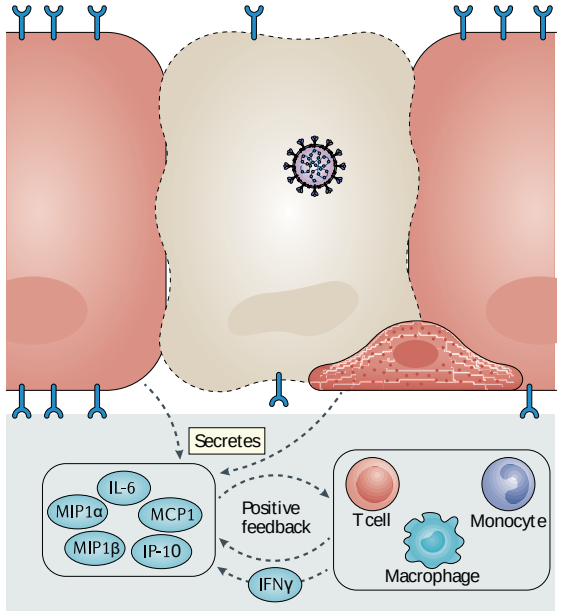


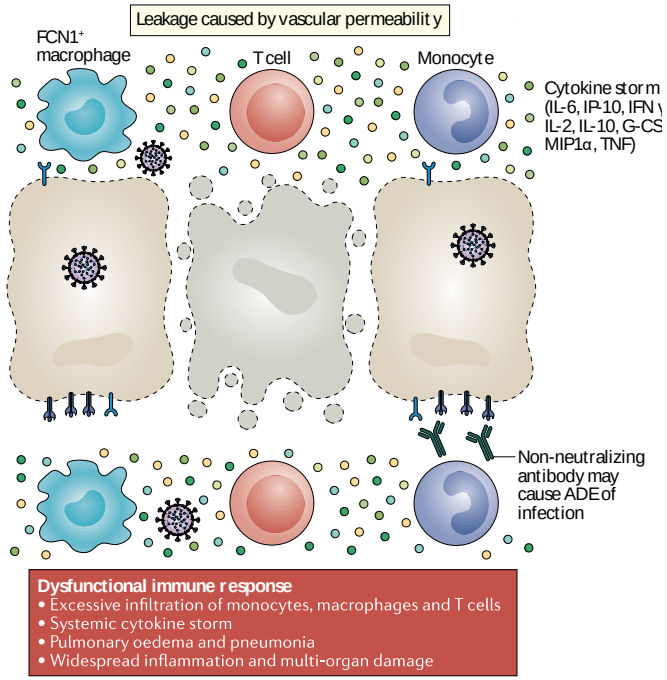


Nat Rev Immunol **20,** 363–374 (2020). https://doi.org/10.1038/s41577-020-0311-8



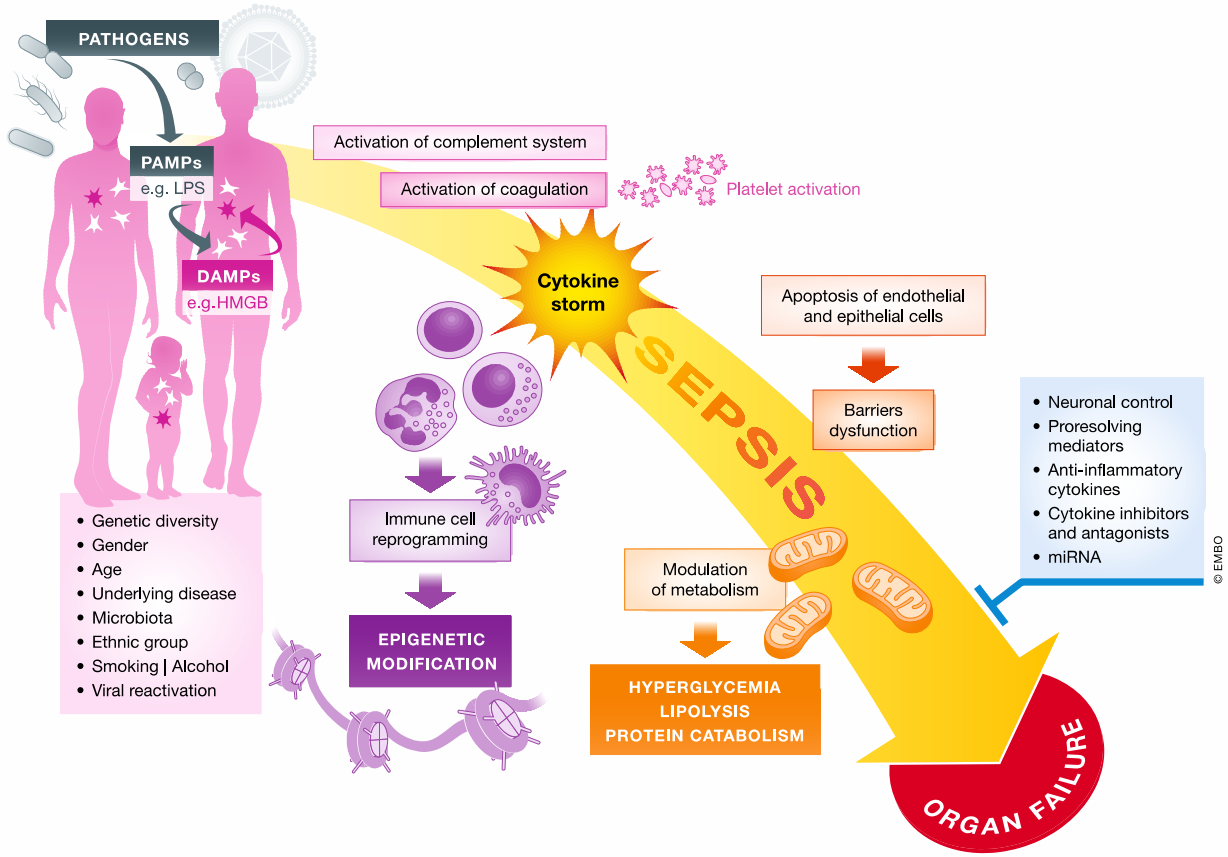




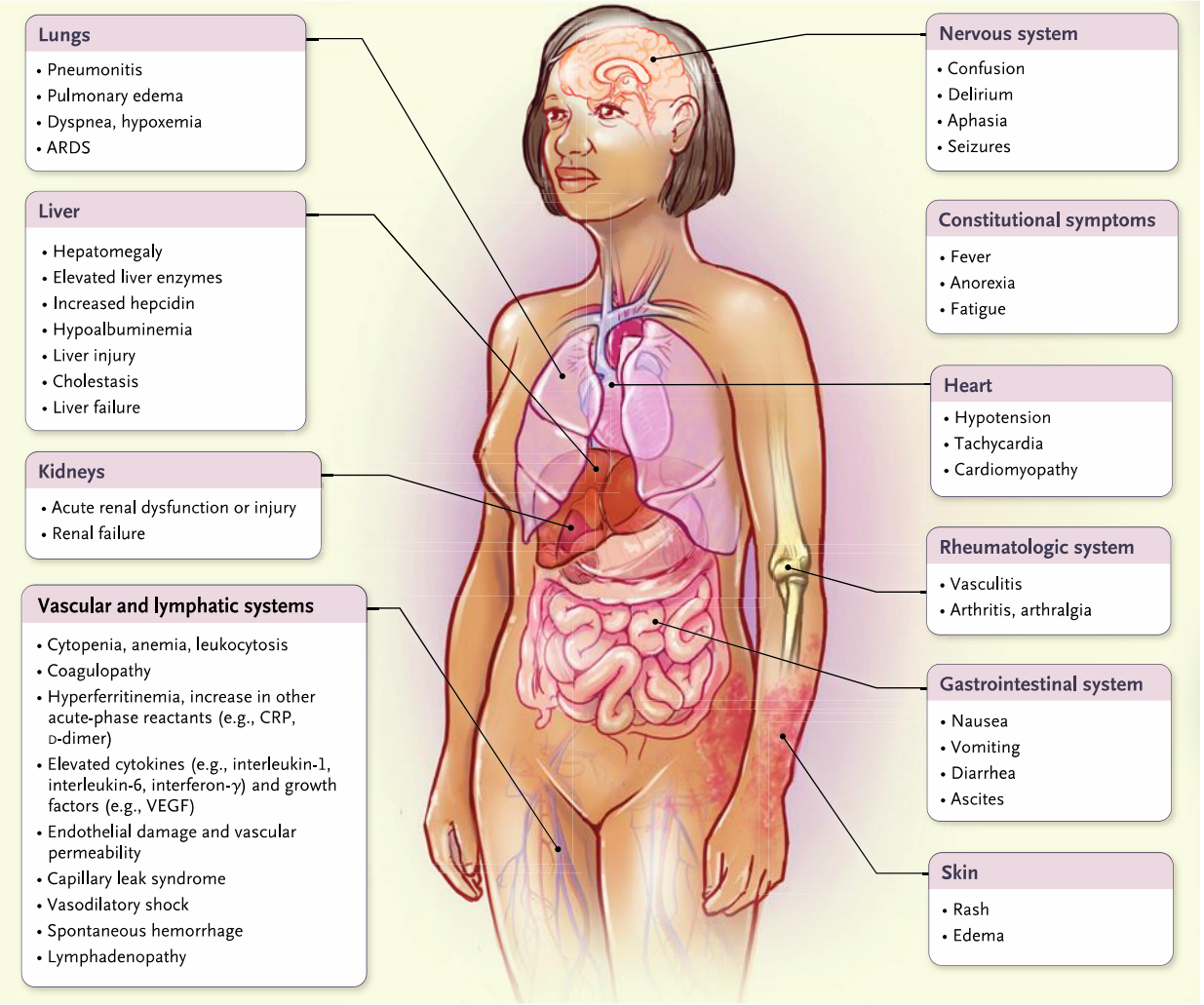


Nat Rev Immunol **20,** 363–374 (2020).
https://doi.org/10.1038/s41577-020-0311-8

2. Because its complex pathophysiology involves many actors



Molecular players



Clinical presentation of cytokine storm

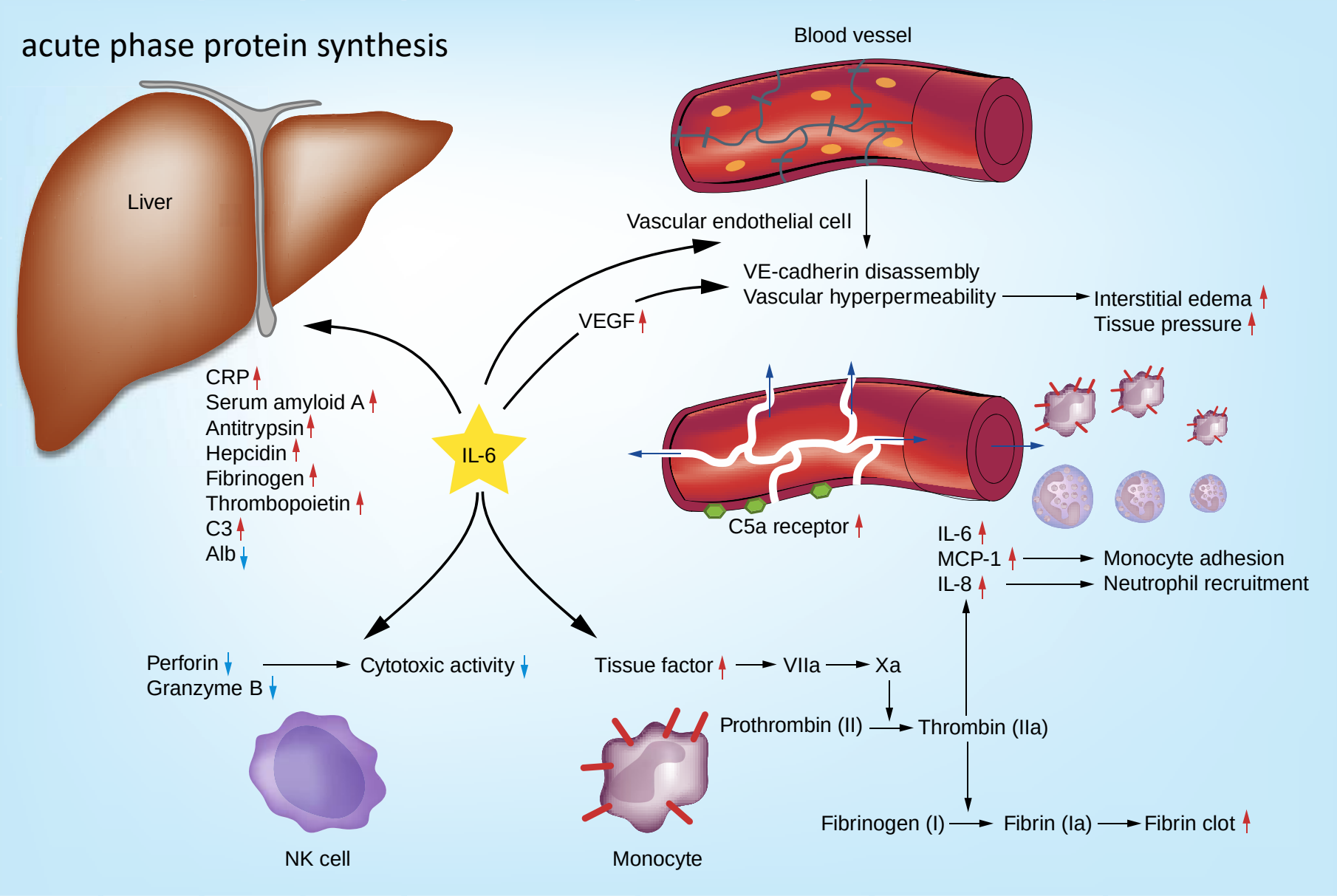
N Engl J Med 2020;383:2255-73. DOI: 10.1056/NEJMra2026131

