Pathogenesis of sepsis and septic shock

Dr. Barbara Adamik, Assist. Prof.
Department of Anesthesiology and Intensive Therapy
Wroclaw Medical University

Pathogenesis of sepsis and septic shock

- ✓ **Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection.**

- ✓ **In 2017, an estimated 48,9 million incident cases of sepsis were recorded worldwide and 11,0 million sepsis-related deaths were reported, representing 19,7% of all global deaths*.**

- ✓ **Furthermore, there is increasing awareness that patients who survive sepsis often have long-term physical, psychological, and cognitive disabilities These symptoms can last for months or even years and can have significant health care and social implications.**

**Rudd KE et al., Global, regional, and national sepsis incidence and mortality,1990–2017: analysis for the Global Burden of Disease Study, Lancet 2020; 395: 200–11*

Incident cases of sepsis for both sexes, and all locations, 2017

	Male		Female		Both sexes	
	Incident cases (95% UI)	Age-standardised incidence per 100 000 population (95% UI)	Incident cases (95% UI)	Age-standardised incidence per 100 000 population (95% UI)	Incident cases (95% UI)	Age-standardised incidence per 100 000 population (95% UI)
Infections	15 961 632 (11 416 679–22 490 150)	453·5 (323·5–641·6)	17 165 460 (12 324 759–24 539 248)	482·4 (344·1–695·4)	33 127 159 (24 112 267–45 885 664)	466·8 (337·4–654·8)
Injuries	1 202 056 (916 529–1 548 161)	31·7 (24·2–40·8)	663 329 (494 773–850 850)	17·8 (13·2–23·1)	1 865 358 (1 421 131–2 392 774)	24·7 (18·8–31·7)
Non-communicable diseases	5 567 578 (4 499 826–7 157 847)	157·6 (126·8–203·8)	8 349 730 (6 520 440–11 096 832)	216·4 (167·6–290·8)	13 917 451 (11 313 974–17 629 415)	186·0 (150·0–237·0)
All causes	22 731 266 (18 037 098–29 410 723)	642·8 (507·7–834·8)	26 178 518 (20 630 286–33 702 305)	716·5 (560·2–925·1)	48 909 968 (38 929 606–62 859 320)	677·5 (535·7–876·1)

Data are n (95% UI), unless otherwise stated. UI=uncertainty interval.

Table 1: **Incident cases of sepsis and age-standardised incidence of sepsis, for all ages, both sexes, and all locations, according to category of underlying cause, 2017**

Rudd KE et al., Global, regional, and national sepsis incidence and mortality,1990–2017: analysis for the Global Burden of Disease Study, Lancet 2020; 395: 200–11

Leading causes of sepsis in 1990, 2007, and 2017

Leading causes, 2017	Mean % change in number of cases, 2007–17	Mean % change in age-standardised incidence, 2007–17
1 Diarrhoeal diseases	−14·9	−23·2
2 Lower respiratory infections	−8·8	−20·0
3 Maternal disorders	−19·2	−25·6
4 Neonatal disorders	−7·8	−10·1
5 Malaria	−29·8	−34·6
6 Typhoid and paratyphoid	−4·4	−10·4
7 Urinary diseases	55·1	19·4
8 Cirrhosis	13·6	−9·5
9 Stroke	7·3	−19·2
10 HIV/AIDS	−51·1	−57·0
11 Meningitis	−14·8	−20·7
12 Tuberculosis	−19·1	−33·4
13 COPD	9·4	−18·3
14 Diabetes	27·3	−3·0
15 Dengue	61·8	45·8
16 Alzheimer's disease	37·4	−3·0
17 Measles	−48·1	−50·9
18 Chronic kidney disease	18·9	−6·2
19 Road injuries	−8·5	−19·5
20 iNTS	−1·3	−7·8
23 Ischaemic heart disease		
28 Protein–energy malnutrition		
61 Tetanus		
98 Leishmaniasis		

diarrheal diseases: cholera (Vibrio cholerae), ETEC (E. coli), rotavirus, shigellosis, typhoid (Salmonella typhi)

Infections
Non-communicable diseases
Injuries

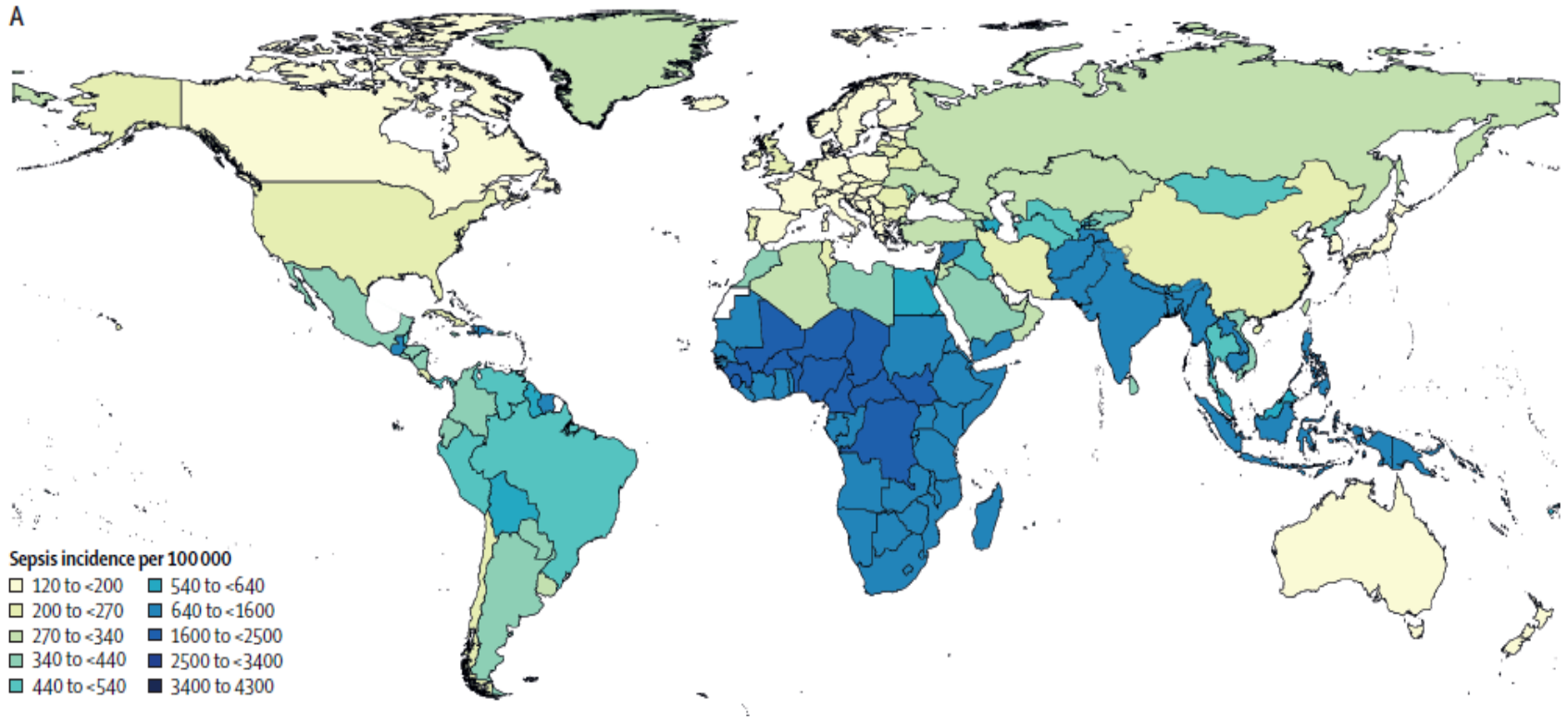
COPD=chronic obstructive pulmonary disease.

iNTS=invasive non-typhoidal salmonella.

