Sepsis and inflammatory mediators

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Disclosure

- Lecture was financially supported by company Medis.

Outline

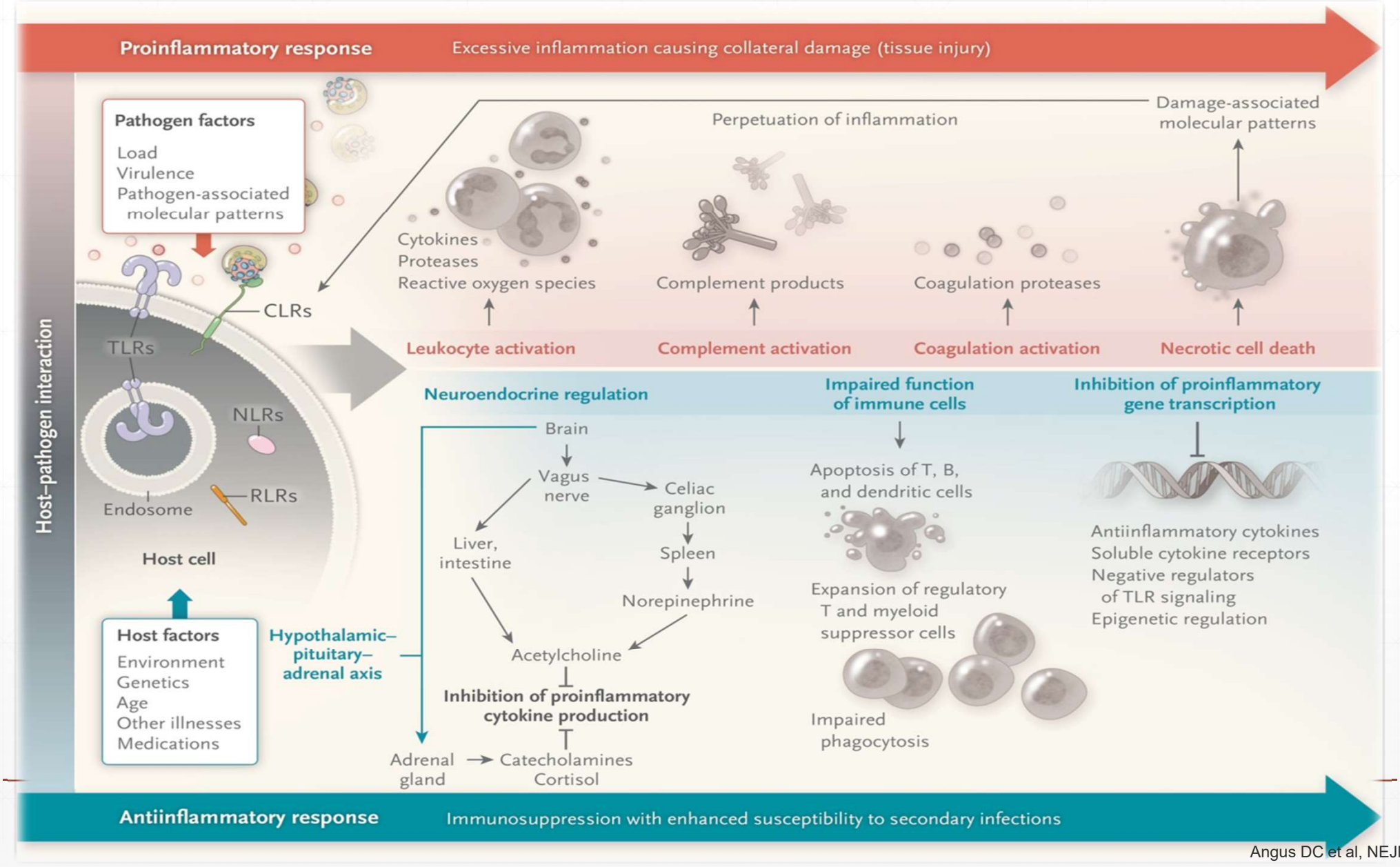
- Pathophysiology of sepsis
- Cytokines – short review and evidence in septic patients
- Immunomodulatory therapies in sepsis

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

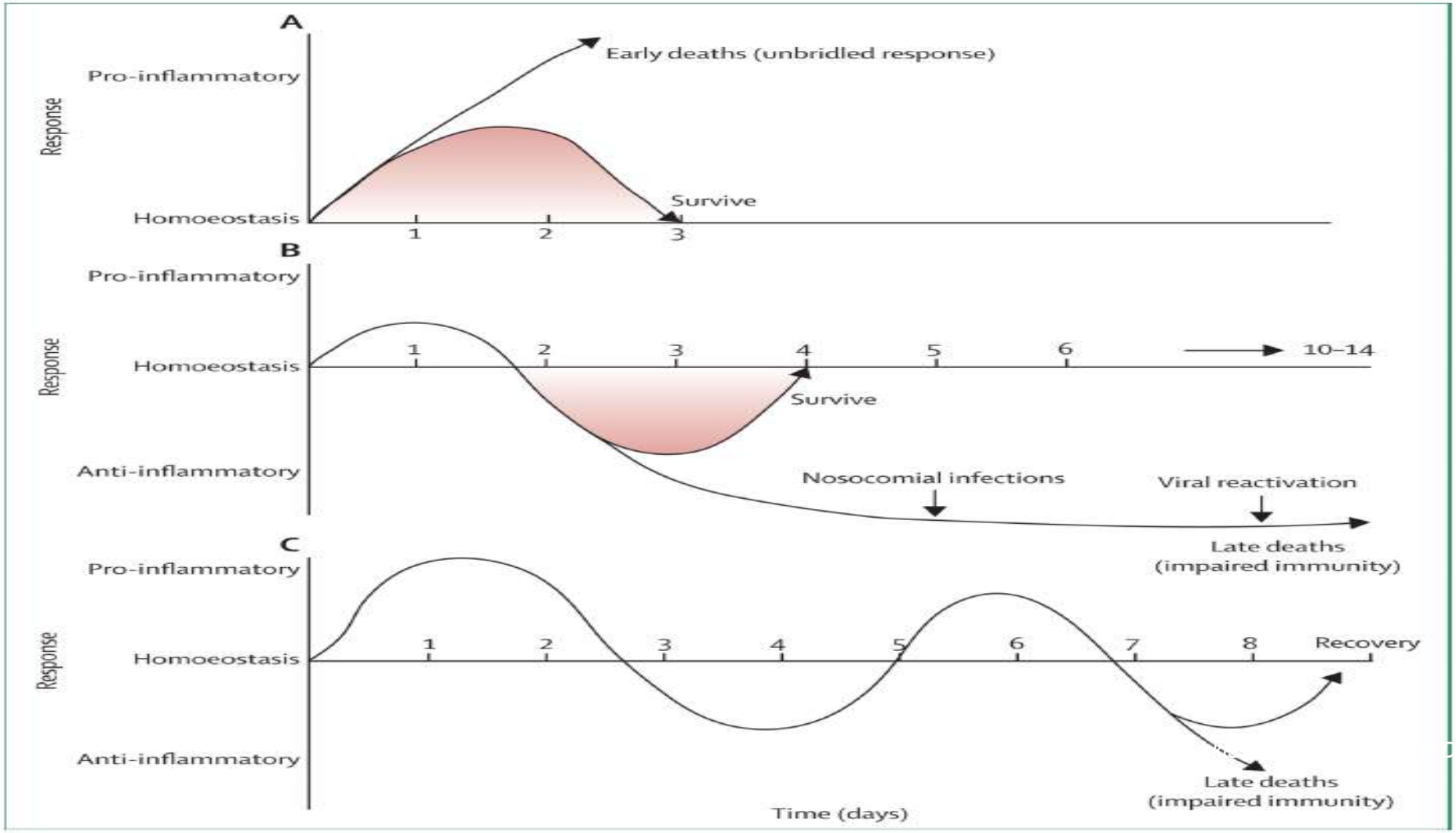
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.