Table 1. Soluble Mediators in Cytokine Storm.*

Mediator	Main Cell Source	Type and Function
Cytokines and growth factors		
Interleukin-1	Macrophages, epithelial cells; pyroptotic cells	Proinflammatory alarmin cytokine; pyrogenic function, macrophage and Th17 cell activation
Interleukin-2	T cells	Effector T-cell and regulatory T-cell growth factor
Interleukin-6	Macrophages, T cells, endothelial cells	Proinflammatory cytokine; pyrogenic function, increased antibody production, induction of acute-phase reactants
Interleukin-9	Th9 cells	Protection from helminth infections, activation of mast cells, association with type I interferon in Covid-19[26]
Interleukin-10	Regulatory T cells, Th9 cells	Antiinflammatory cytokine; inhibition of Th1 cells and cytokine release
Interleukin-12	Dendritic cells, macrophages	Activation of the Th1 pathway; induction of interferon-γ from Th1 cells, CTLs, and NK cells; acting in synergy with interleukin-18
Interleukin-17	Th17 cells, NK cells, group 3 innate lymphoid cells	Promoting neutrophilic inflammation, protection from bacterial and fungal infections
Interleukin-18	Monocytes, macrophages, dendritic cells	Proinflammatory alarmin cytokine; activation of Th1 pathway, acting in synergy with interleukin-12
Interleukin-33	Macrophages, dendritic cells, mast cells, epithelial cells	Proinflammatory alarmin cytokine; amplification of Th1 and Th2 cells, activation of NK cells, CTLs, and mast cells
Interferon-γ	Th1 cells, CTLs, group 1 innate lymphoid cells, and NK cells	Proinflammatory cytokine; activation of macrophages
Tumor necrosis factor	Macrophages, T cells, NK cells, mast cells	Increasing vascular permeability; pyrogenic function
GM-CSF	Th17 cells	Proinflammatory cytokine
VEGF	Macrophages	Angiogenesis
Chemokines		
Interleukin-8 (CXCL8)	Macrophages, epithelial cells	Recruitment of neutrophils
MIG (CXCL9)	Monocytes, endothelial cells, keratinocytes	Interferon-inducible chemokine; recruitment of Th1 cells, NK cells, plasmacytoid dendritic cells
IP-10 (CXCL10)	Monocytes, endothelial cells, keratinocytes	Interferon-inducible chemokine; recruitment of macrophages, Th1 cells, NK cells
MCP-1 (CCL2)	Macrophages, dendritic cells, cardiac myocytes	Recruitment of Th2 cells, monocytes, dendritic cells, basophils
MIP-1α (CCL3)	Monocytes, neutrophils, dendritic cells, NK cells, mast cells	Recruitment of macrophages, Th1 cells, NK cells, eosinophils, dendritic cells; pyrogenic function
MIP-1β (CCL4)	Macrophages, neutrophils, endothelium	Recruitment of macrophages, Th1 cells, NK cells, dendritic cells
BLC (CXCL13)	B cells, follicular dendritic cells	Recruitment of B cells, CD4 T cells, dendritic cells†
Plasma proteins		
CRP	Hepatocytes	Monomeric CRP increases interleukin-8 and MCP-1 secretion; interleukin-6 increases CRP expression
Complement	Hepatocytes, other cells	Complement activation contributes to tissue damage in cytokine storm; complement inhibition can reduce immunopathologic effects of cytokine storm
Ferritin	Ubiquitous	Primary site of iron storage in cells

Molecular players

Role of Il-6 in acute inflammation



Immunotherapy . 2016 Jul;8(8):959-70. doi: 10.2217/imt-2016-0020

Molecular players

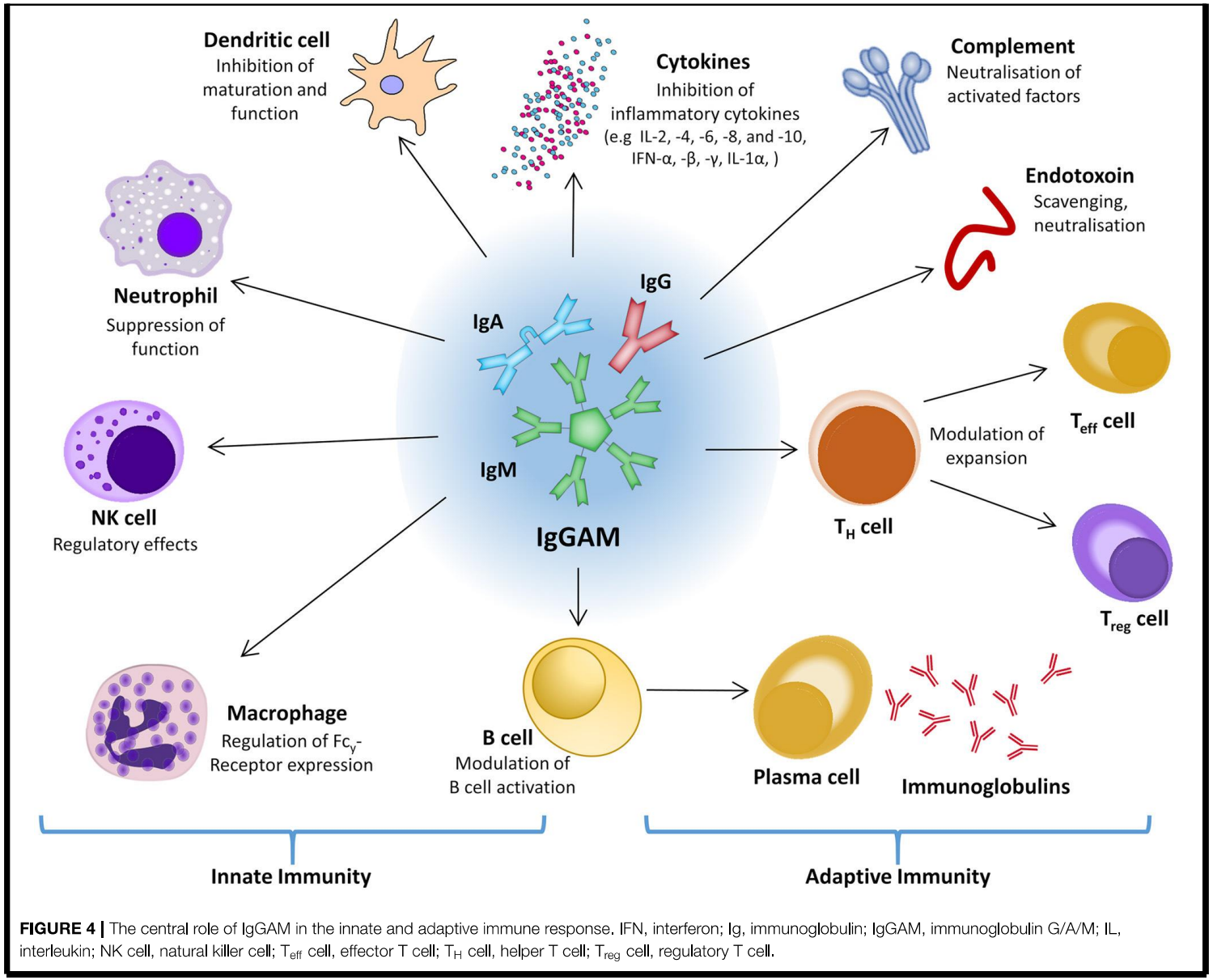


FIGURE 4 | The central role of IgGAM in the innate and adaptive immune response. IFN, interferon; Ig, immunoglobulin; IgGAM, immunoglobulin G/A/M; IL, interleukin; NK cell, natural killer cell; T_{eff} cell, effector T cell; T_H cell, helper T cell; T_{reg} cell, regulatory T cell.

Front Med 2021 May 14;8:628302. doi: 10.3389/fmed.2021.628302

Circulating cells

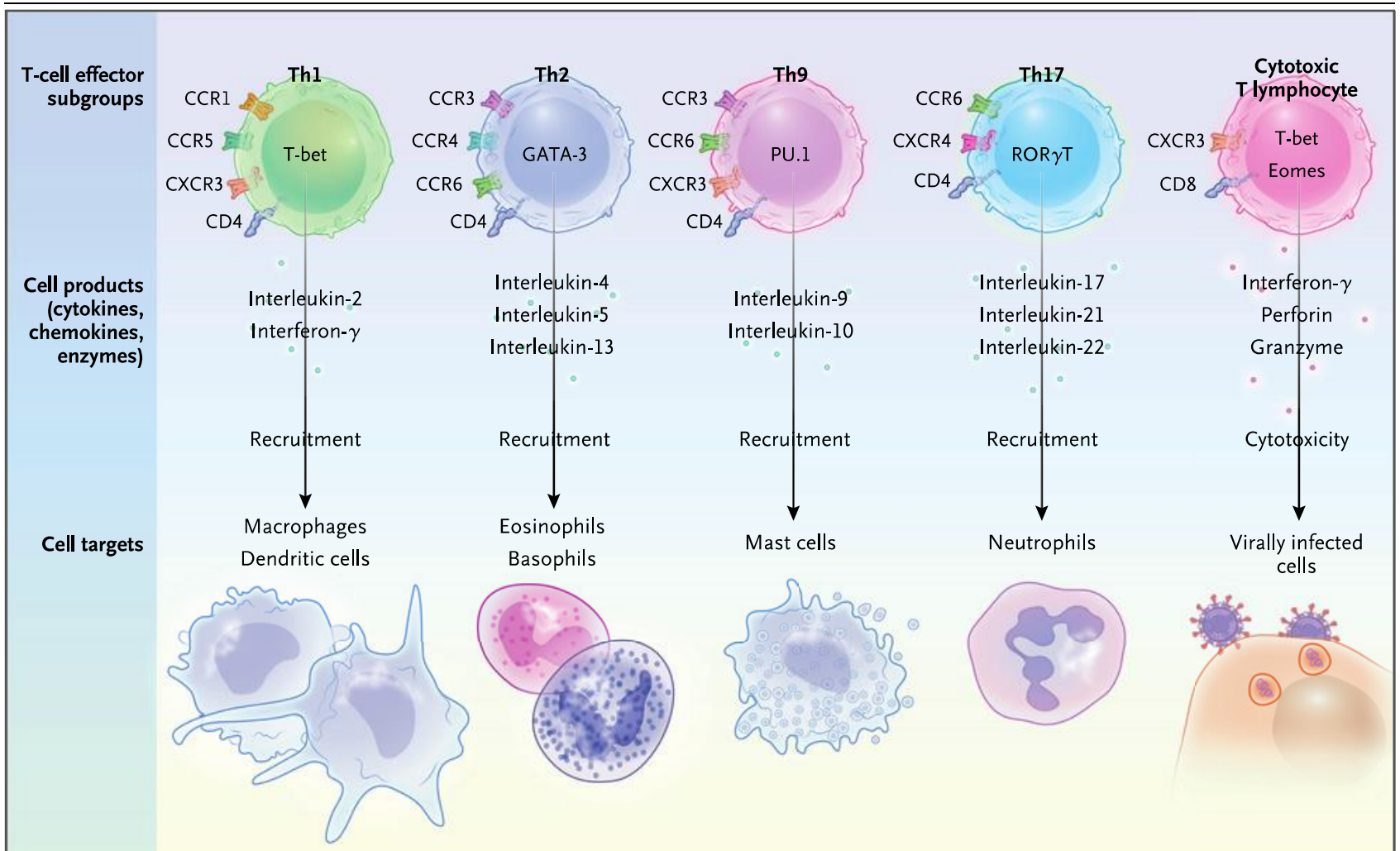


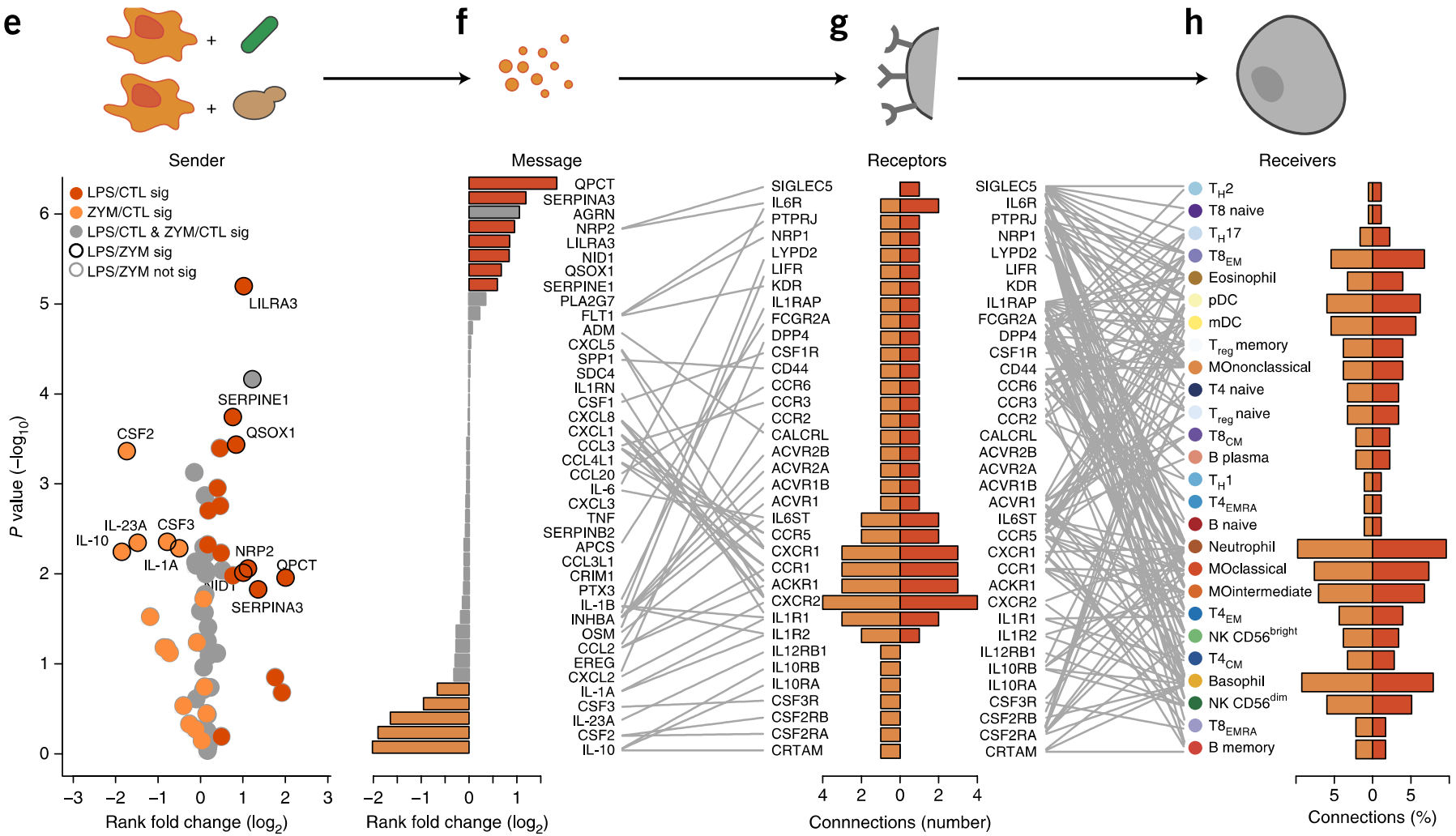
Figure 3. T-Cell Effector Subgroups Involved in Cytokine Storm.