Rudd KE et al., Global, regional, and national sepsis incidence and mortality,1990–2017: analysis for the Global Burden of Disease Study, Lancet 2020; 395: 200–11

Sepsis incidence per 100 000 population in 2017

- ✓ **there are significant regional disparities in sepsis incidence**
- ✓ **approximately 85.0% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries.**



Rudd KE et al., Global, regional, and national sepsis incidence and mortality,1990–2017: analysis for the Global Burden of Disease Study, Lancet 2020; 395: 200–11

Pathogenesis of sepsis

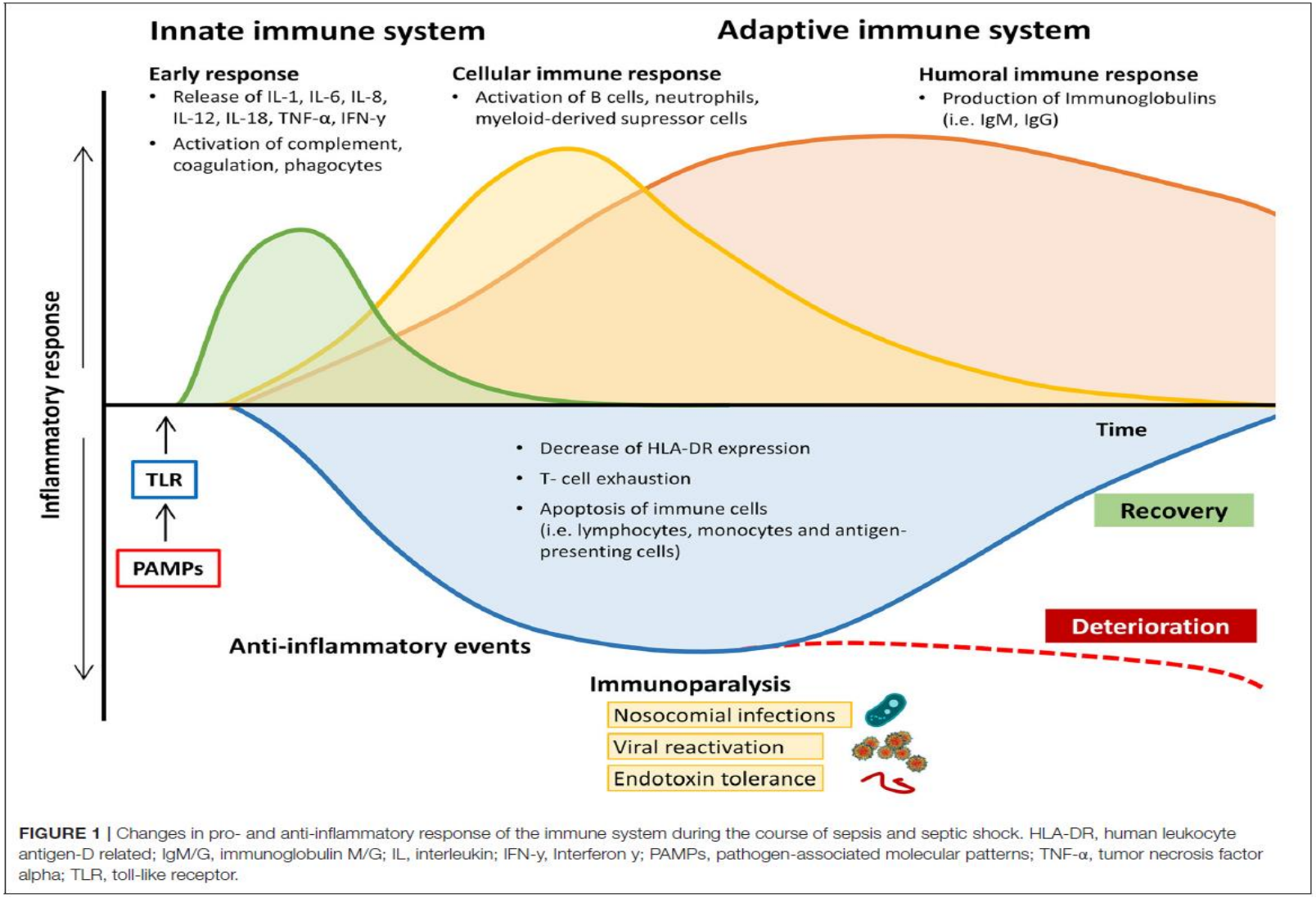


FIGURE 1 | Changes in pro- and anti-inflammatory response of the immune system during the course of sepsis and septic shock. HLA-DR, human leukocyte antigen-D related; IgM/G, immunoglobulin M/G; IL, interleukin; IFN-γ, Interferon γ; PAMPs, pathogen-associated molecular patterns; TNF-α, tumor necrosis factor alpha; TLR, toll-like receptor.

Jarczak D et al. (2021) Sepsis—Pathophysiology and Therapeutic Concepts. Front. Med. 8:628302.

Pathogenesis of sepsis

1. Pathogen recognition system detects pathogens via pattern-recognition receptors (PRRs). **PRRs can identify a diverse collection of microbial pathogens,** which include: bacteria, viruses, parasites, and fungi. PRRs are primarily expressed by antigen presenting macrophage and dendritic cells but can also be expressed by other cells (both immune and non-immune cells).
2. PRRs recognise components that are expressed only by pathogens. These microbial components are known as **pathogen-associated molecular patterns (PAMPs).**
3. Pattern-recognition receptors (PRRs) may warn the host of danger in general by their ability to recognise endogenous mediators released during injury, such as trauma, ischemia, or necrosis.
4. Such endogenous danger signals have been termed **danger-associated molecular patterns (DAMPs).**