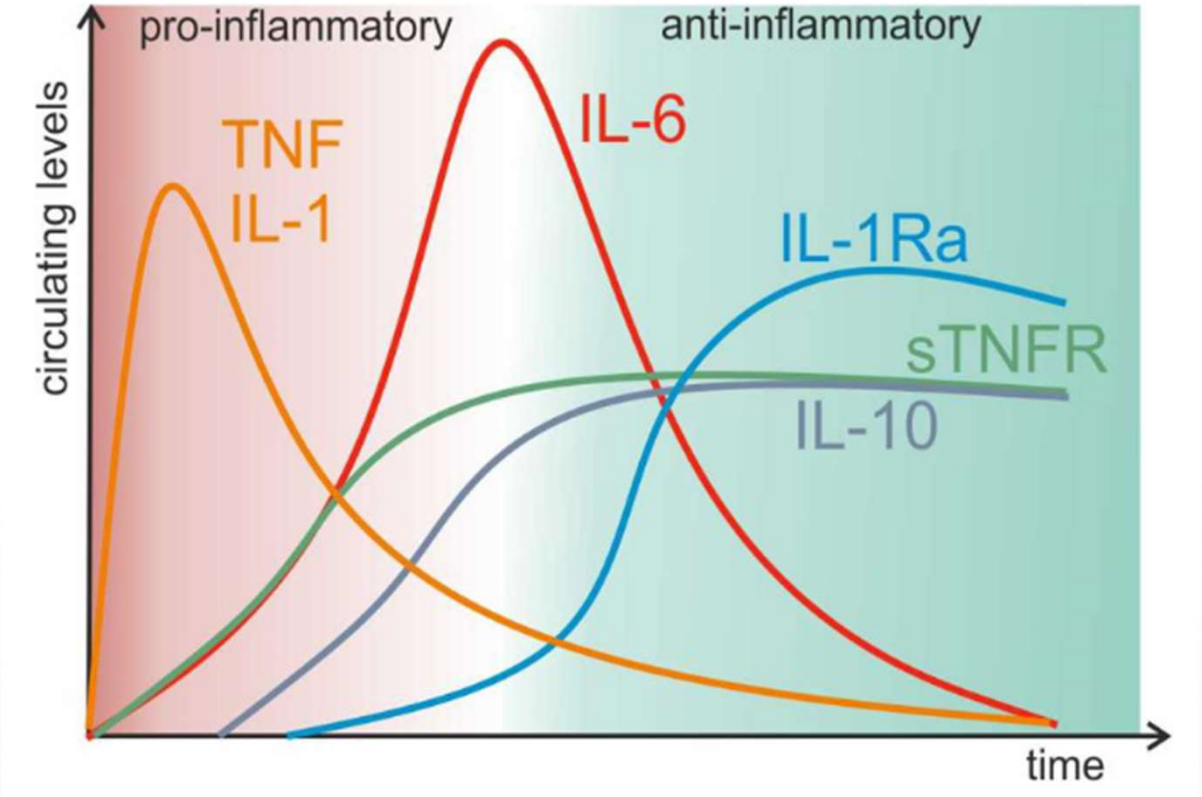
Singer M et al, JAMA 2016; 315: 801-10.