The master transcription factors (T-bet, GATA-3, PU.1, RORγT, and eomesodermin [eomes]), effector molecules, and cell targets are shown for the following T-cell subgroups: types 1, 2, 9, and 17 helper T (Th1, Th2, Th9, and Th17, respectively) cells and cytotoxic T lymphocytes.

N Engl J Med 2020;383:2255-73. DOI: 10.1056/NEJMra2026131

Circulating cells

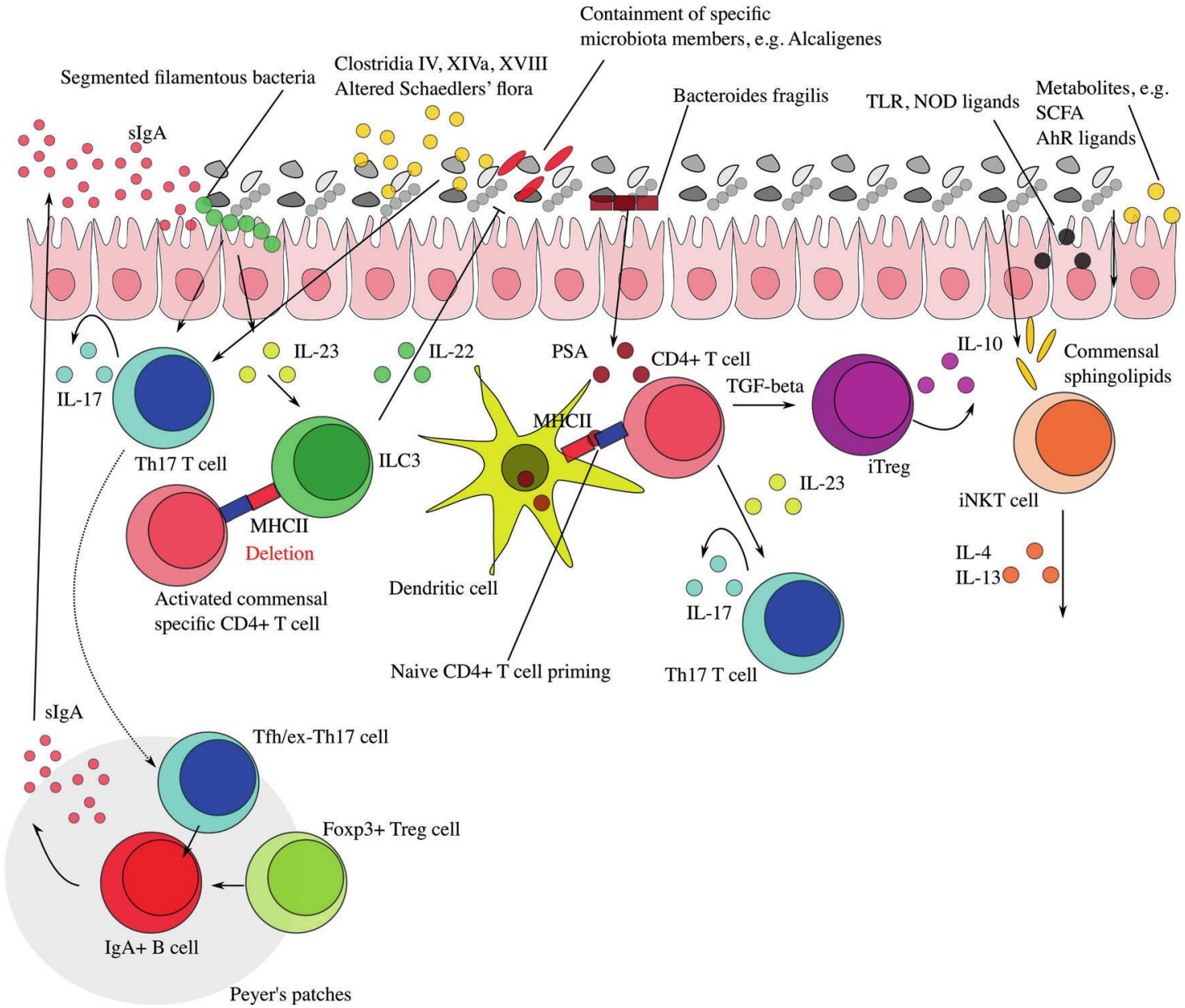
Social network architecture of human immune cells unveiled by quantitative proteomics



Nat Immunol. 2017 May;18(5):583-593. doi: 10.1038/ni.3693. Epub 2017 Mar 6

Host-pathogen interactions and microbiology of sepsis

Interaction between microbiota and immunity in health and disease



Cell Res . 2020 Jun;30(6):492-506. doi: 10.1038/s41422-020-0332-7

Clinical Infectious Diseases

INVITED ARTICLE

REVIEWS OF ANTI-INFECTIVE AGENTS: Louis Saravolatz, Section Editor

Busting the Myth of "Static vs Cidal": A Systemic Literature Review

Noah Wald-Dickler,[1,2] Paul Holtom,[1,2] and Brad Spellberg[1,2]

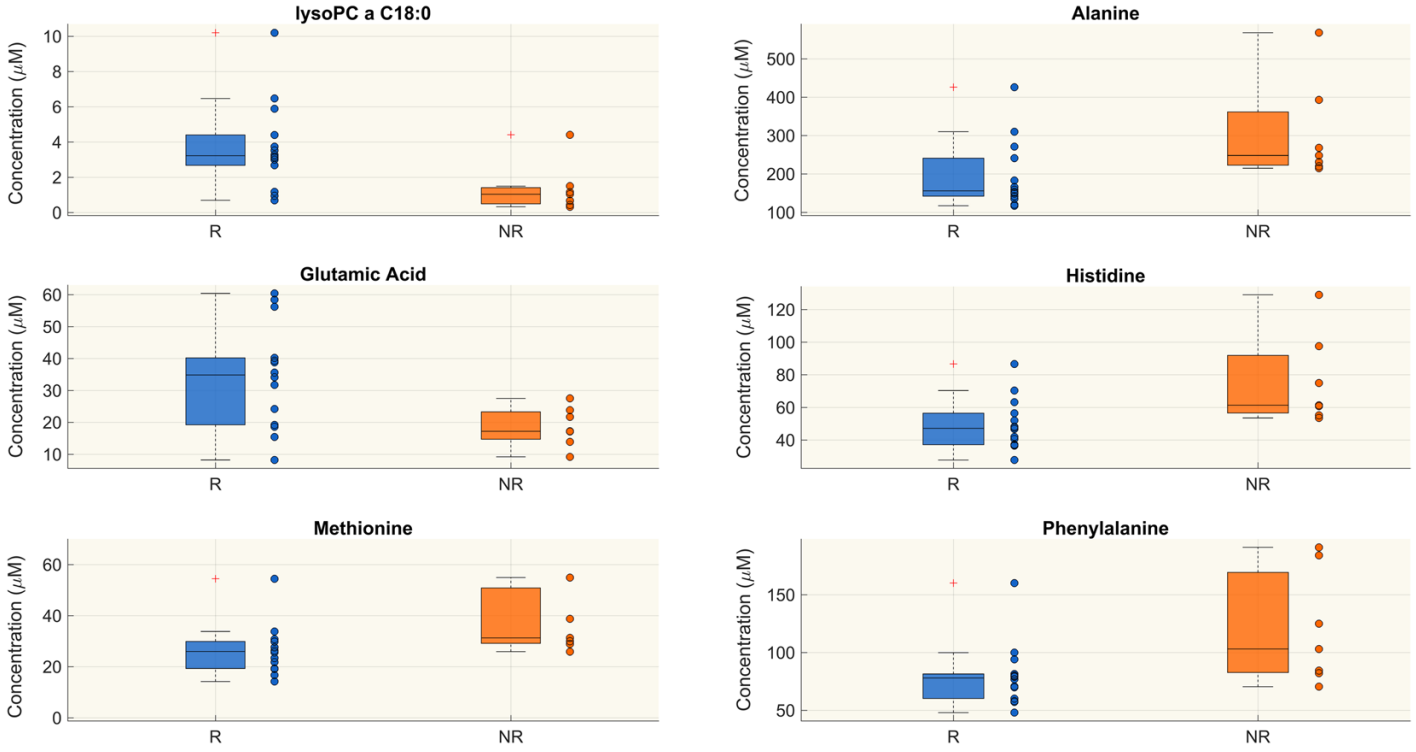
[1]Los Angeles County + University of Southern California Medical Center and [2]Division of Infectious Diseases, Keck School of Medicine at the University of Southern California, Los Angeles

We sought to determine if clinical data validate the dogma that bactericidal antibiotics are more clinically effective than bacteriostatic agents. We performed a systematic literature review of published, randomized, controlled trials (RCTs) that compared a bacteriostatic agent to a bactericidal agent in the treatment of clinical, bacterial infections. Of 56 identified trials published since 1985, 49 found no significant difference in efficacy between bacteriostatic and bactericidal agents. In 6 trials it was found that the bacteriostatic agent was superior to the bactericidal agent in efficacy. Only 1 trial found that the bactericidal agent was superior; in that case, the inferiority of the static agent was explainable by underdosing of the drug based on pharmacokinetic–pharmacodynamic analysis. Thus, virtually all available data from high-quality, RCTs demonstrate no intrinsic superiority of bactericidal compared to bacteriostatic agents. Other drug characteristics such as optimal dosing, pharmacokinetics, and tissue penetration may be more important efficacy drivers.

Modulation of metabolism

Characterization of a metabolomic profile associated with responsiveness to therapy in the acute phase of septic shock

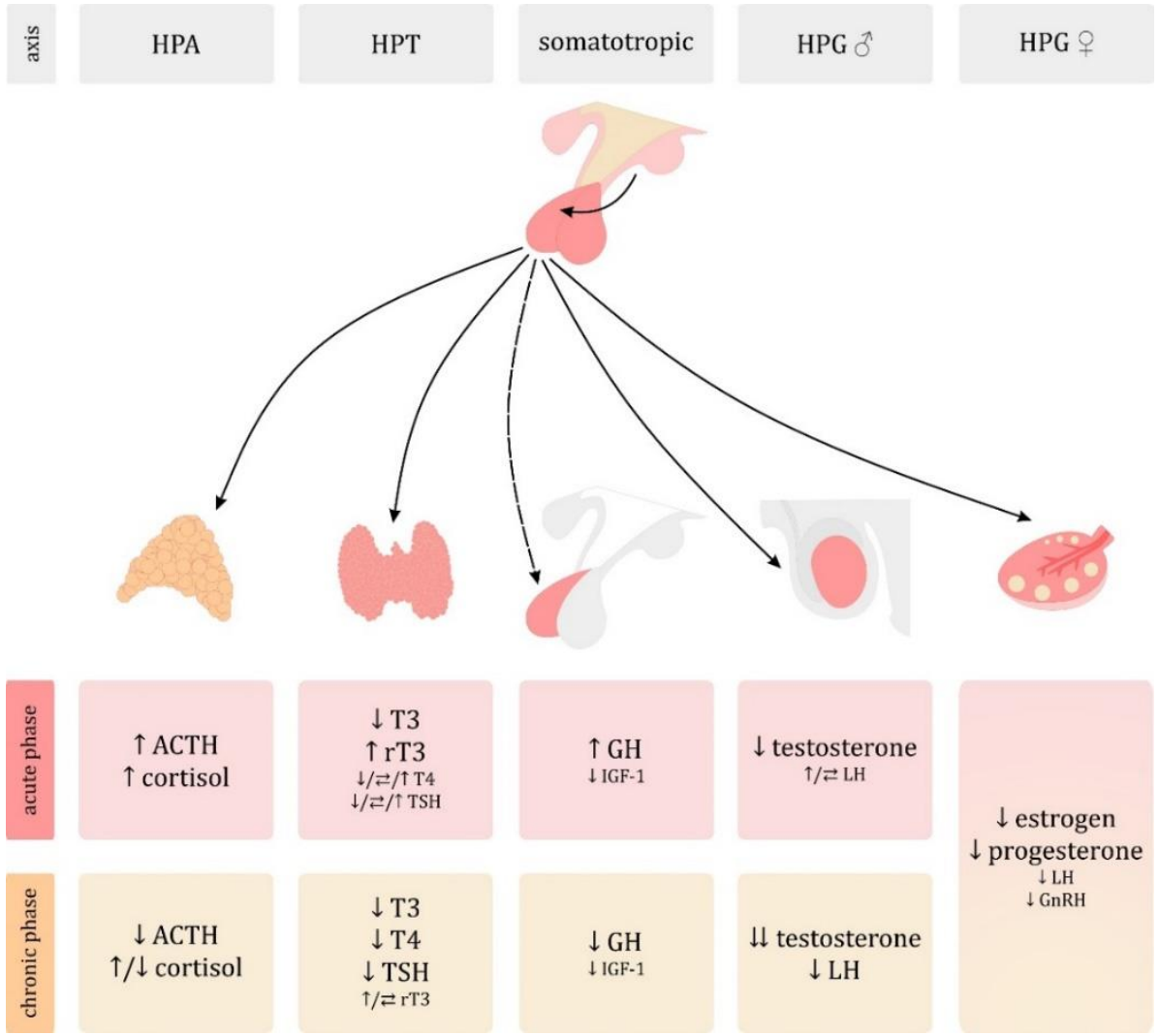
Alice Cambiaghi[1], Bernardo Bollen Pinto[2], Laura Brunelli[3], Francesca Falcetta[3], Federico Aletti[1], Karim Bendjelid[2], Roberta Pastorelli[3] & Manuela Ferrario[1]