T van der Poll, SM Opal - The Lancet infectious diseases, 2008

Pathogenesis of sepsis

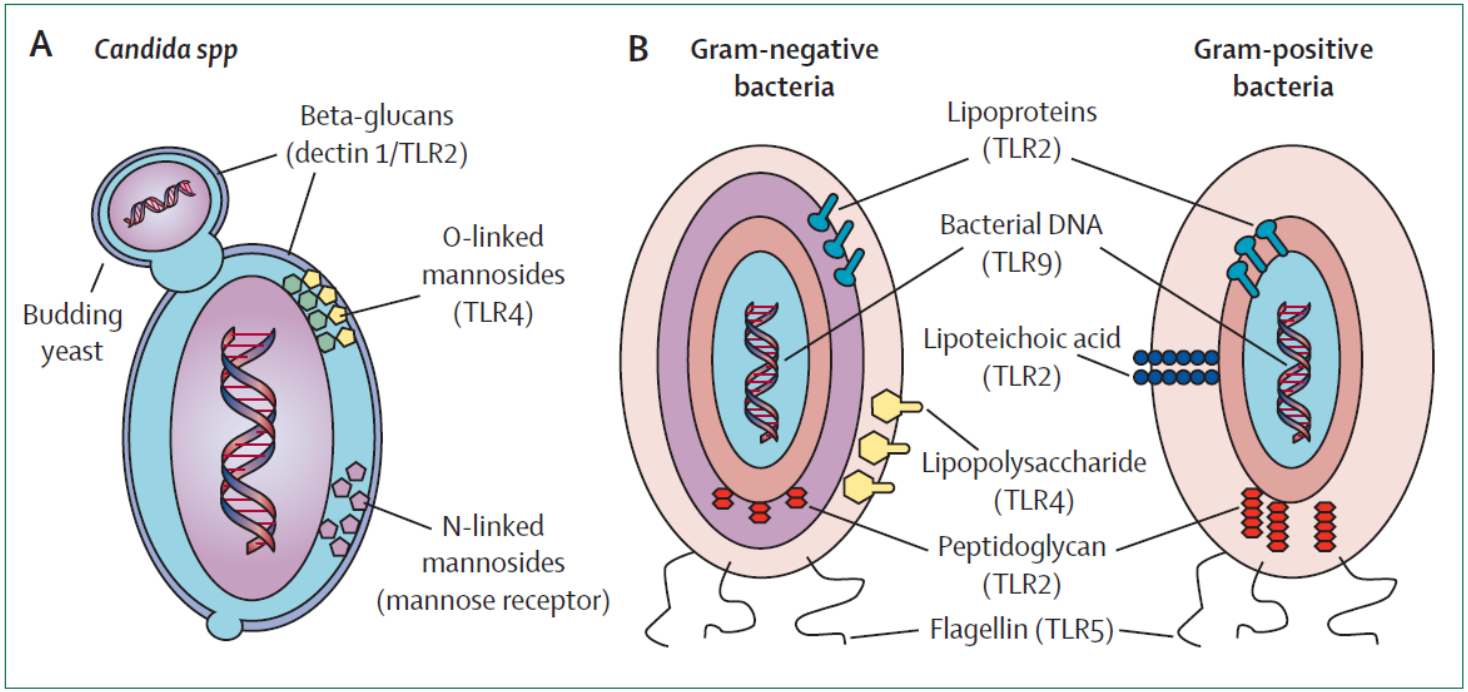


Figure 3: **Innate recognition of pathogens by Toll-like (and related) receptors (TLRs)**
(A) The complexity of the interaction between innate immune receptors and fungi. Three distinct components of the cell wall of *Candida albicans* are recognised by four different host receptors: N-linked mannosyl residues are detected by the mannose receptor, O-linked mannosyl residues are sensed by TLR4, and β-glucans are recognised by the dectin 1–TLR2 complex.[40] (B) Gram-positive and Gram-negative bacteria are recognised by partly overlapping and partly distinct repertoire of TLRs. Gram-positive pathogens exclusively express lipoteichoic acid, Gram-negative pathogens exclusively express lipopolysaccharide; common pathogen-associated molecular patterns include peptidoglycan, lipoproteins, flagellin, and bacterial DNA.

T van der Poll, SM Opal - The Lancet infectious diseases, 2008

Pathogenesis of sepsis – immunological dysfunction

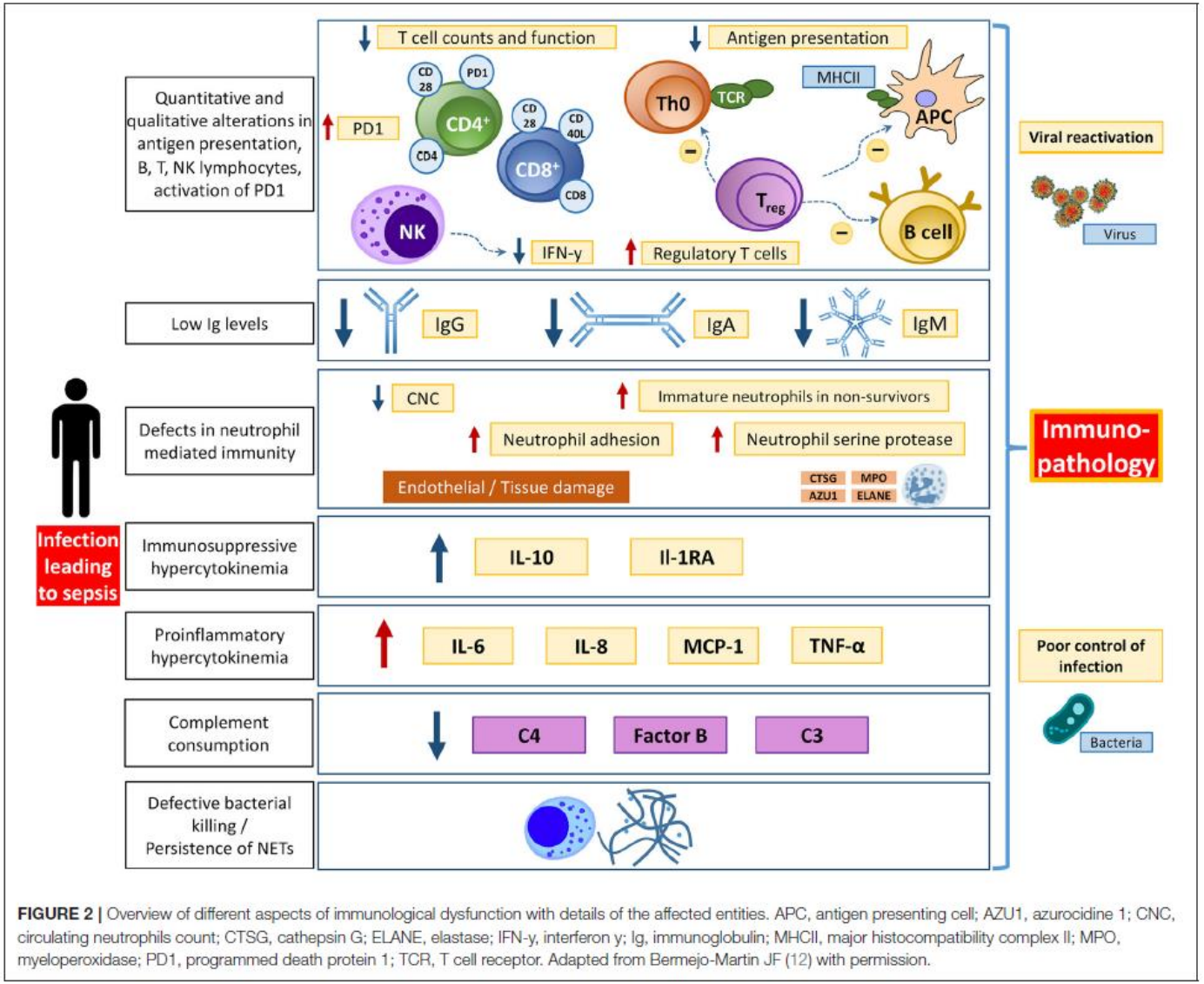
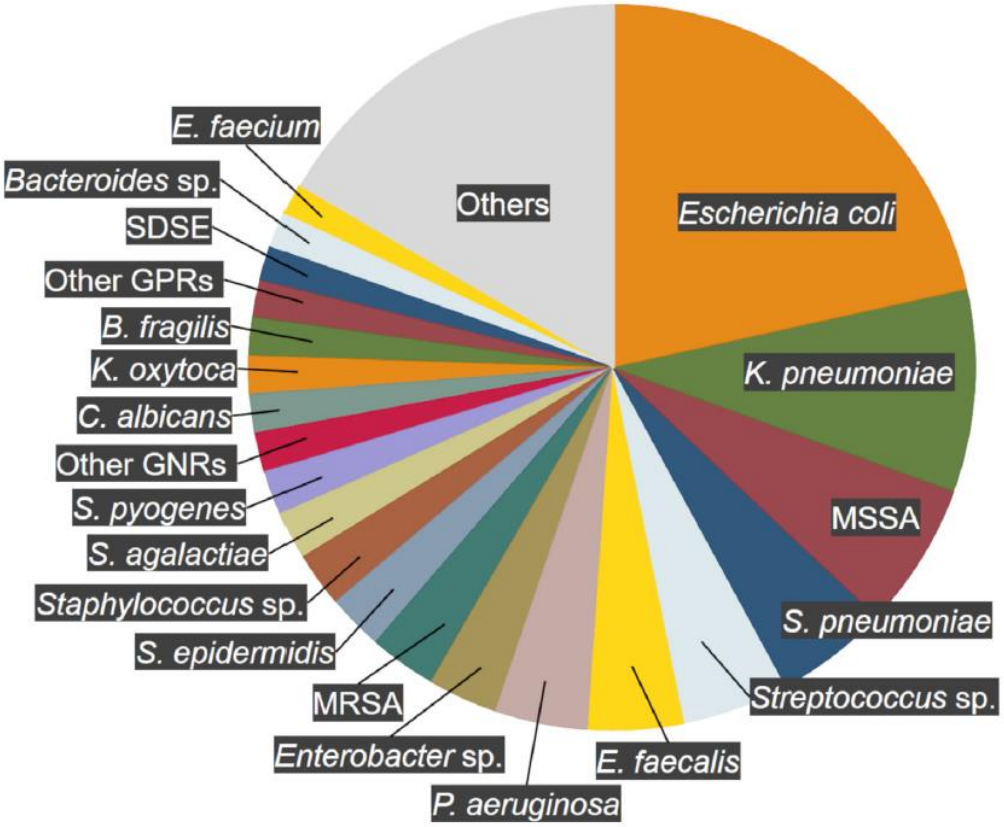