Angus DC et al, NEJM 2013

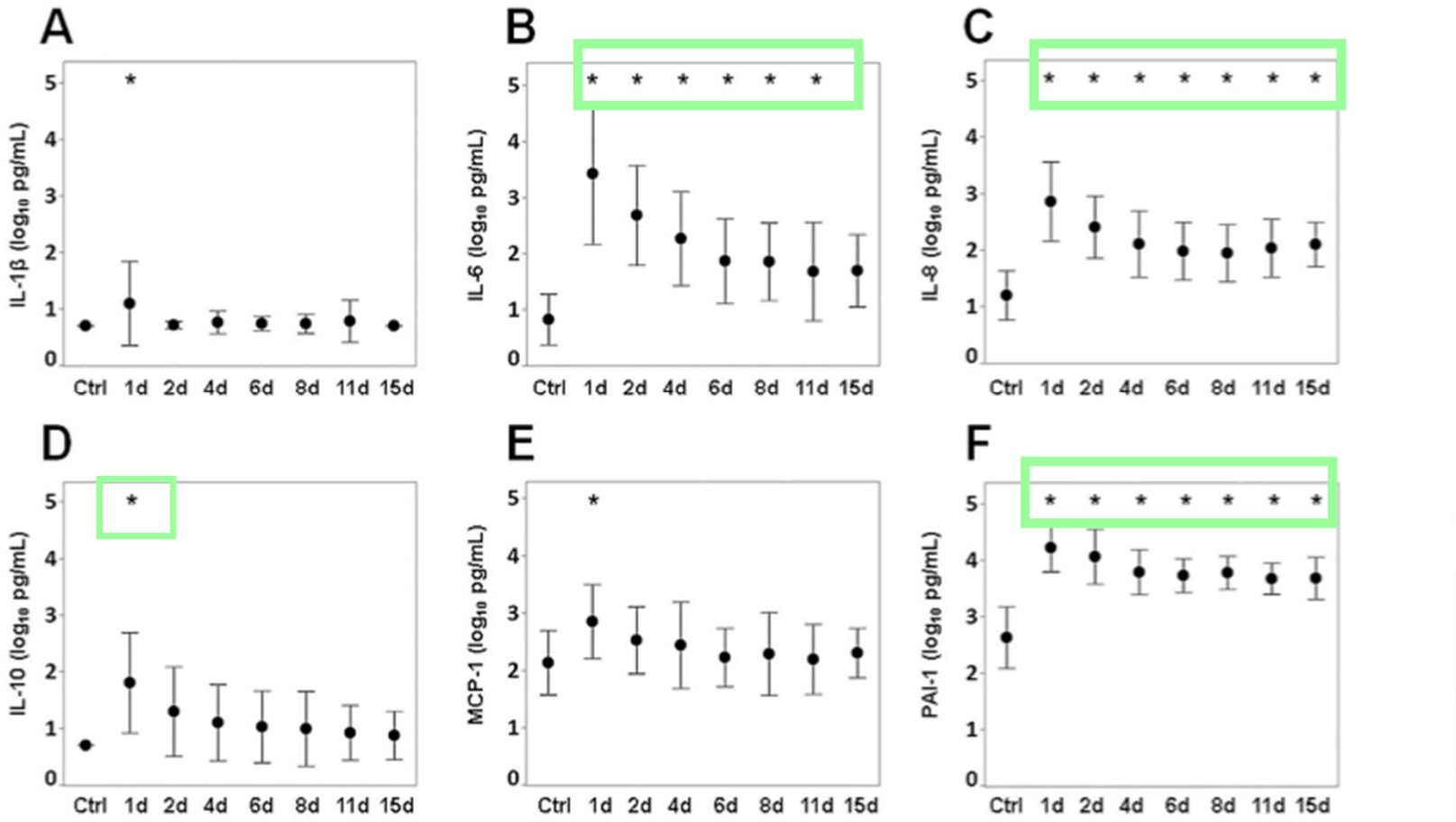


Hotchkiss et al. Lancet Infect Dis 2013
Steeland et al, Int J Mol Sci 2018



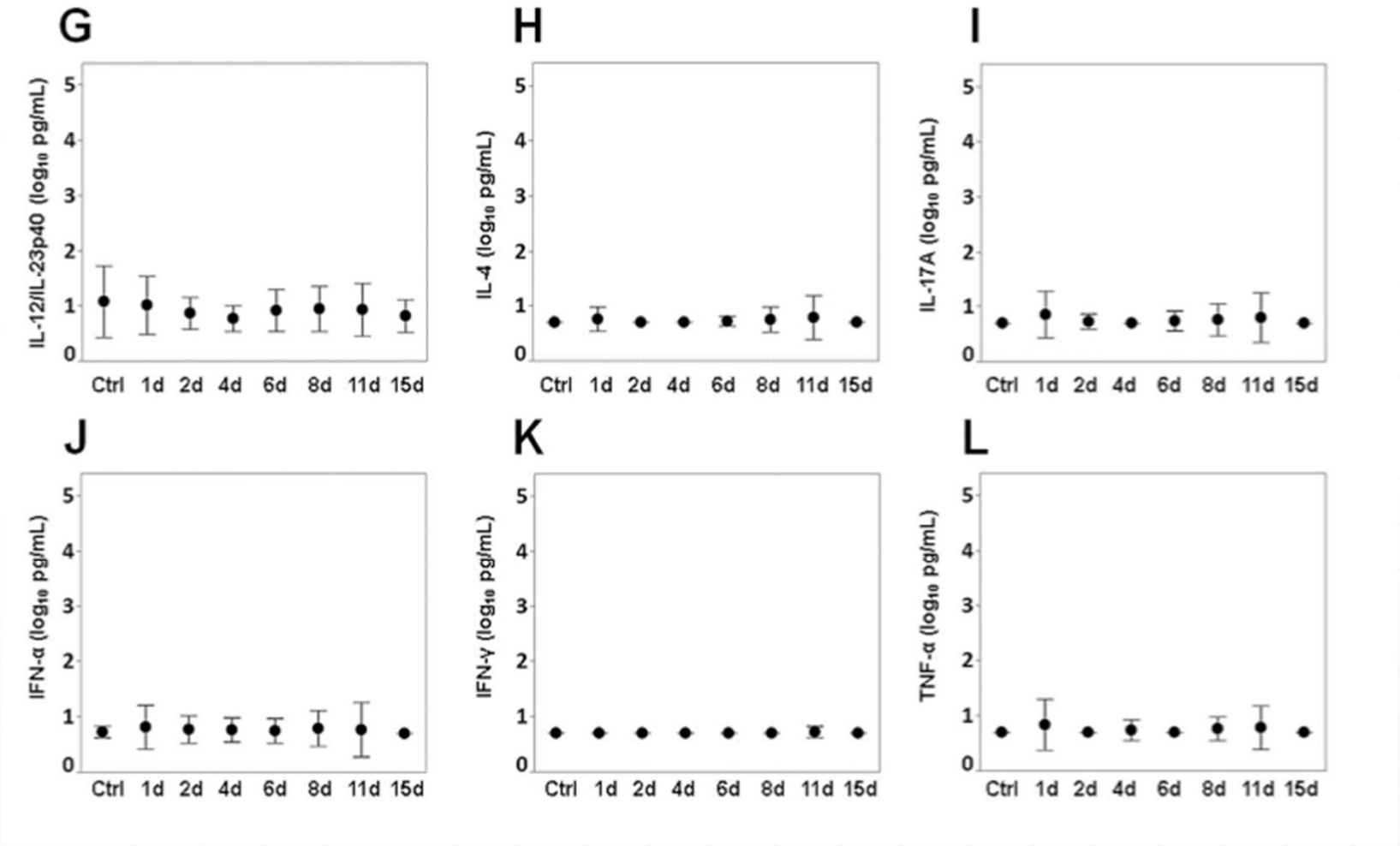
Steeland et al, Int J Mol Sci 2018

n= 31, APACHEII 21, SOFA 9, 22% smrtnost



MCP-1 monocyte chemotactic protein-1, PAI-1- platelet activating factor-1

Matsumoto H et al. Sci Rep 2018; 8: 13395

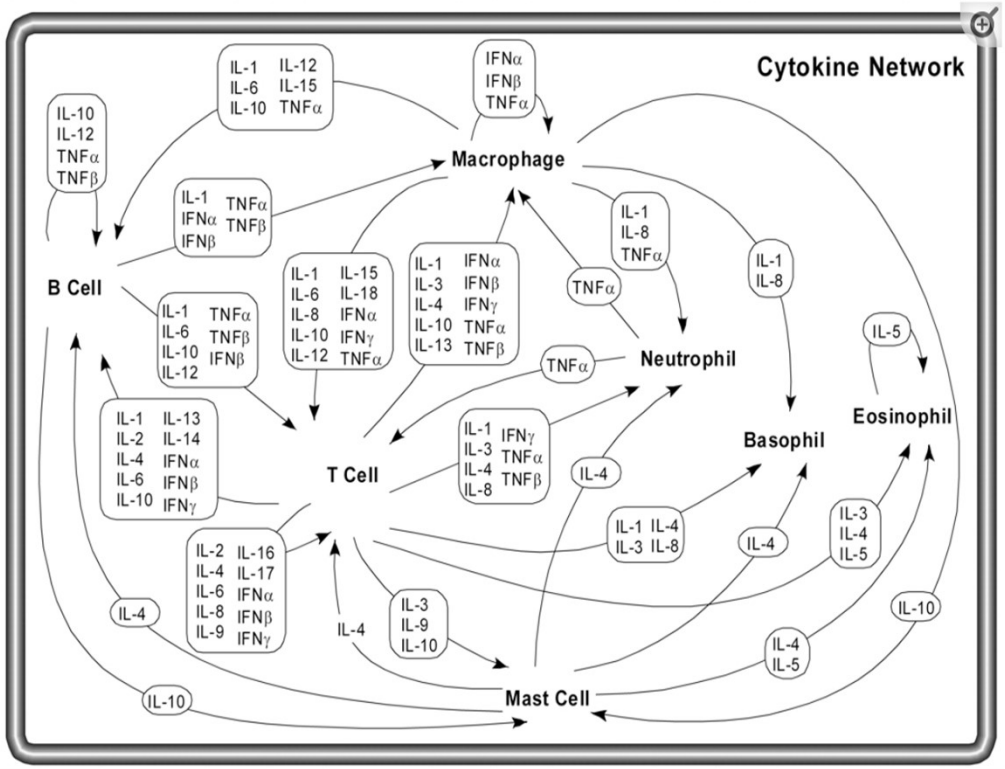

G
IL-12/IL-23p40 (log10 pg/mL)
H
IL-4 (log10 pg/mL)
I
IL-17A (log10 pg/mL)
J
IFN-α (log10 pg/mL)
K
IFN-γ (log10 pg/mL)
L
TNF-α (log10 pg/mL)
0
1
2
3
4
5
Ctrl
1d
2d
4d
6d
8d
11d
15d

Inflammatory mediator