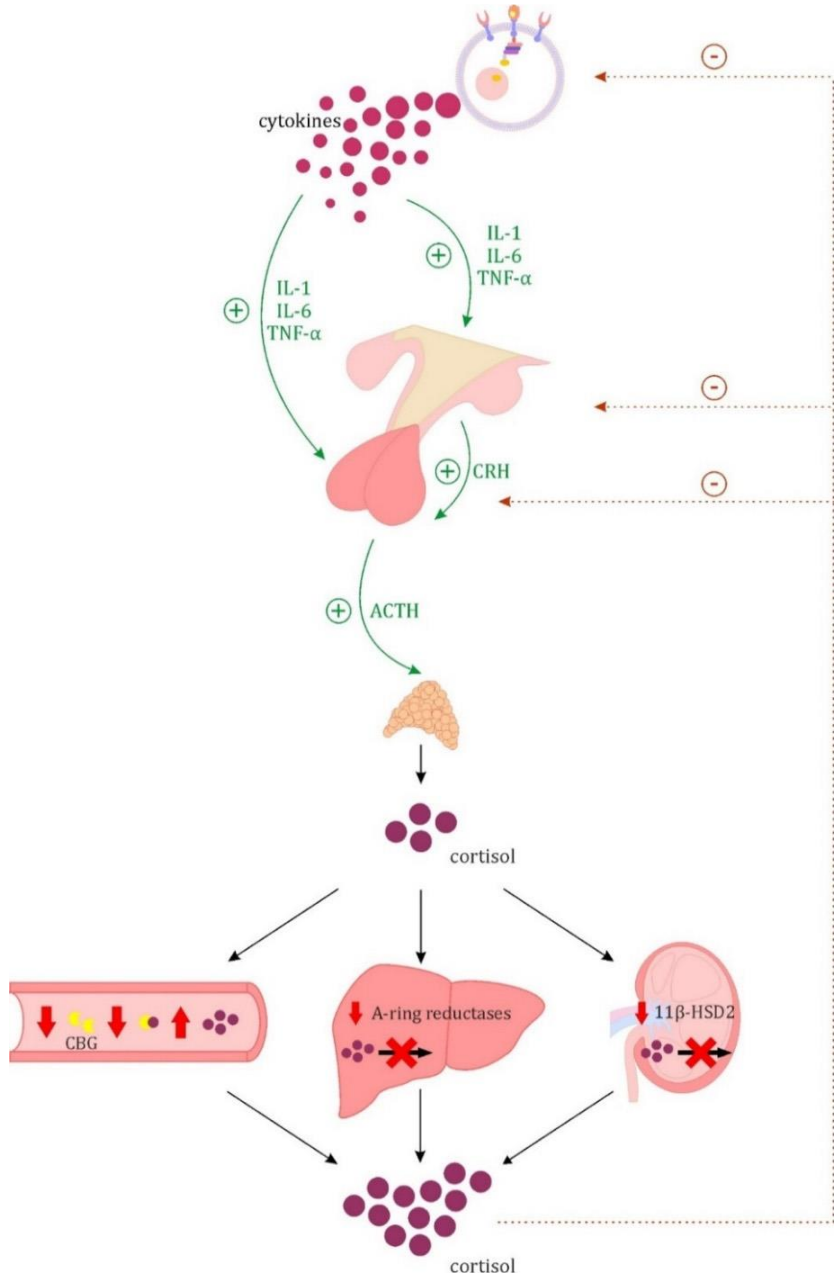


	R	NR	R vs NR
lysoPC a C16:0	15.700 (10.300, 17.500)	4.020 (1.400, 6.572)	↑
lysoPC a C16:1	0.604 (0.470, 0.690)	0.158 (0.099, 0.238)	↑
lysoPC a C18:0	3.220 (2.680, 4.400)	1.040 (0.494, 1.415)	↑
lysoPC a C18:1	6.090 (3.010, 6.770)	1.470 (1.170, 2.200)	↑
lysoPC a C18:2	6.075 (2.330, 8.060)	1.160 (0.916, 2.310)	↑
lysoPC a C20:3	0.474 (0.333, 0.834)	0.222 (0.147, 0.275)	↑
PC aa C36:0	2.645 (1.900, 3.270)	1.880 (1.580, 1.980)	↑
PC aa C36:3	188 (136, 227)	120 (110.25, 133.5)	↑
PC aa C36:6	0.888 (0.841, 1.050)	0.570 (0.534, 0.717)	↑
PC aa C38:3	36.750 (29.200, 47.700)	25.300 (18.750, 30.025)	↑
PC aa C38:6	88.150 (70.800, 101.000)	62.200 (57.175, 77.900)	↑
PC aa C40:5	6.670 (6.220, 7.350)	5.500 (4.575, 6.715)	↑
PC aa C40:6	23.800 (17.700, 25.400)	19.400 (16.025, 19.800)	↑
PC aa C42:2	0.154 (0.121, 0.176)	0.111 (0.102, 0.116)	↑
PC ae C38:0	1.415 (1.280, 1.620)	0.970 (0.954, 1.238)	↑
PC ae C38:3	4.040 (2.960, 4.480)	2.920 (2.353, 3.075)	↑
SM C18:0	7.385 (6.880, 8.770)	6.430 (4.728, 6.750)	↑
SM C24:0	1.235 (1.020, 1.560)	0.954 (0.882, 1.115)	↑
Alanine	156 (142, 241)	248 (222.75, 361.75)	↓
Glutamic acid	34.850 (19.200, 40.200)	17.200 (14.700, 23.275)	↑
Histidine	47.100 (37.100, 56.400)	61.300 (56.500, 91.850)	↓
Methionine	25.950 (19.300, 29.900)	31.300 (29.175, 50.875)	↓
Phenylalanine	77.900 (60.100, 81.400)	103 (82.650, 169.250)	↓

Sci Rep. 2017 Aug 29;7(1):9748. doi: 10.1038/s41598-017-09619-x.

Endocrinopathy

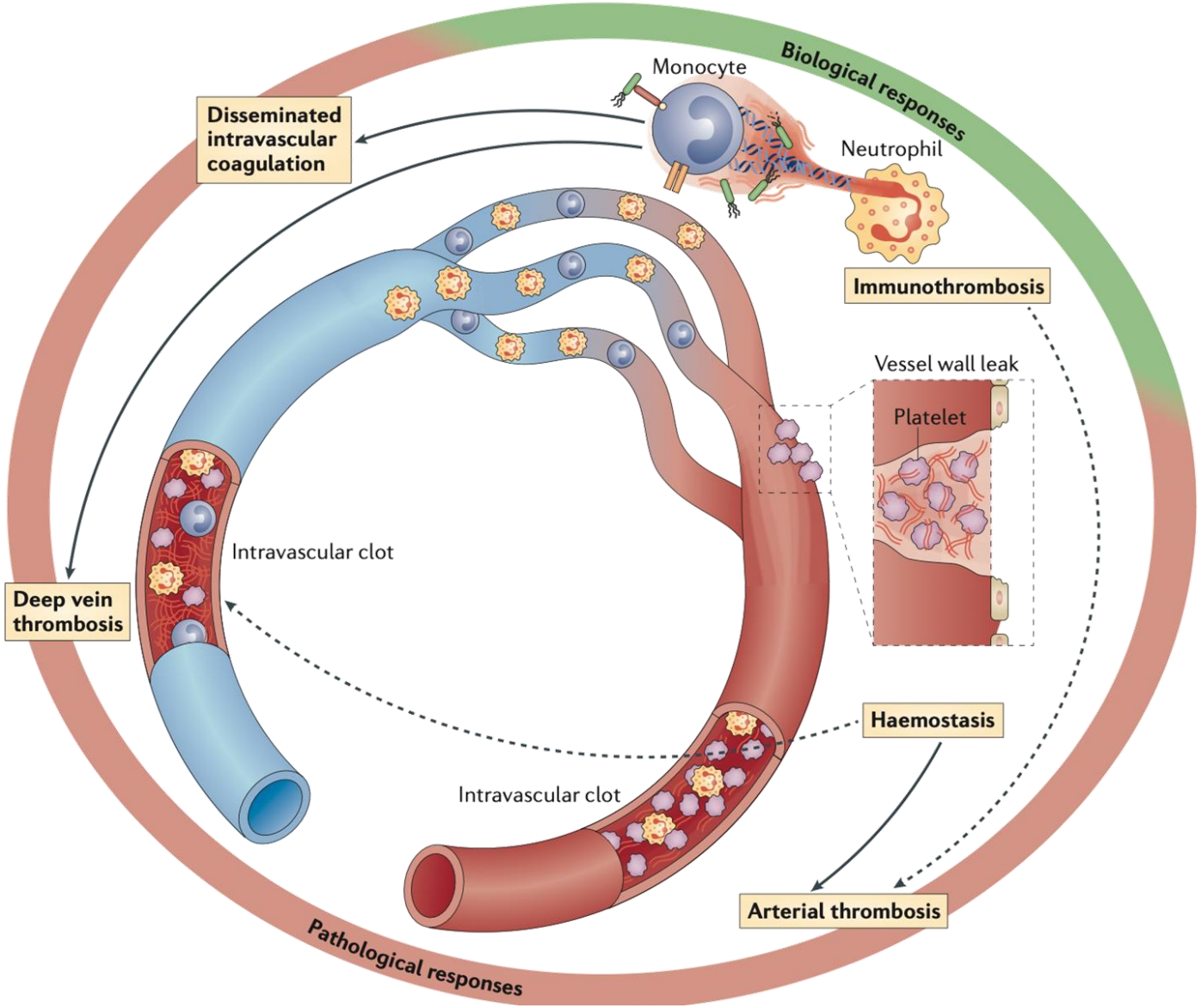




J. Clin. Med. 2021, *10*(10), 2075; doi.org/10.3390/jcm10102075

Vascular endothelium and immunothrombosis

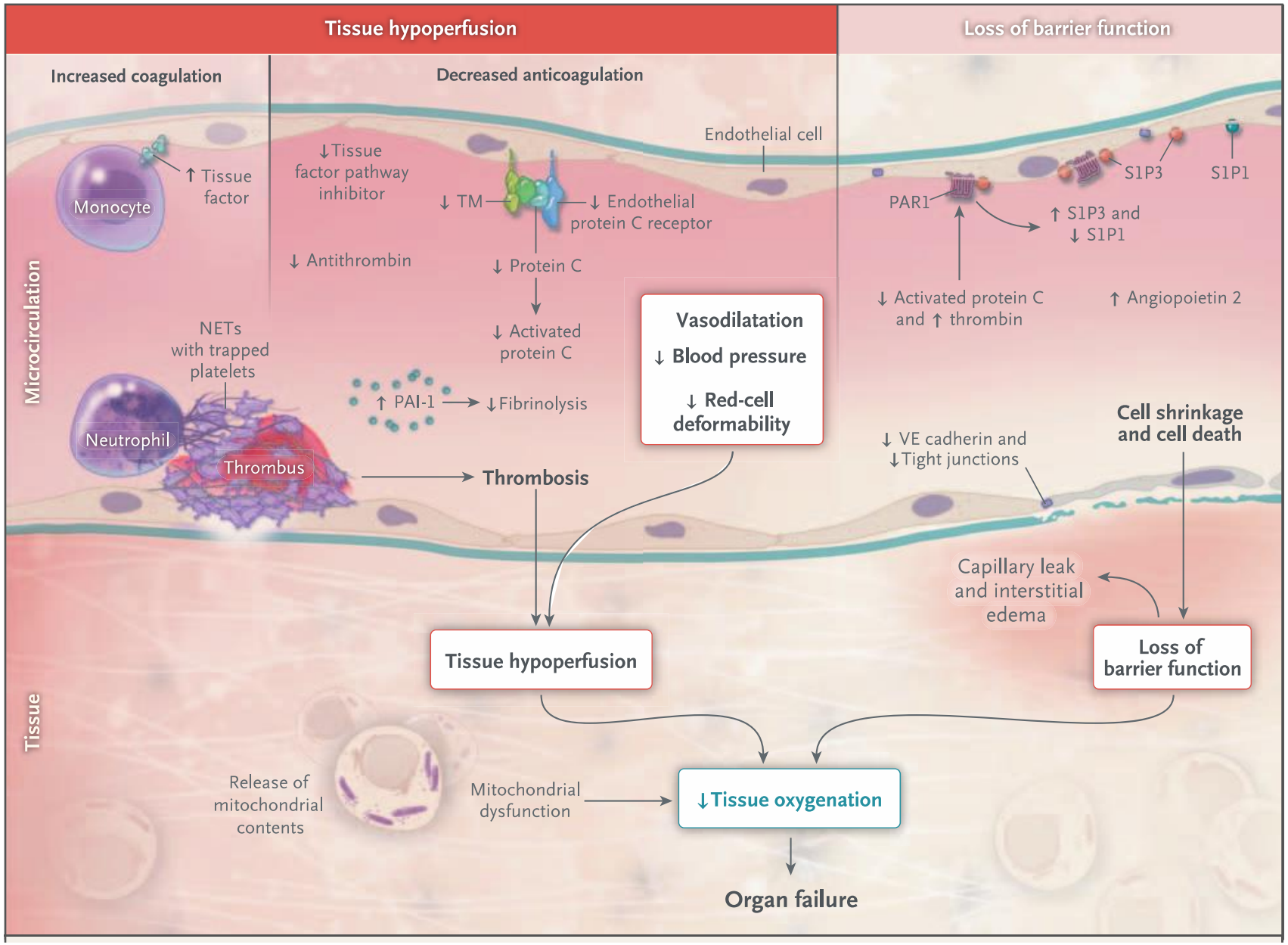
The thrombotic continuum- uncontrolled haemostasis and immunothrombosis trigger disease