FIGURE 2 | Overview of different aspects of immunological dysfunction with details of the affected entities. APC, antigen presenting cell; AZU1, azurocidine 1; CNC, circulating neutrophils count; CTSG, cathepsin G; ELANE, elastase; IFN-γ, interferon γ; Ig, immunoglobulin; MHCII, major histocompatibility complex II; MPO, myeloperoxidase; PD1, programmed death protein 1; TCR, T cell receptor. Adapted from Bermejo-Martin JF (12) with permission.

Jarczak D et al. (2021) Sepsis—Pathophysiology and Therapeutic Concepts. Front. Med. 8:628302.

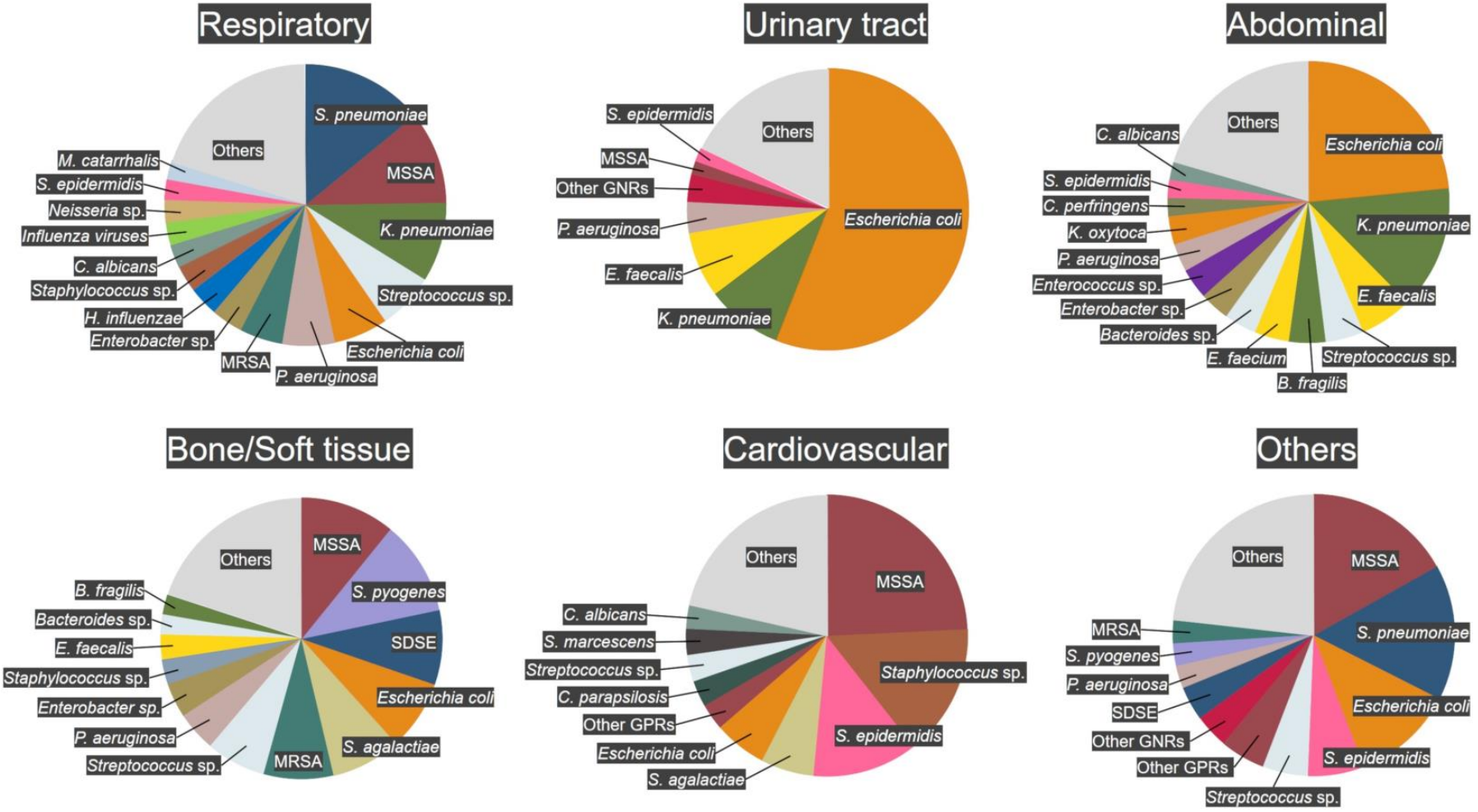
Spectrum of causative pathogens



Others: Mycobacterium tuberculosis, *Mycobacterium* spp, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Chlamydophila* spp, *Mycoplasma pneumoniae*, *Mycoplasma* spp, *Rickettsia* spp, *Pneumocystis jirovecii*, cytomegalovirus, Epstein–Barr virus, influenza viruses