- any messenger that acts on endothelial cells, immune cells or other cells to modulate inflammatory response
- CELL - DERIVED:
  - vasoactive amines, arachidonic acid metabolites, lysosomal components, platelet activating factor, cytokines, free radicals
- PLASMA PROTEIN - DERIVED:
  - products of kinin system, complement system, fibrinolytic system, clotting system

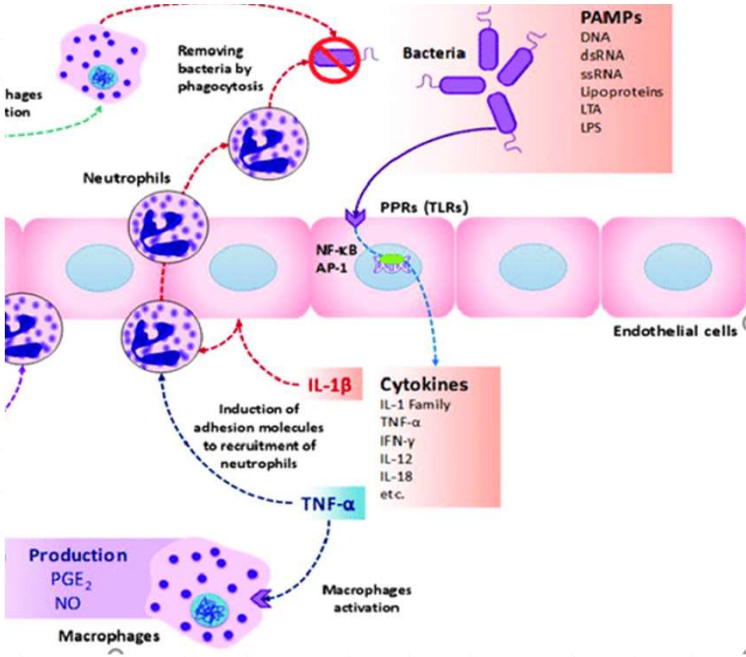
Cytokines

- small proteins (< 25 kDa)
- released by immune cells, endothelial cells
- autocrine, paracrine and endocrine action
- additive, synergistic, antagonistic action
- pro-inflammatory/anti-inflammatory
- modify cell function
- 6 superfamilies: IL1, TNF, IL17, IL6, type 1, type 2