Nat Rev Immunol. 2013 Jan;13(1):34-45. doi: 10.1038/nri3345. Epub 2012 Dec 7

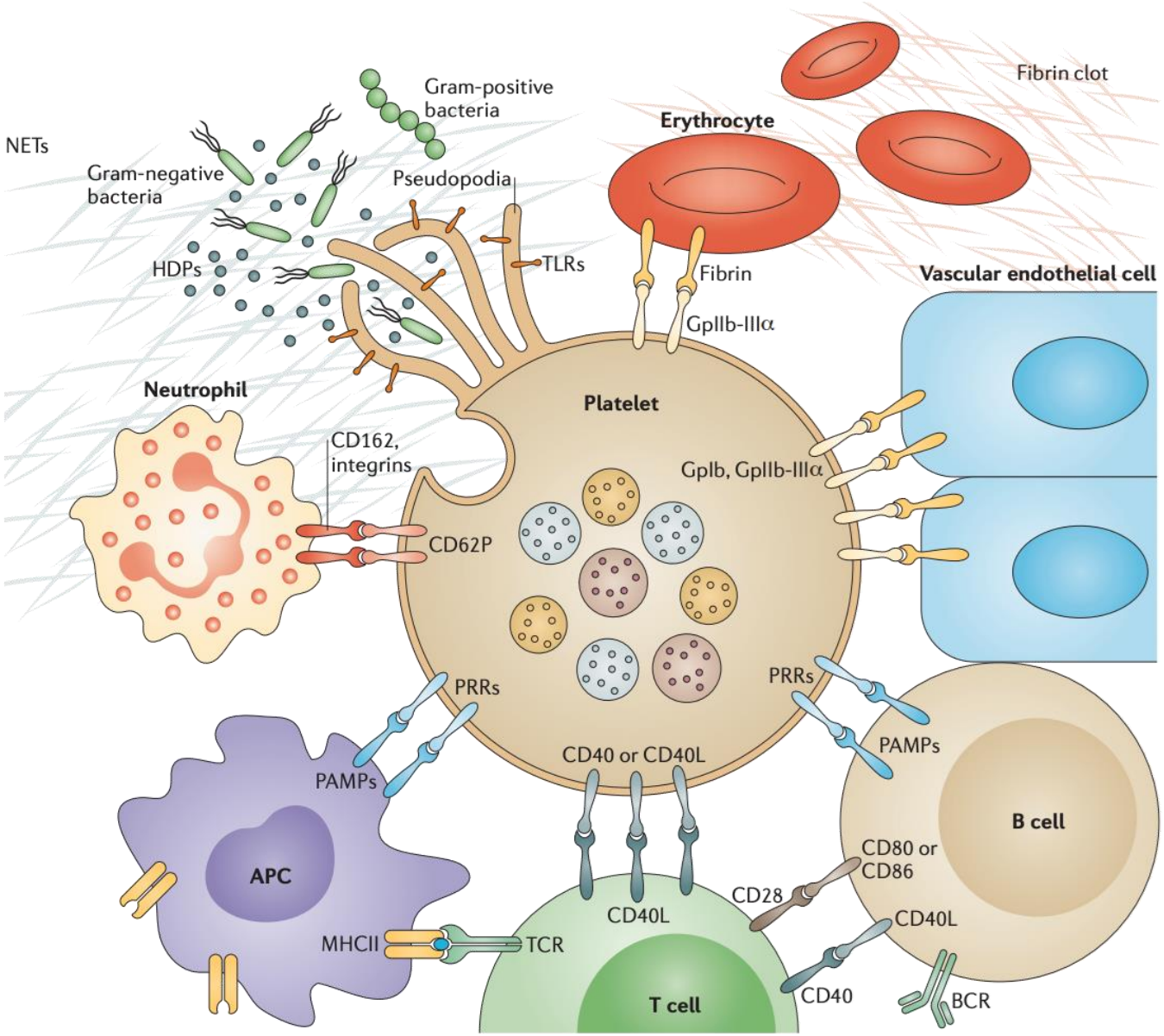
Vascular endothelium and immunothrombosis

Dysfunction of the Vascular Endothelium and Mitochondria



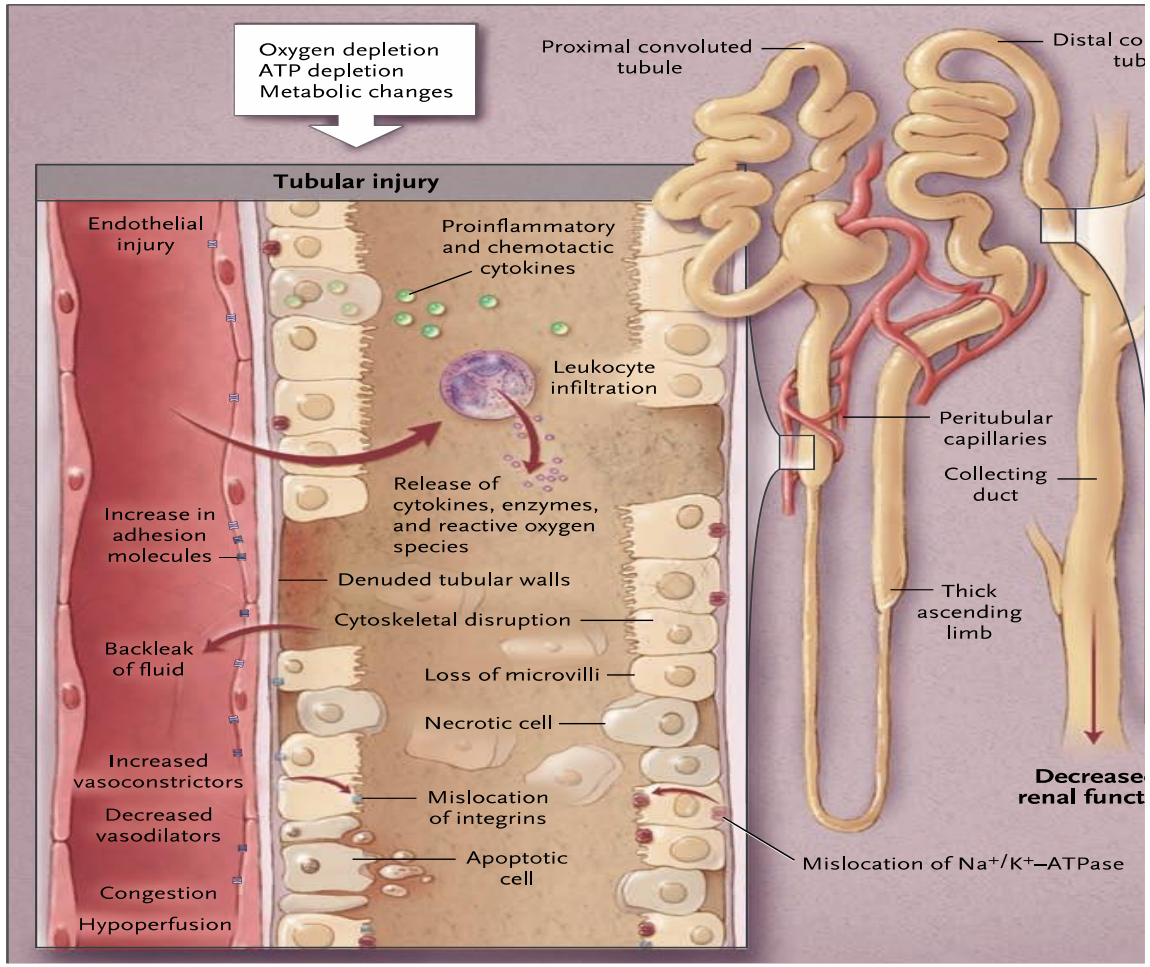
N Engl J Med 2013; 369:840-851 DOI: 10.1056/NEJMra1208623

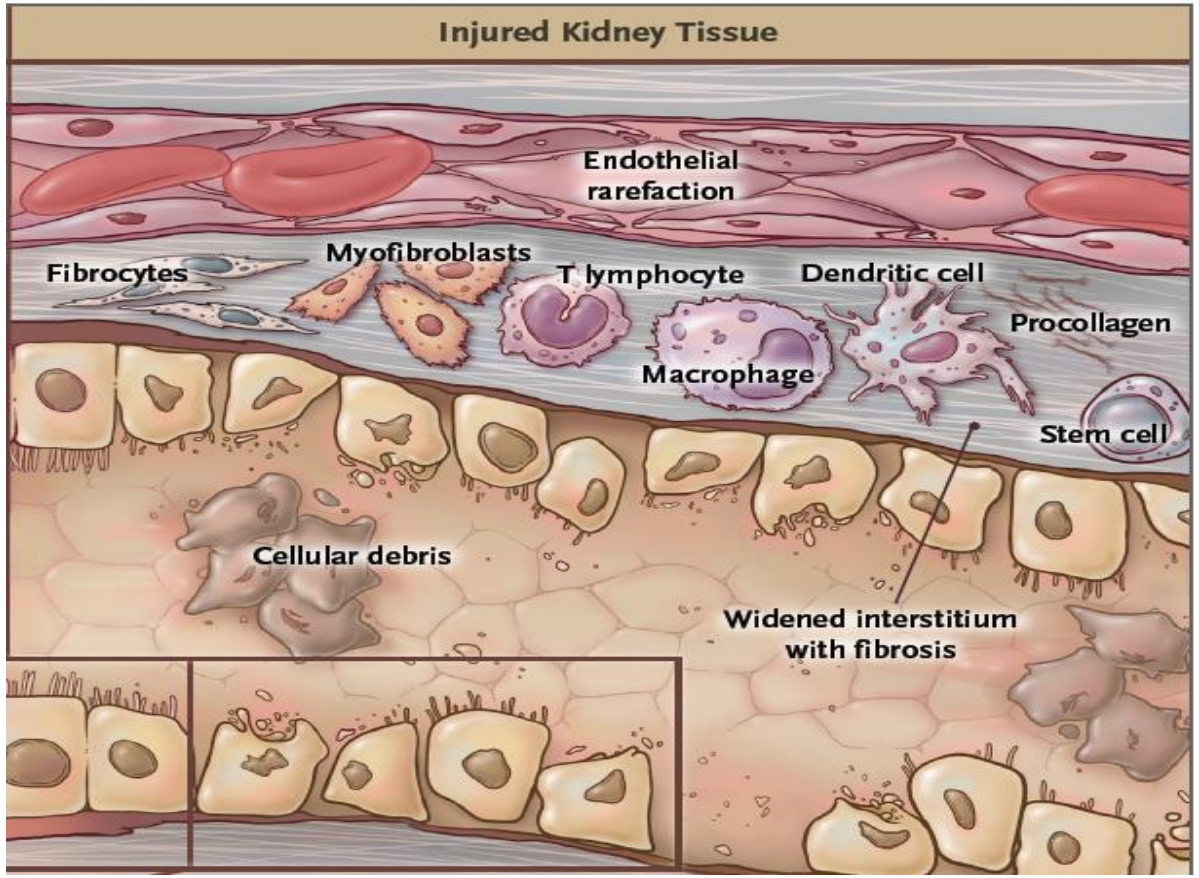
Vascular endothelium and immunothrombosis



Nature Reviews Microbiology. June, 2014, Vol. 12 Issue 6, p426, 12 p.