Umemura Y et al., Current spectrum of causative pathogens in sepsis: A prospectivenationwide cohort study in Japan. International Journal of Infectious Diseases. 2021

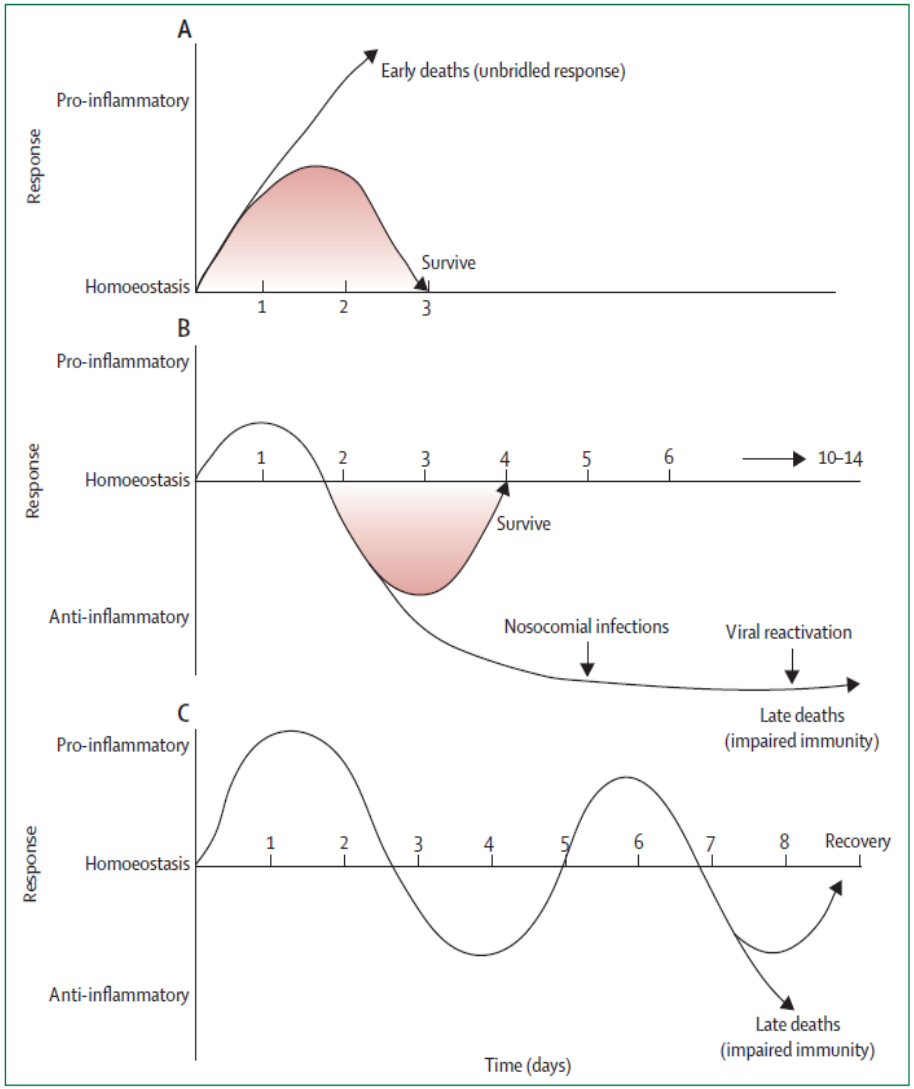
Spectrum of causative pathogens in subgroups by site of infection



Others: Mycobacterium tuberculosis, *Mycobacterium* spp, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Chlamydophila* spp, *Mycoplasma pneumoniae*, *Mycoplasma* spp, *Rickettsia* spp, *Pneumocystis jirovecii*, cytomegalovirus, Epstein–Barr virus, influenza viruses

Umemura Y et al., Current spectrum of causative pathogens in sepsis: A prospectivenationwide cohort study in Japan. International Journal of Infectious Diseases. 2021

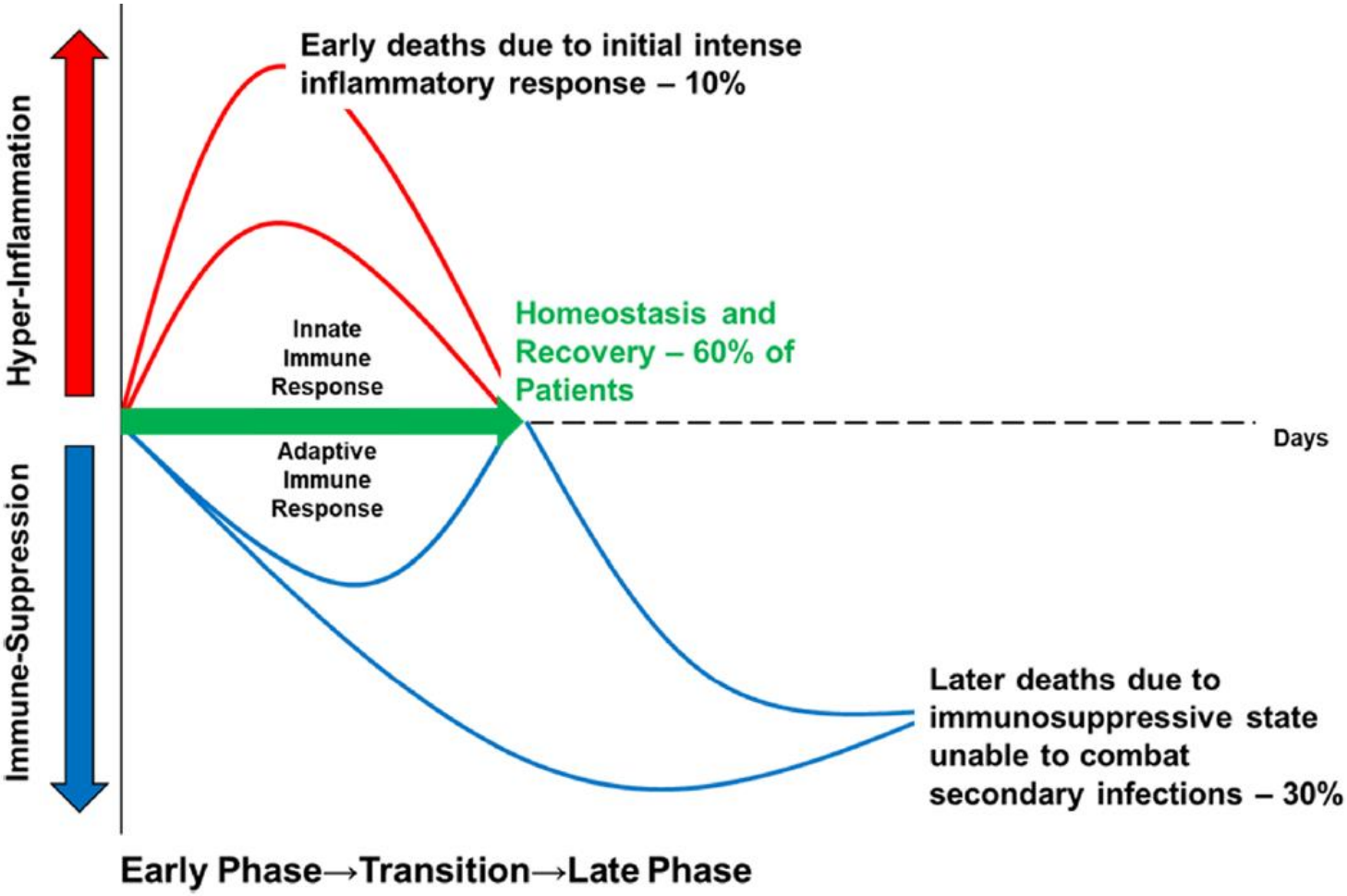
Potential inflammatory responses in sepsis