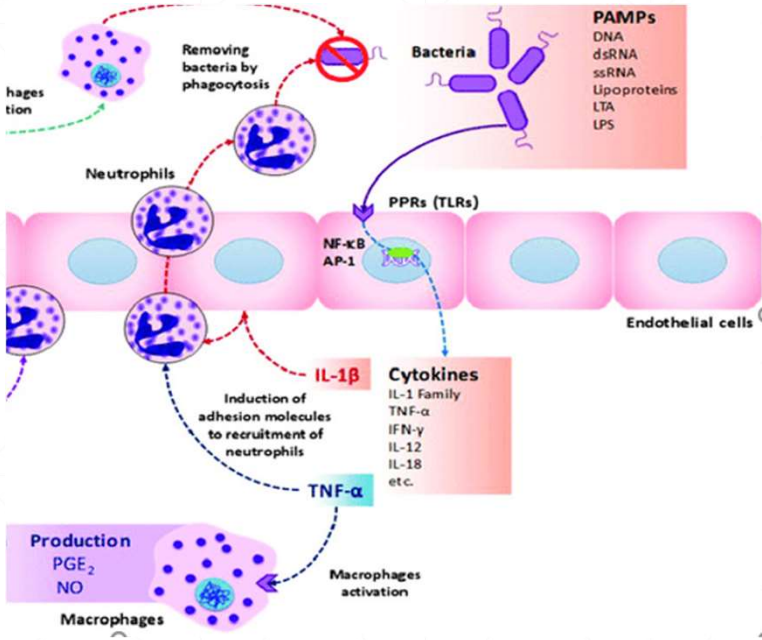
Zhang et al. Int Anesthesiol Clin 2007; 45: 27-37.

IL-1 superfamily



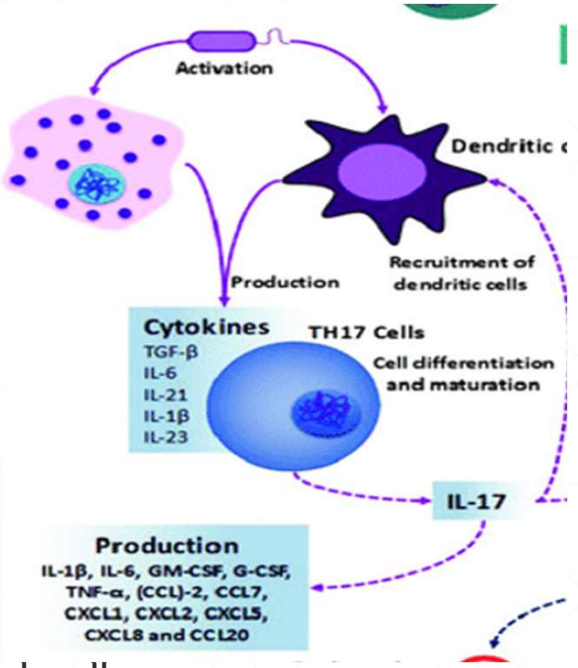
- 11 cytokines, 10 receptors
- main source: monocytes, macrophages
- most associated with damaging inflammation
- increase nonspecific resistance to infection and the development of an immune response to a foreign antigen
- **IL1β** – major inflammatory cytokine
  - expression of adhesion molecules in the endothelial cells, promotes the recruitment of neutrophils and monocytes to the site of inflammation, stimulatory effect on phagocytosis, induces the production of other inflammatory mediators of the lipid type, and other cytokines
  - associated with auto-inflammatory diseases (therapy target)

TNF superfamily



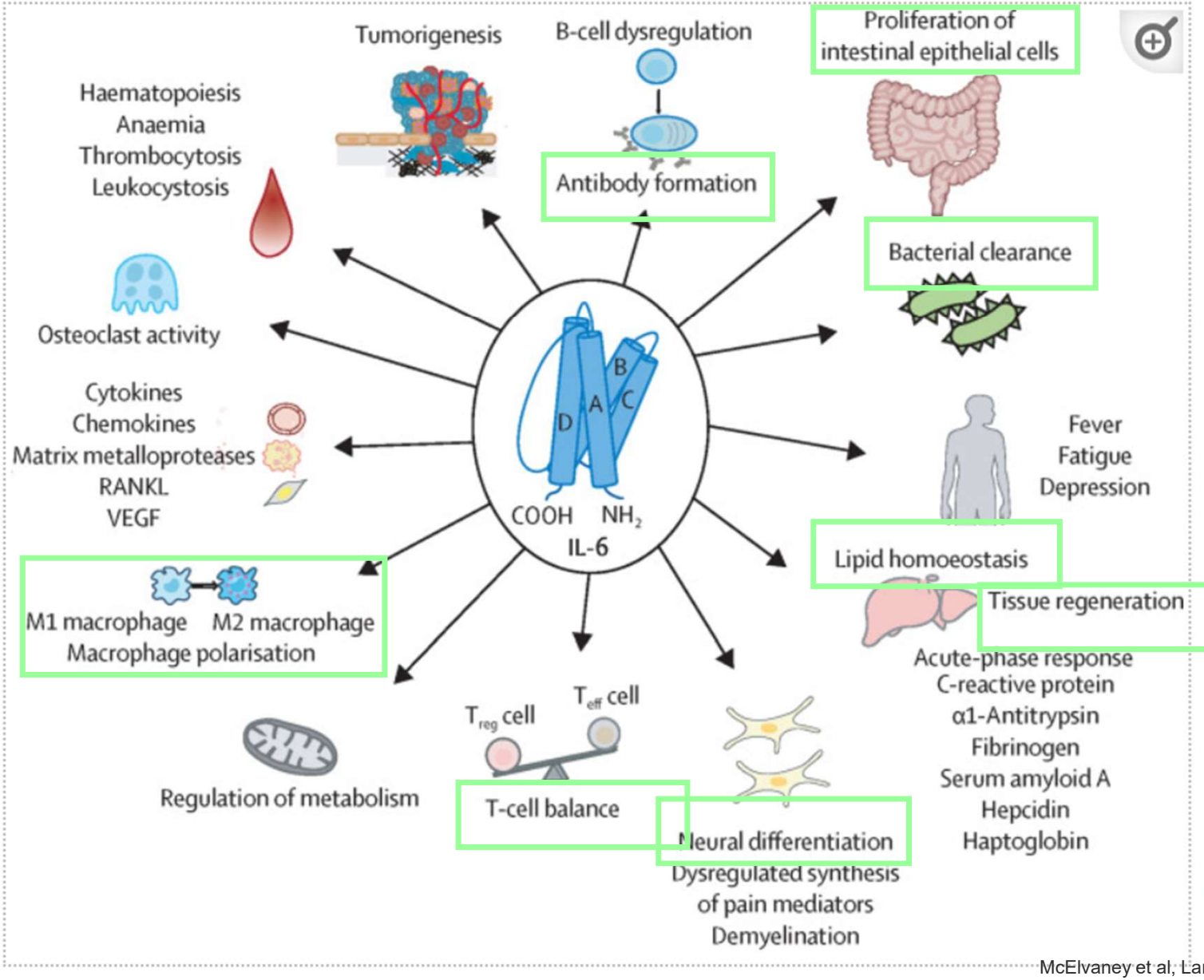
- 19 ligands, 24 receptors
- **TNFα**
  - main source: activated macrophages, CD4+ T cells, NK cells, neutrophils, mast cells
  - complex and contradictory actions
  - immunostimulation, resistance to infection agents, resistance to tumors, sleep regulation and embryonic development
  - released 30 min after the inciting event
  - induction of acute phase reactant protein by the liver
  - promotes activation and differentiation of macrophages, enhances expression of adhesion molecules on endothelial cells, extravasation of neutrophils to tissues
  - infections become fatal due to TNF circulation in blood