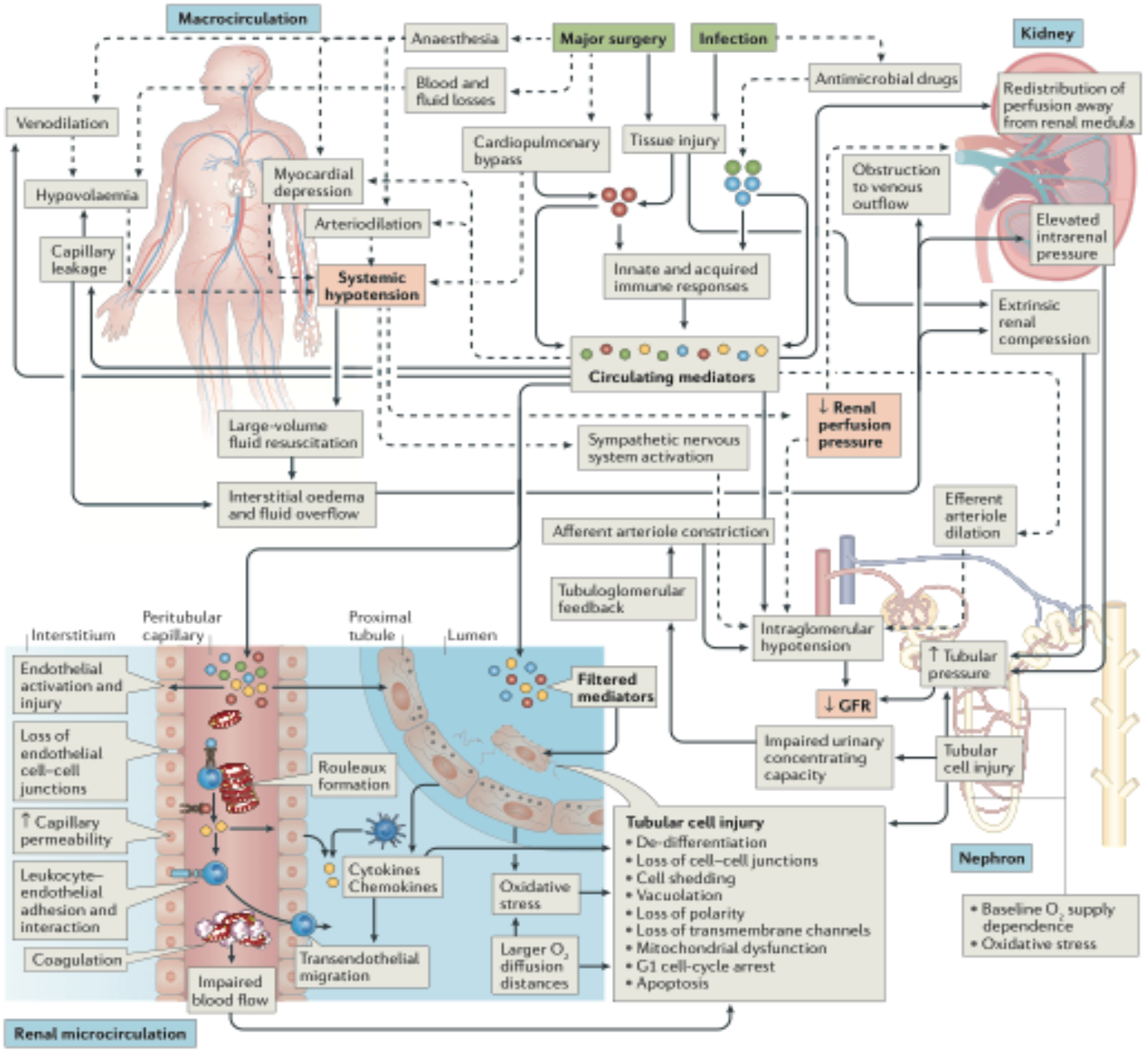
Epithelial injury





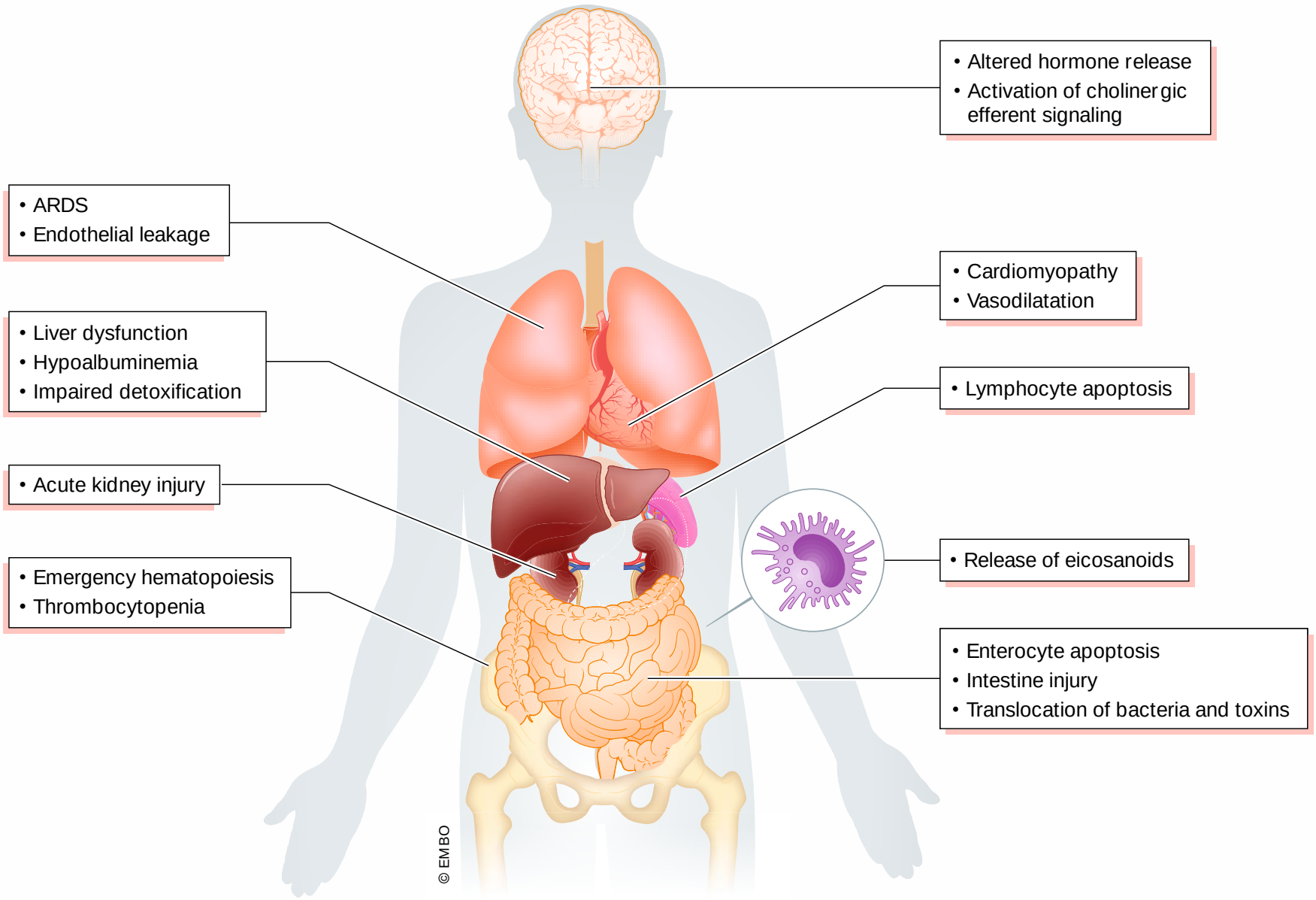
ChawlaL. N Engl J Med 2014;371:58-66

Epithelial injury



Nat Rev Nephrol. 2018 Apr;14(4):217-230.

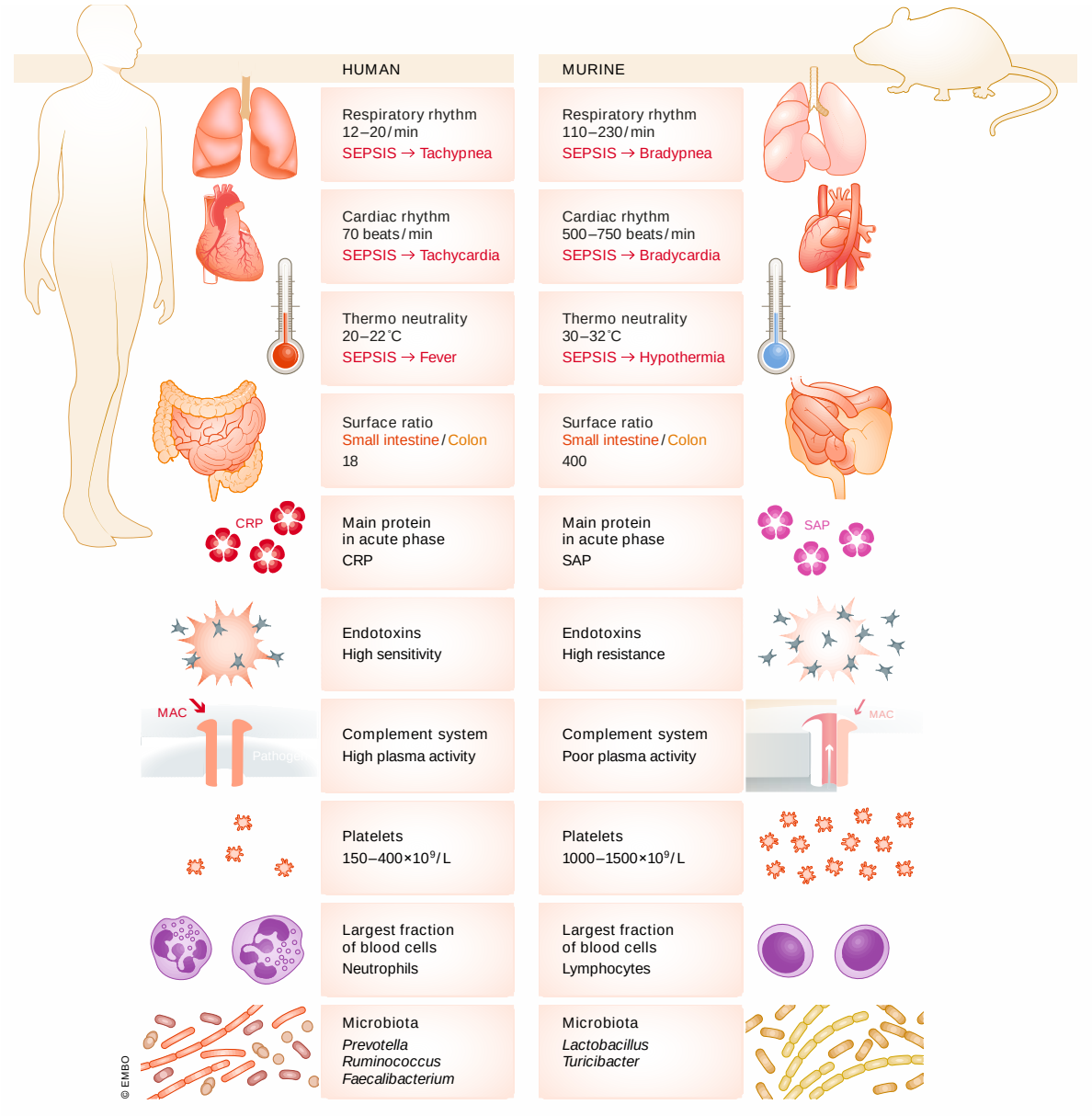
Crosstalking between organs



EMBO Molecular Medicine 12: e10128 | 2020

Because our experimental models are not appropriate

Experimental models of sepsis



EMBO Molecular Medicine 12: e10128 | 2020

Experimental models of sepsis

Table 1. Some physiologic and immunologic differences between mice and humans that may affect the host response to infection, the development of sepsis, and its monitoring.

	Mice	Humans
Physiology		
Circadian rhythm	Nocturnal	Diurnal
Nutrition	Standardized chow diet	Varied
Glucose levels	↓ after sepsis	↑ after sepsis
Temperature	↓ after sepsis	↑ after sepsis
Metabolic rate	↓ after sepsis	↑ with initial sepsis, normalizes with increasing severity
Immune system		
Predominant white blood cell type	Lymphocyte	Neutrophil
Enzymatic content in neutrophils	Low	High
α-defensin production by neutrophils	No	Yes
Expression of CXCR1 on neutrophils	No	Yes
NETosis after sepsis	Increased	Decreased
Missing genes	IL-8, IL-32, IL-37, LFA-3	TLR11, TLR12
	TLR10, Caspase 10	MCP-5
Main inflammasome player in LPS sensing	Caspase 11	Caspase 4 and 5

Because studies are difficult to design

Inappropriate selection of patients

Enrollment of a heterogeneous population of patients:

- intrinsic individual heterogeneity reflecting genetic and epigenetic diversity
- underlying comorbidities (obesity, medications)
- reactivation of asymptomatic viral infections
- Age
- Sex

Described endotypes of sepsis

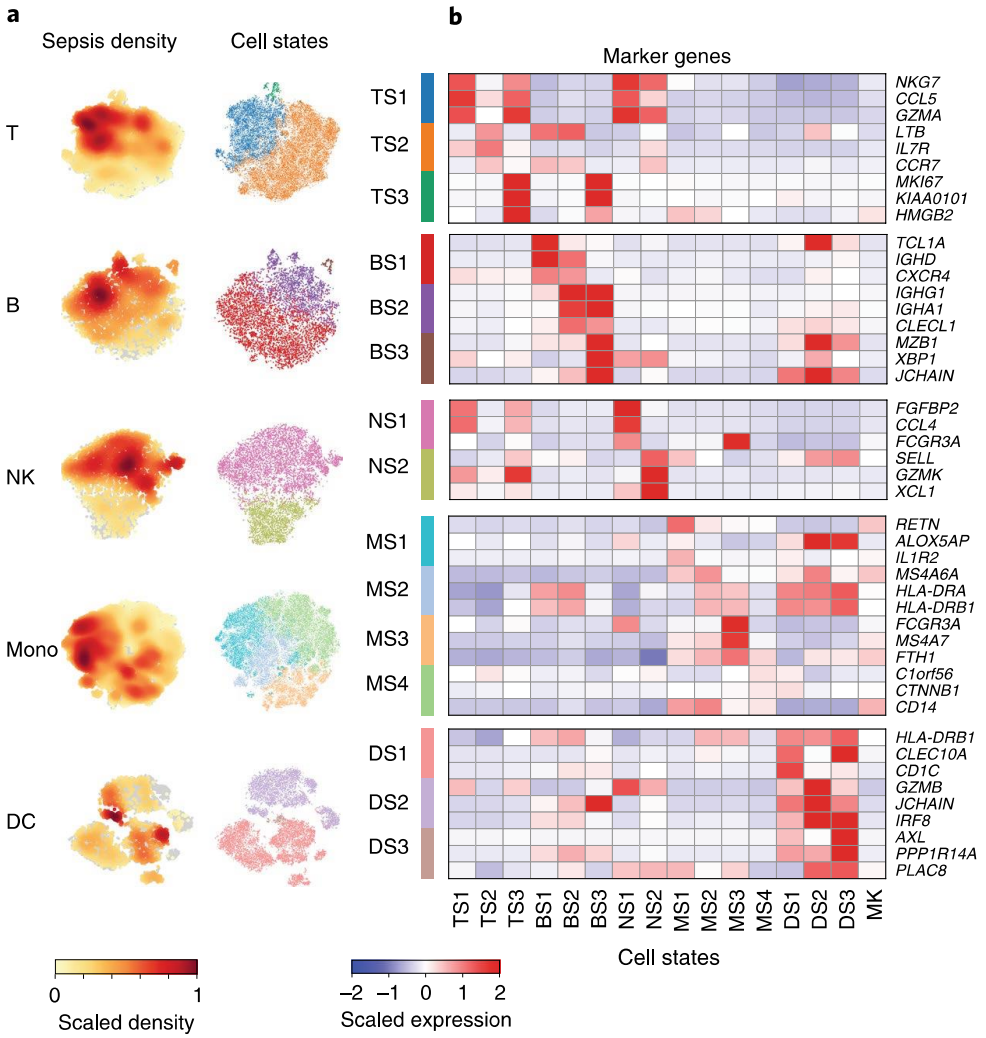
Endotypes	Methodology	Studied group	Implications	References
Subclass A: repression of adaptive immunity and zinc-related biology Subclass B Subclass C	Genome-wide expression profiling, unsupervised hierarchical clustering of genes which expression was ≥ 2-fold changed (comparing to controls) in 25–50% of patients	Children with septic shock (n = 98)	Identification of high-risk subpopulation by subclass An assessment identification of novel therapeutic targets	Wong *et al* (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 *et al* (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	Sciclunа *et al* (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 *et al* (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 *et al* (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 *et al* (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 *et al* (2017b)
SRS1 SRS2	Genome-wide microarray, allocation based on the generalized linear model based on 7 genes (from Davenport *et al*, 2016)	Sepsis (n = 177)	Hydrocortisone treatment increases mortality in SRS2	Antcliffe *et al* (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 *et al* (2018a)