- ✓ Overwhelming hyperinflammatory phase. Death in this early phase of sepsis is generally due to cardiovascular collapse, metabolic derangements, and multiple organ dysfunction.
- ✓ Many patients with sepsis are elderly with numerous comorbidities that impaire immune response. A blunt or absent hyperinflammatory phase is common, and patients rapidly develop an anti-inflammatory state.
- ✓ Response to sepsis characterised by cycling between hyperinflammatory phase followed by a hypoinflammatory phase. The longer the sepsis continues the more likely a patient is to develop profound immunosupession.

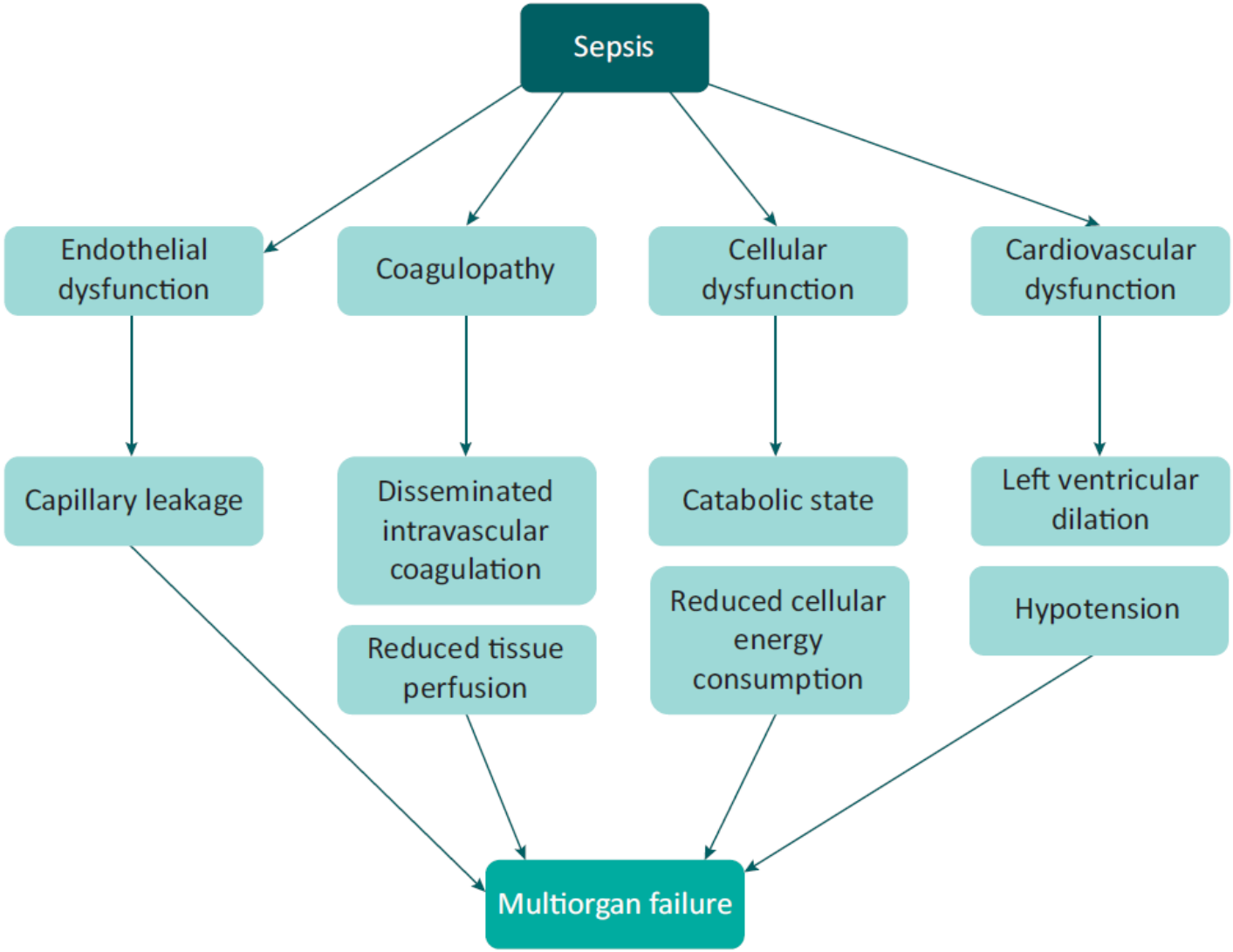
Hotchkiss RS, Monneret G, Payen D. Lancet Infect Dis. 2013 Mar;13(3):260-8.

Inflammatory responses in sepsis



Hotchkiss RS et al. (2013) Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol 13:862–874

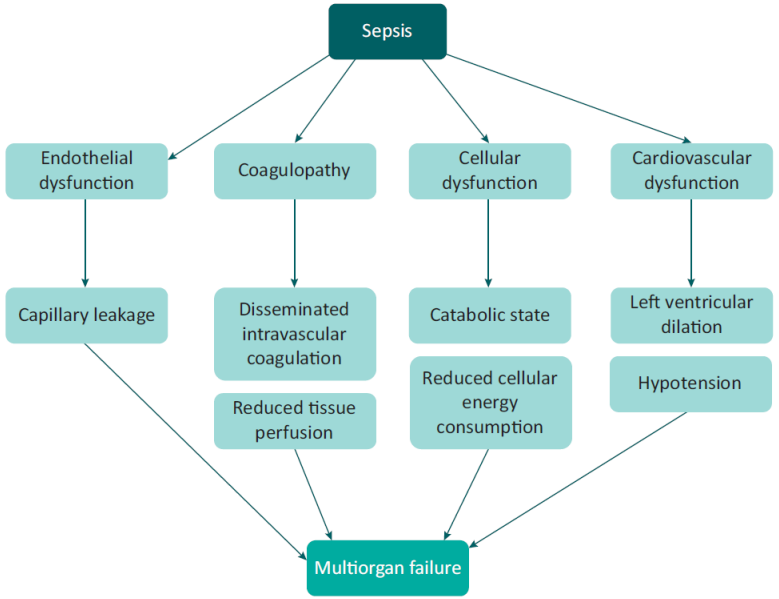
The key pathophysiological changes of sepsis



The key pathophysiological changes of sepsis - endothelial dysfunction

- ✓ Endothelium – role in regulating vasomotor tone, the movement of cells and nutrients into and out of tissues, the coagulation system, and the balance of inflammatory and antiinflammatory signaling.