IL-6 superfamily



- IL-6, IL-27, IL-31, IL-35, CSF
- **IL-6** (master regulator of inflammation)
  - main source: macrophages, dendritic cells, lymphocytes, endothelial cells, fibroblasts, smooth muscle cells
  - in response to LPS, IL-1, TNF-α, viral infection
  - induction of fever & mediation of acute phase response
  - elevated in sepsis, ARDS, covid-19

Schulte W et al. Med Inflamm 2013; 2013: 165974

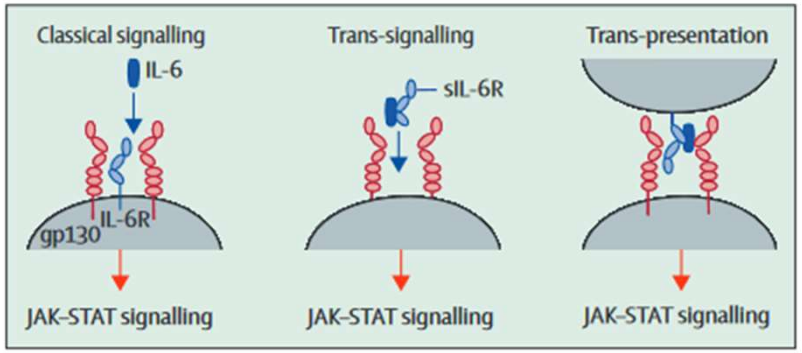


McElvaney et al, Lancet Resp Med 2021; 9: 643-54

IL-6 signaling

- IL-6R is expressed by only a few cell types – hepatocytes, macrophages, some T cell subtypes
- gp130 is expressed by all cell types
- IL-6 has affinity for IL-6R and not gp130
- all cells are not IL-6 responsive!
- anti-inflammatory and anti-bacterial activities are mediated through classical signaling

PROINFLAMMATORY STATES



epithelial cells, smooth muscle cells and endothelial cells become responsive to IL-6 in critical illness

McElvaney et al, Lancet Resp Med 2021; 9: 643-54

Proinflammatory cytokines

Cytokine	Normal physiologic role	Evidence in sepsis
IL-1ß	Immune cell proliferation and differentiation	↑ serum levels in non-survivors Levels frequently raised at tissue site of infection
IL-6	Stimulates B and T lymphocytes, has both pro and anti-inflammatory actions	↑ serum level vs controls Serum levels correlate with septic shock and disease severity Persistently ↑ serum levels associated with increased risk of death Decreasing trend in serum levels associated with better prognosis
IL-8	Promotes granulocyte chemotaxis, induces phagocytosis, stimulates angiogenesis	Predictor of 28-d mortality Persistently higher serum level seen in patients with sepsis compared with uncomplicated infection
IL-12	Induces differentiation of Th1 cells from naive T cells	Serial increase in serum levels noted in survivors vs non-survivors
IL-18	Induces production of a wide variety of cytokines and chemokines	Increased plasma levels associated with poor outcome

Conway-Morris A, Shankar-Hari M. Crit Care Clin 2018: 34: 29-42.

Proinflammatory cytokines

Cytokine	Normal physiologic role	Evidence in sepsis
TNF-α	Activates inflammatory cascade	↑ serum level vs controls Associated with development of renal failure Potential as therapeutic target
IFN-β	Stimulates chemokine and cytokine production, activates adaptive immunity	Evidence of contribution to **both** hyperinflammatory and immunosuppressed states Inhibits secretion of pro-inflammatory cytokines
GM-CSF	Stimulates neutrophil, monocyte and macrophage development from stem cells	↓ serum levels in non-survivors Potential therapeutic agent
Macrophage migration inhibitory factor (MIF)	Recruitment of leukocytes to sites of inflammation Inhibits immune cell apoptosis	↑ serum level vs controls Levels correlate with mortality

Conway-Morris A, Shankar-Hari M. Crit Care Clin 2018: 34: 29-42.