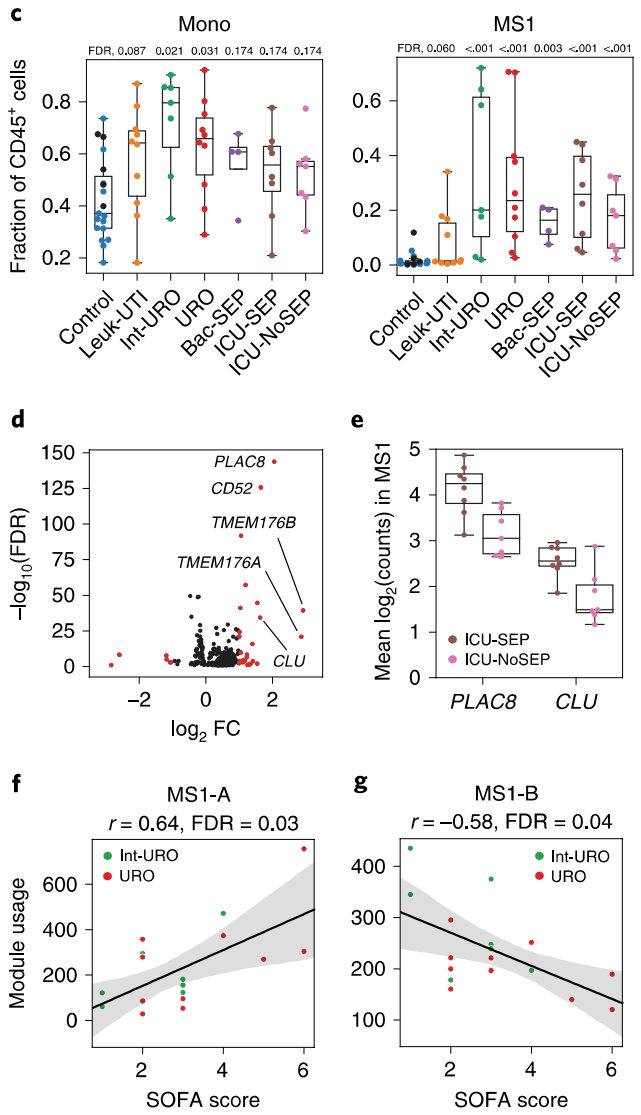
Inappropriate selection of patients: lack of biomarkers

An immune-cell signature of bacterial sepsis

Miguel Reyes[1,2,7], Michael R. Filbin[1,3,7], Roby P. Bhattacharyya[1,4], Kianna Billman[1], Thomas Eisenhaure[1], Deborah T. Hung[1,5], Bruce D. Levy[5], Rebecca M. Baron[5], Paul C. Blainey[1,2*], Marcia B. Goldberg[1,4*] and Nir Hacohen[1,6*]

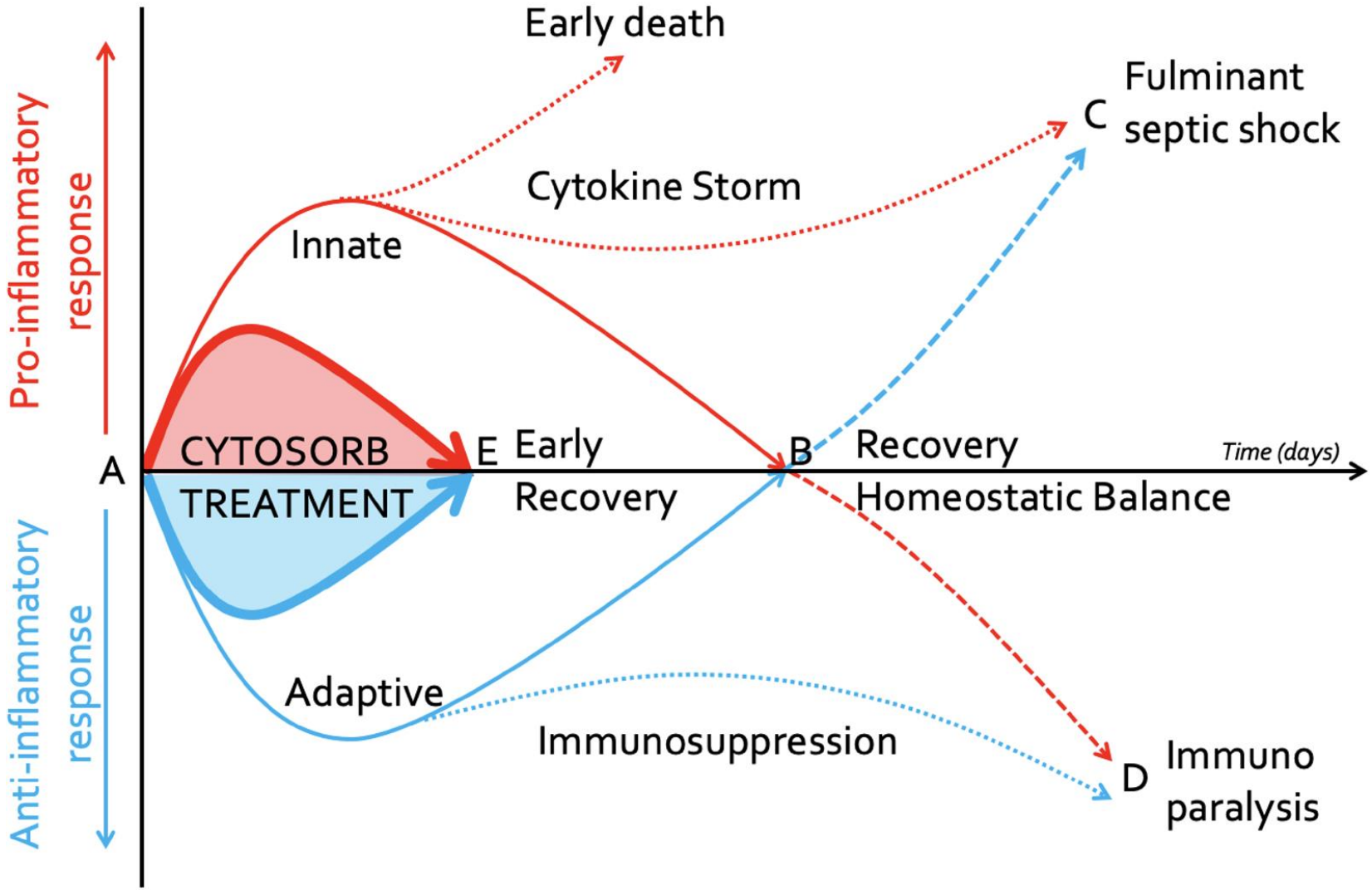
scRNA-seq identifies sepsis-specific immune-cell states and gene signatures





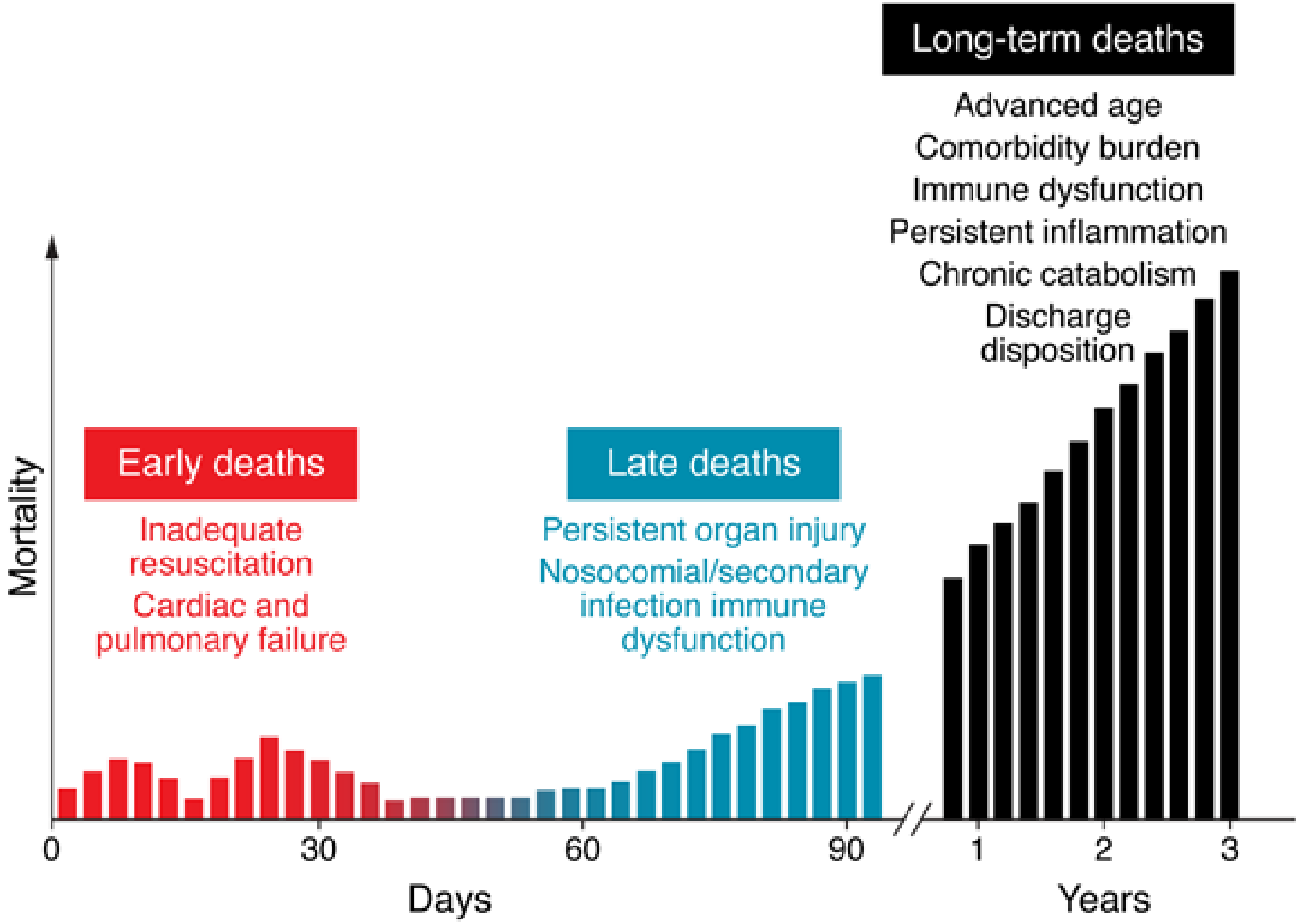
Nat Med . 2020 Mar;26(3):333-340. doi: 10.1038/s41591-020-0752-4

The time period for inclusion is difficult to determine



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

Mortality is not the only endpoint



J Clin Invest. 2016;126(1):23–31. doi:10.1172/JCI82224.

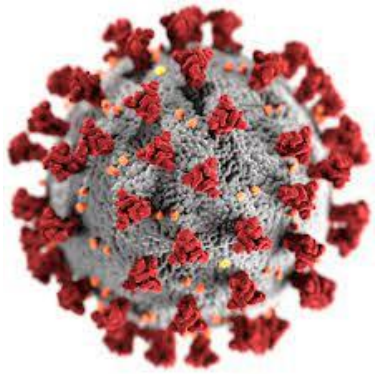
Why should we remain optimistic?