- ✓ **<u>Endothelial dysfunction in sepsis</u>**: profound alterations occur, including 1.) increased leukocyte adhesion with increased transmigration into tissues, 2.) vasodilatation, and 3.) loss of barrier function, which all lead to widespread tissue edema.

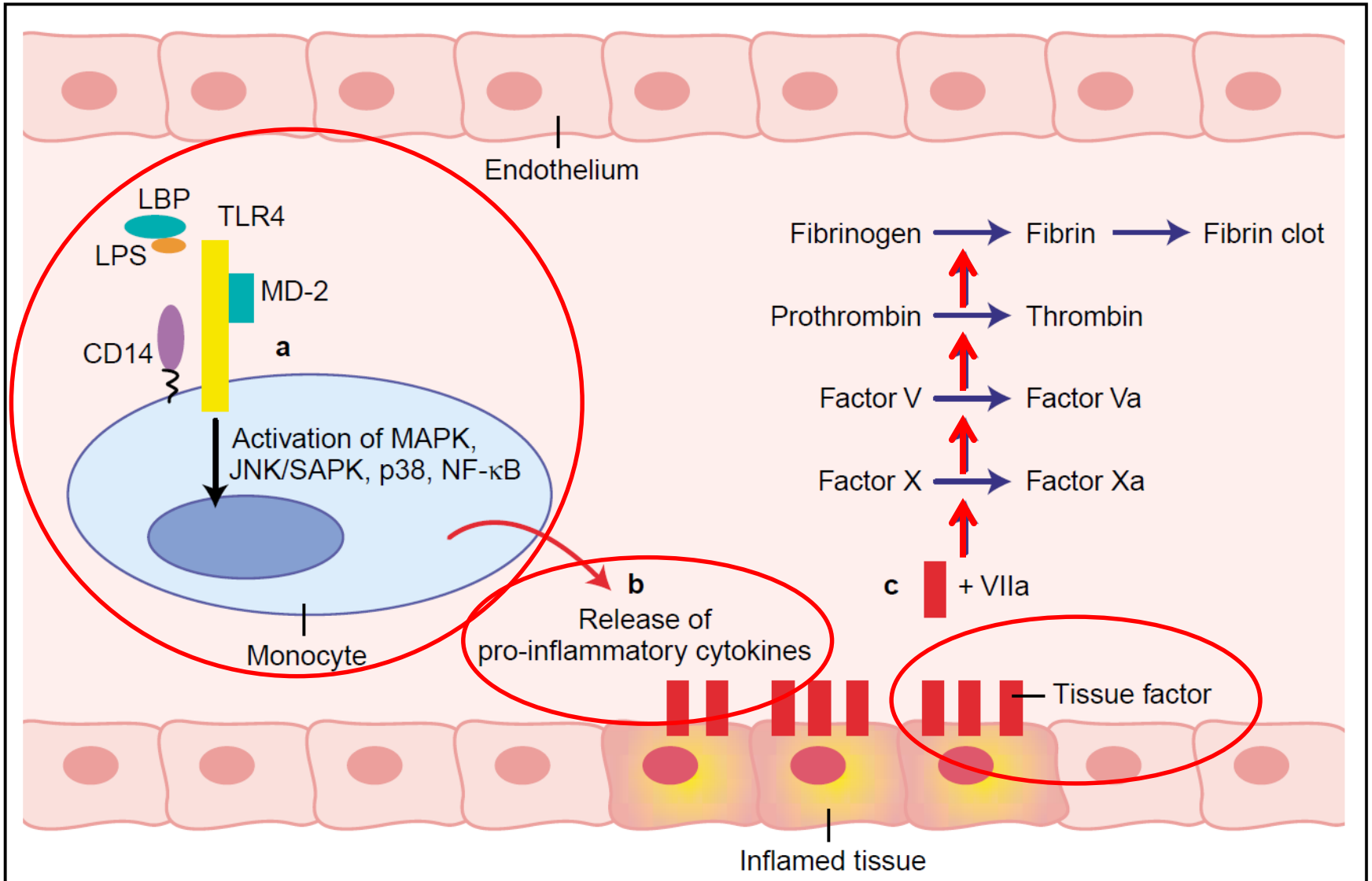


The key pathophysiological changes of sepsis - coagulopathy

Sepsis is almost always associated with haemostatic abnormalities ranging

- ✓ from isolated activation of blood coagulation which may contribute to localized venous thrombosis

- ✓ to acute disseminated intravascular coagulation (DIC) with systemic clotting activation, massive thrombin and fibrin formation and subsequent consumption and depletion of platelets and coagulation proteins. Sepsis and DIC may lead to simultaneous thrombosis and bleeding.



The coagulation cascade in sepsis

The key pathophysiological changes of sepsis – sepsis and anticlotting mechanisms

Anticoagulant System limits fibrin formation

1. **Tissue Factor Pathway Inhibitor ↓**
2. **Antithrombin pathway ↓**
3. **Protein C pathway ↓**

Fibrinolysis „dissolves" already formed clots

1. **Plasminogen/plasmin activators: ↓**
   - ✓ **tissue-type plasminogen activator**
   - ✓ **urokinase-type plasminogen activator**
   - ✓ **fibrin as a cofactor for plasminogen activation**
2. **Plasminogen/plasmin inhibitors: ↑**
   - ✓ **plasminogen activator inhibitors ↑**
   - ✓ **direct inhibitors of plasmin ↑**
   - ✓ **thrombin-activatable fibrinolysis inhibitor ↑**

Non-specific mechanisms

1. **Coagulation factors „washed away" effect**
2. **Adsorption and containment of coagulation factors by polymerized fibryn**

The key pathophysiological changes of sepsis – coagulopathy

In sepsis the contributing agent (pathogen) and the associated inflammatory response drive fibrin formation and deposits by several at the same time acting mechanisms which include:

1. **up-regulation of procoagulant pathways,**
2. **down-regulation of physiological anticoagulants and**
3. **suppression of fibrinolysis.**

Increased fibrin formation associated with impaired fibrinolysis may contribute to vascular oclusion, organ ischemia, organ damage and development of MODS.