Anti-inflammatory cytokines

Cytokine	Normal physiologic role	Evidence in sepsis
IL-4	Promotes proliferation of B and T cells Promotes differentiation of CD4 T cells into Th2 cells Induces release of IL-13 from macrophages	IL-4 mRNA expression higher in sepsis survivors In mouse studies blockade of IL-4 prevents shift toward Th-2 profile and improves survival
IL-10	Inhibits synthesis of proinflammatory cytokines by macrophages and helper T cells	Sustained upregulation associated with worse prognosis Mediator of monocyte endotoxin tolerance
IL-13	Inhibits proinflammatory cytokine production Associated with prolonged monocyte survival	↑ serum levels in non-survivors
IL-35	Converts naive T cells into regulatory T cells Stimulates proliferation of regulatory T cells	Levels correlating with severity

Conway-Morris A, Shankar-Hari M. Crit Care Clin 2018: 34: 29-42.

Immunomodulatory therapies in sepsis

Anti-inflammatory therapy: FAILED

- MD2 TLR4
- anti IL-1RA
- anti IL-1β
- anti TNFα – increased risk of infections, increased mortality
- anti LPS
- ….anti-inflammatory strategy may be wrong?

Adjuvant therapy – immune system regulation

- decreasing harmful capillary leak and oedema formation by protecting or restoring endothelial cell function
- reversing sepsis-induced immunosuppression by immunostimulation
- removal of harmful mediators from the blood using extracorporeal techniques

Endothelial cell protection

- **Vasopressin** – catecholamine sparing strategy

JAMA. 2019 Oct 15;322(15):1476-1485. doi: 10.1001/jama.2019.14607.

Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial

Conclusions and relevance: Among patients with septic shock receiving norepinephrine, administration of selepressin, compared with placebo, did not result in improvement in vasopressor- and ventilator-free days within 30 days. Further research would be needed to evaluate the potential role of selepressin for other patient-centered outcomes in septic shock.

Endothelial cell protection

- **Interferon-beta**
  - helps restore endothelial integrity by increasing local adenosine levels
  - treatment prevented vascular leakage in mouse model with acute lung injury
  - recombinant IFN-ß1a and ARDS: increased survival compared with control patients (8 % vs 32 %, OR 0.19; 95% CI 0.03-0.72)
- **Thrombomodulin**
  - natural anticoagulant, binds thrombin and enhances activation of protein C
  - inhibits complement, neutralizes HMGB1 – proinflammatory protein, associated with vascular integrity
  - phase 3 trial results awaited

Kiss J et al. Eur J Immunol 2007; 37: 3334-8.
Bellingan et al. Lancet Resp Med 2014; 2: 98-107.
Vincent J et al. Crit Care Clinics 2018; 34: 161-173.

Immunostimulation

- Granulocyte-colony stimulating factor (**G-CSF**) and granulocyte-macrophage colony stimulating factor (**GM-CSF**)
  - aim: to reverse sepsis-induced monocyte and dendritic cell deactivation
  - clinical trials not showing effects on mortality
  - positive results in patients with proven immunosuppression – increased mHLA-DR levels and inflammatory cytokine production, reduced duration of mechanical ventilation, no effect on mortality
  - multicentre phase 3 trial results awaited (Lyon)

Vincent J et al. Crit Care Clinics 2018; 34: 161-173
Meisel C e al. Am J Resp Crit Care Med 2009; 180: 640-8.

Immunostimulation

- **IFNγ:**
  - secreted predominantly by T-helper cells and natural killer cells
  - key role in mounting an efficient immune response
  - secretion reduced in sepsis ----correlates with death and secondary infections
  - healthy volunteers – endotoxin: IFNγ reduced inflammatory response and increased monocyte HLA-DR expression
  - patients with invasive fungal infection – IFNγ therapy restored immune function
  - in unselected trauma patients – no reduction in secondary infections

Vincent J et al. Crit Care Clinics 2018; 34: 161-173
Leentjens J et al. Am J Respir Crit Care Med 2012; 186: 838-45.
Deising et al. BMC Infect Dis 2014; 14:166
Mock et al. Shock 1996; 5: 235-40.

Immunostimulation

- IL-7 and IL-15
  - promote lymphocyte proliferation and IFNγ production
  - trials showing conflicting results – IL 15 administration - increased release of multiple inflammatory cytokines, hypotension, thrombocytopenia, liver damage

Vincent J et al. Crit Care Clinics 2018; 34: 161-173

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]