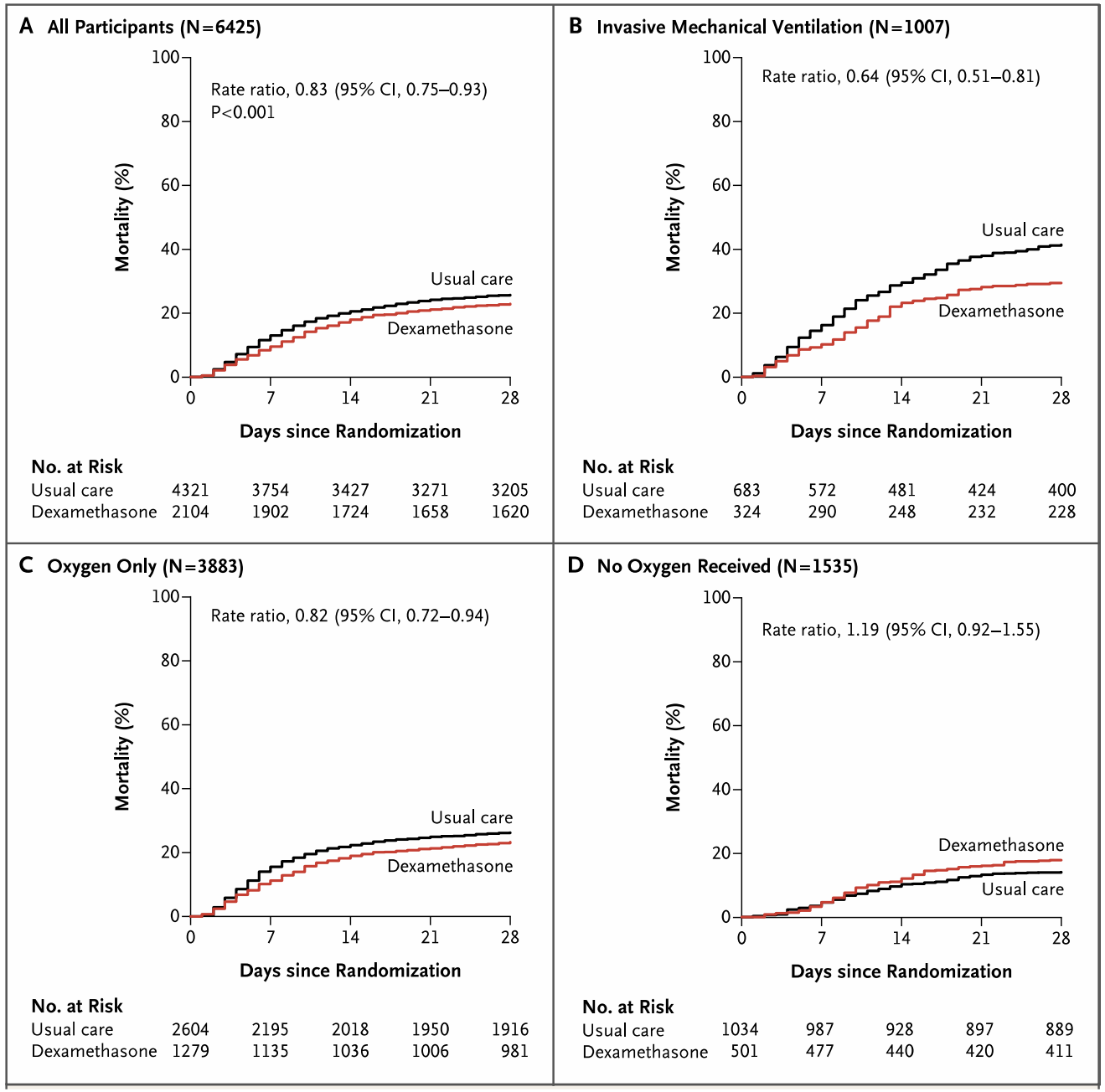
Improving the chances of therapeutic success

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 *et al* (2004)
GM-CSF	Monocytic HLA-DR < 8,000 antibodies per cell	Time of mechanical ventilation 148 ± 103 vs. 207 ± 58 h (placebo), $P = 0.04$	Prospective	Meisel *et al* (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 *et al* (2016)
Trimodulin (polyclonal immunoglobulin preparation)	CRP ≥ 70 mg/l and IgM ≤ 0.8 g/l	28-day mortality 11.8% vs. 36.6% placebo ($P = 0.006$)	Exploratory *post hoc*	Welte *et al* (2018)

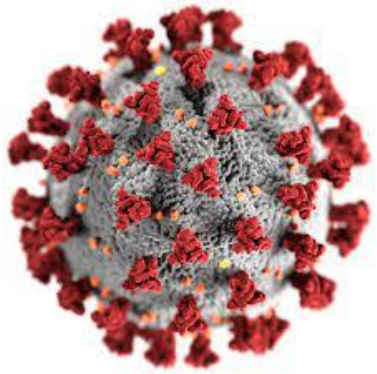
Improving the chances of therapeutic success

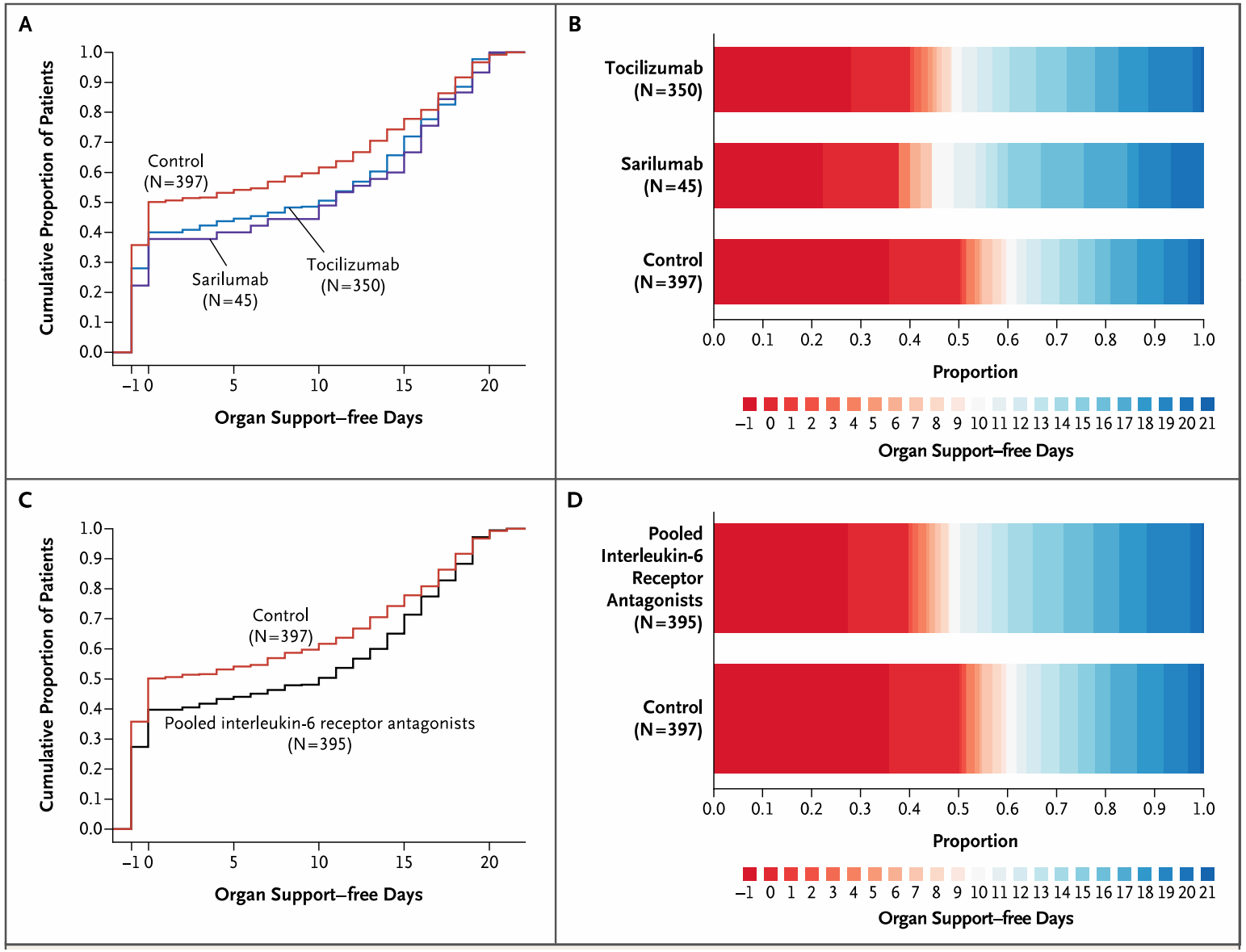




N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436. Epub 2020 Jul 17.

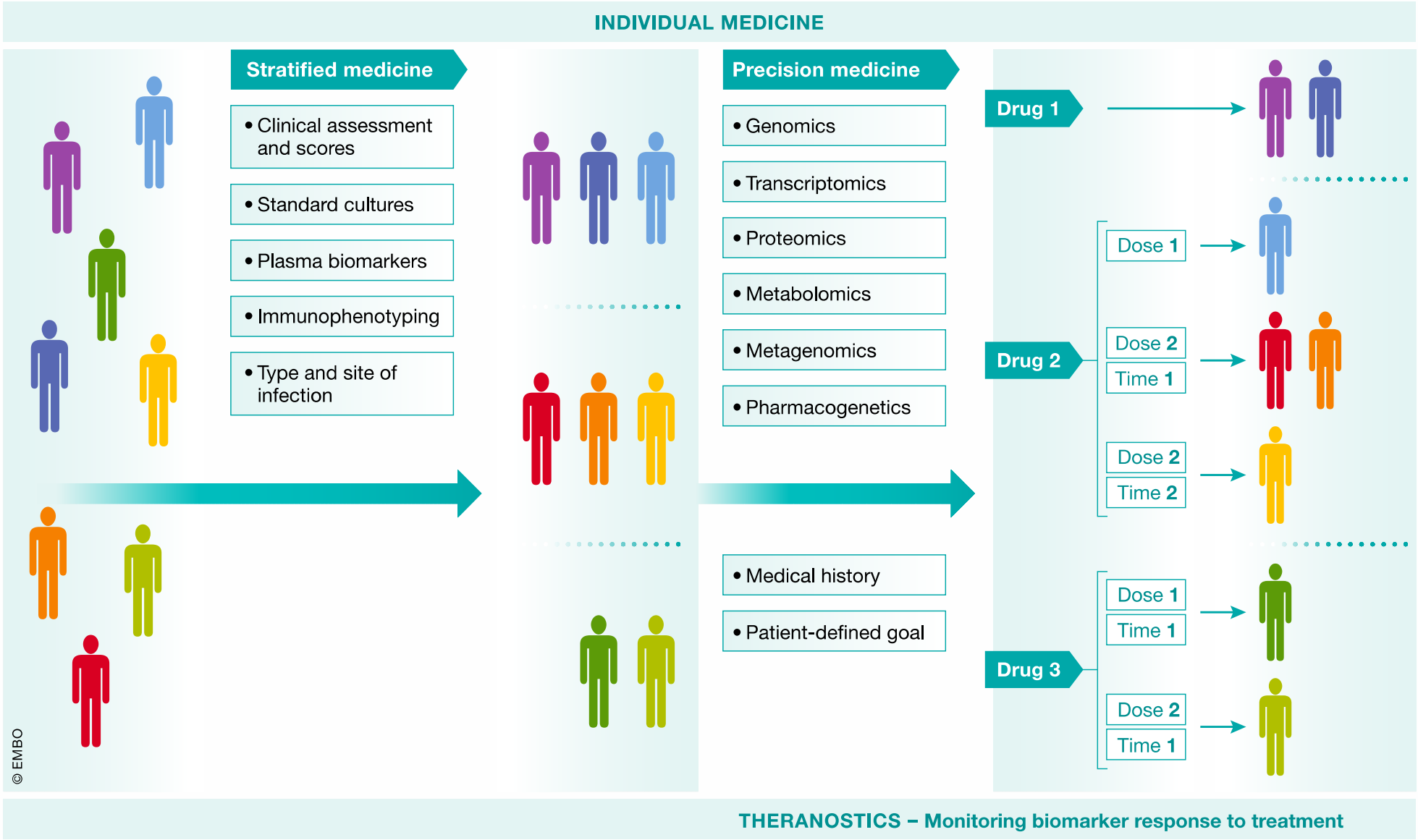
Improving the chances of therapeutic success





N Engl J Med . 2021 Sep 16;385(12):1147. doi: 10.1056/NEJMc2108482

Improving the chances of therapeutic success



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EDITORIAL Open Access

Equilibrating SSC guidelines with individualized care

Jean-Louis Vincent[1*], Mervyn Singer[2], Sharon Einav[3], Rui Moreno[4], Julia Wendon[5], Jean-Louis Teboul[6], Jan Bakker[7,8,9,10], Glenn Hernandez[11], Djillali Annane[12], Angélique M. E. de Man[13], Xavier Monnet[14], V. Marco Ranieri[15], Olfa Hamzaoui[16], Jukka Takala[17], Nicole Juffermans[18,19], Jean-Daniel Chiche[20], Sheila N. Myatra[21] and Daniel De Backer[22]

Crit Care. 2021 Nov 17;25(1):397. doi: 10.1186/s13054-021-03813-0.

Thank you for your attention

a

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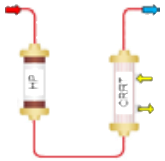
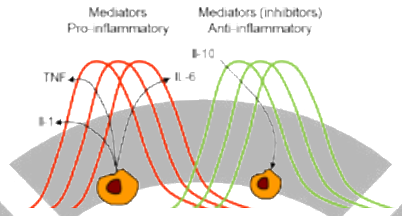


Cytokine Removal
-Hemoadsorption
-Hemofiltration - CVVH
-High dose CVVH

c

Cytokines
-Cytokine release syndrome
-Mechanical ventilation
-ECMO
-CRRT circuit
-Hemophagocytic syndrome



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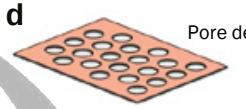
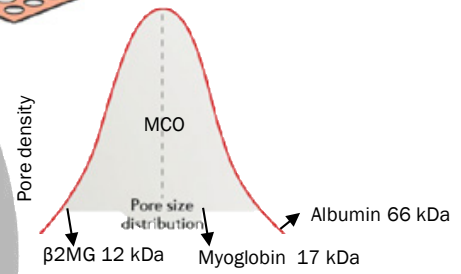


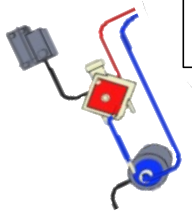


Cytokine Removal
--HCO membrane
-MCO membrane

e

Crosstalk Interventions
-Cardiomyopathy → LVAD; AV ECMO
-Peak airway pressure + IAH → VV ECMO, $ECCO_2R$, CRRT
-Rhabdomyolysis → CRRT, HCO or MCO membranes

Crosstalk
-Cardiomyopathy → Cardiorenal syndrome type 1
-Alveolar damage → Renal medullary hypoxia
-Peak airway pressure + IAH → Renal compartiment syndrome
-Rhabdomyolysis → Tubular toxicity



Systemic
-Positive Fluid Balance → Renal compartiment syndrome
-Endothelial damage + Third space fluid loss + Hypotension → Renal hypoperfusion
-Nephrotoxins
-Metabolic acidosis
-Hyperkalemia

f

Systemic Interventions
-Positive Fluid Balance → Continuous ultrafiltration + Diuretics
-Endothelial damage + Third space fluid loss + Hypotension → Vasopressors + Fluid expansion
-Nephrotoxins
-Metabolic acidosis
-Hypercalemia
→ CRRT

Blood Purif. 2021;50(1):17-27.
doi: 10.1159/000508125. Epub 2020 May 26