The key pathophysiological changes of sepsis - cellular dysfunction

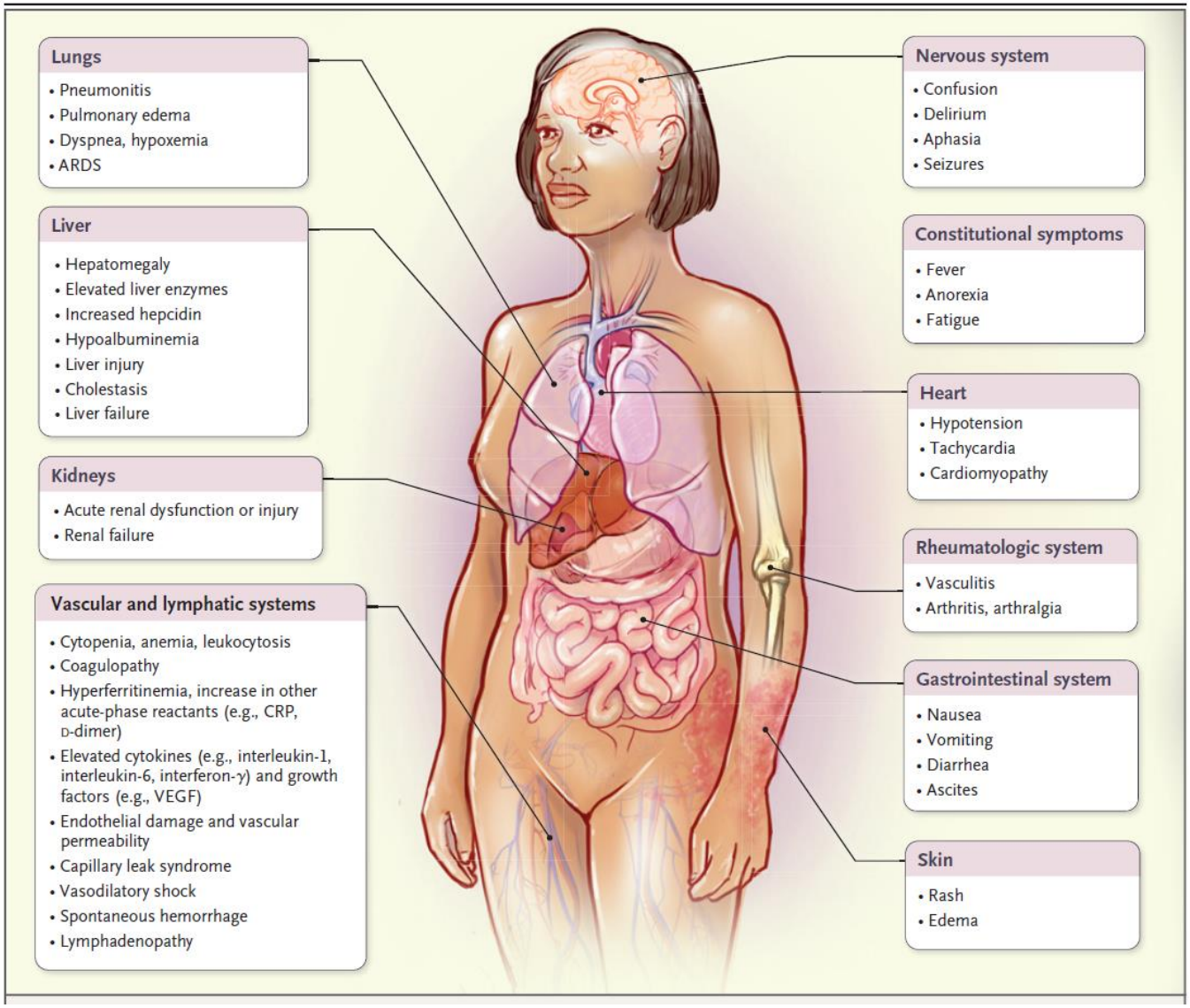
- More than 90% of total body oxygen consumption is used by mitochondria toward generation of ATP
- As mitochondrial ATP generation is the major energy source for most cell types, this implicates mitochondrial dysfunction as central to the pathogenesis of organ dysfunction.
- For mitochondrial dysfunction in sepsis to occur, a possible mechanism may be direct inhibition or damage to mitochondria by inflammatory mediators, notably nitric oxide and its metabolites and other reactive species.

✓ **The reduction in energy availability appears to trigger a metabolic shutdown that impairs normal functioning of the cell.**

The key pathophysiological changes of sepsis – cardiovascular dysfunction

- ✓ Many studies have shown that **patients with sepsis have a decreased systemic vascular resistance** (SVR) with a normal or increased cardiac output (heart rate x stroke volume)
- ✓ Cardiac output is maintained at the expense of left ventricular dilatation, with reduced ejection fraction. These changes can lead to the **hypotension characterizing septic shock.**
- ✓ Changes in SVR are probably largely mediated by **excess production of the vasodilator nitric oxide in the vasculature,** which can be difficult to correct with vasopressors.
- ✓ Poor tissue perfusion underlies the **increased lactate seen in septic shock** (def. of septic shock).

Muliorgan failure in septic patient – clinical presentation



David C. Fajgenbaum, Carl H. June, Cytokine Storm. N Engl J Med 2020;383:2255-73

Examples of sepsis biomarkers

Pro-inflammatory cytokines
IL-1beta, IL-6, TNF-alpha, MCP-1
IL-1RA, TNF-R1/2, HMGB-1

Acute phase proteins
CRP, Procalcitonin,
LBP, PTX3

Complement system
C3b, C5a

Biomarkers of neutrophil activation
Proteins in neuthrophil granules, CD64, CD11b, sCD14, TREM-1, HBP, sRAGE, TLR, suPAR, mHLADR

Biomarkers of immunosupression in sepsis
mHLA-DR, CTLA-4, PD-1
IL-10,IL-1ra

Biomarkers of organ injury
Lactate, NGAL, IGFBP7, TIMP2, troponin, microRNA, S100, ANP, BNP

Biomarkers od endothelium injury
ICAM-1, VCAM-1, E-selectine
Neopterine, NO, Endocan, VEGF

Coagulation activation
Antithrombin, thrombomodulin, C-protein, S-protein, d-dimers, PAI-1

Other
MMP-9, lactoferrin, pro-ADM

Sepsis, septic shock, definition, diagnosis

Special Communication | Caring for the Critically Ill Patient FREE

February 23, 2016

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

Mervyn Singer, MD, FRCP[1]; Clifford S. Deutschman, MD, MS[2]; Christopher Warren Seymour, MD, MSc[3]; et al

Author Affiliations | Article Information

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

Abstract

Importance Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

Objective To evaluate and, as needed, update definitions for sepsis and septic shock.

Sepsis, definition

- ✓ **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.**
  - ✓ The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - ✓ A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

Septic shock, definition

- ✓ **Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.**

- ✓ **Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.**

    - ✓ With these criteria, hospital mortality is in excess of 40%.

SOFA score (Sequential Organ Failure Assessment)

System	Score 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

Abbreviations: FIO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3–15; higher score indicates better neurological function.

GCS (Glasgow coma scale)

Eyes Open	Verbal	Motor
(•) Spontaneous	(•) Converses / Oriented	(•) Obeys
( ) To speech	( ) Converses / Disoriented	( ) Localizes pain
( ) To pain	( ) Inappropriate	( ) Withdraws (flexion)
( ) Absent	( ) Incomprehensible	( ) Decorticate (flexion) rigidity
	( ) Absent	( ) Decerebrate (extension) rigidity
		( ) Absent

Glasgow= 15

Key concepts of sepsis

- ✓ **Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.**
- ✓ **Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an dysregulated host response and the presence of organ dysfunction.**
- ✓ **Sepsis-induced organ dysfunction may be unrevealed; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.**
- ✓ **The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.**
- ✓ **Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.**