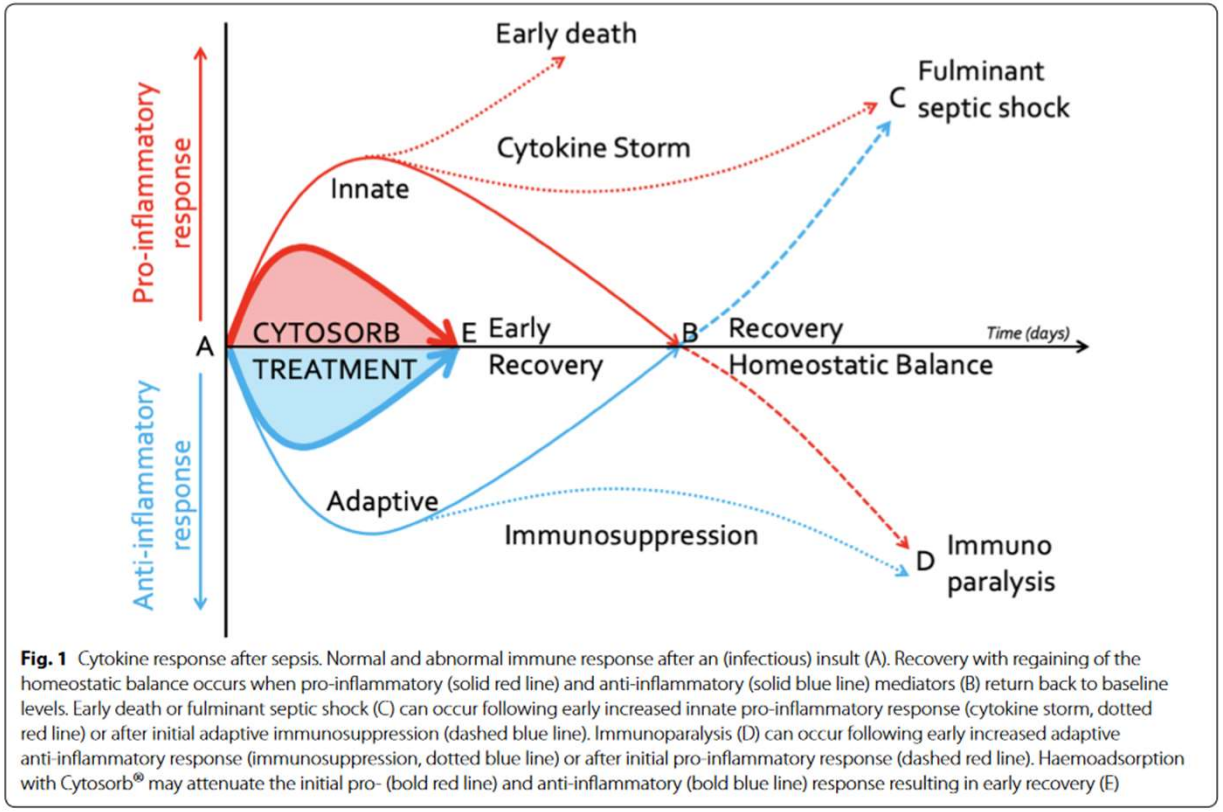
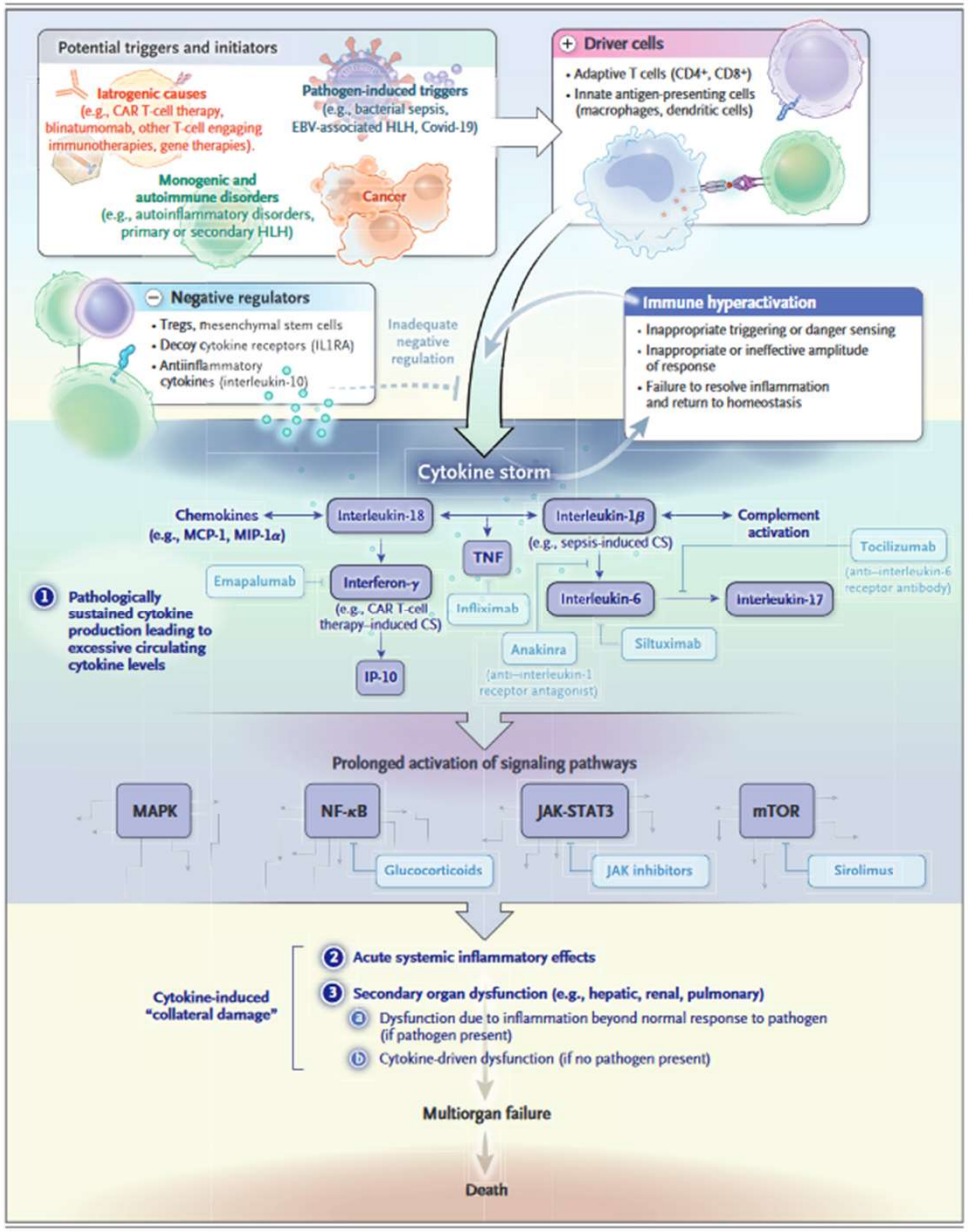


Fig. 1 Cytokine response after sepsis. Normal and abnormal immune response after an (infectious) insult (A). Recovery with regaining of the homeostatic balance occurs when pro-inflammatory (solid red line) and anti-inflammatory (solid blue line) mediators (B) return back to baseline levels. Early death or fulminant septic shock (C) can occur following early increased innate pro-inflammatory response (cytokine storm, dotted red line) or after initial adaptive immunosuppression (dashed blue line). Immunoparalysis (D) can occur following early increased adaptive anti-inflammatory response (immunosuppression, dotted blue line) or after initial pro-inflammatory response (dashed red line). Haemoadsorption with Cytosorb® may attenuate the initial pro- (bold red line) and anti-inflammatory (bold blue line) response resulting in early recovery (E)



Different therapy for different causes, different cytokine profiles?

Conclusion

- Cytokines are not all bad.
- Cytokine profiles/network analysis may be a way of individualizing sepsis therapy.
- To date, anti-cytokine-based therapies have not resulted in improved mortality.