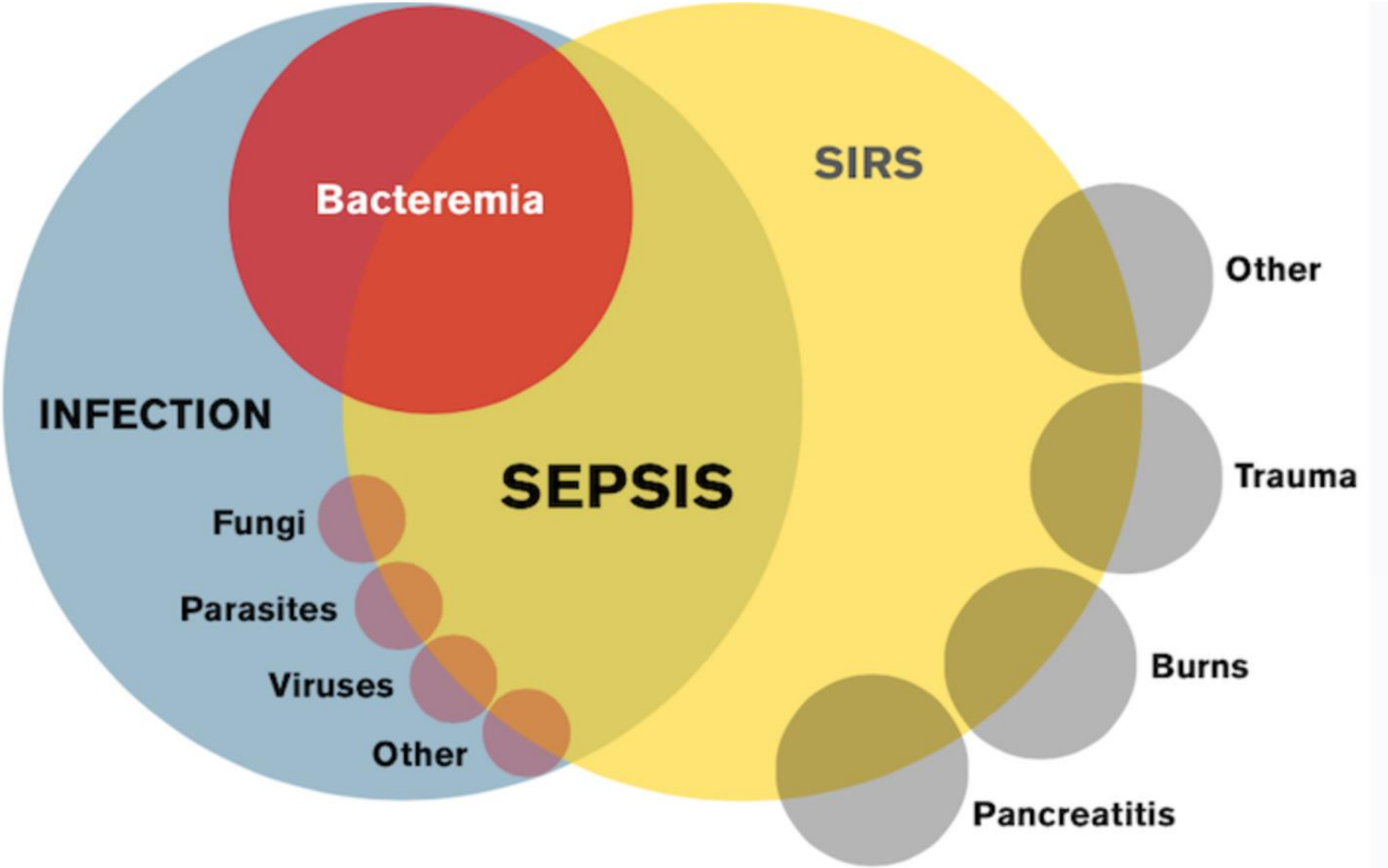
Sepsis

Sepsis

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

- The sepsis-associated host response is characterized by concurrent **excessive inflammatory, catabolic, metabolic and immune-suppressive features**, and a failure to return to homeostasis

Definitions



Infection

- **Presence** of **microorganisms** in a normally sterile site

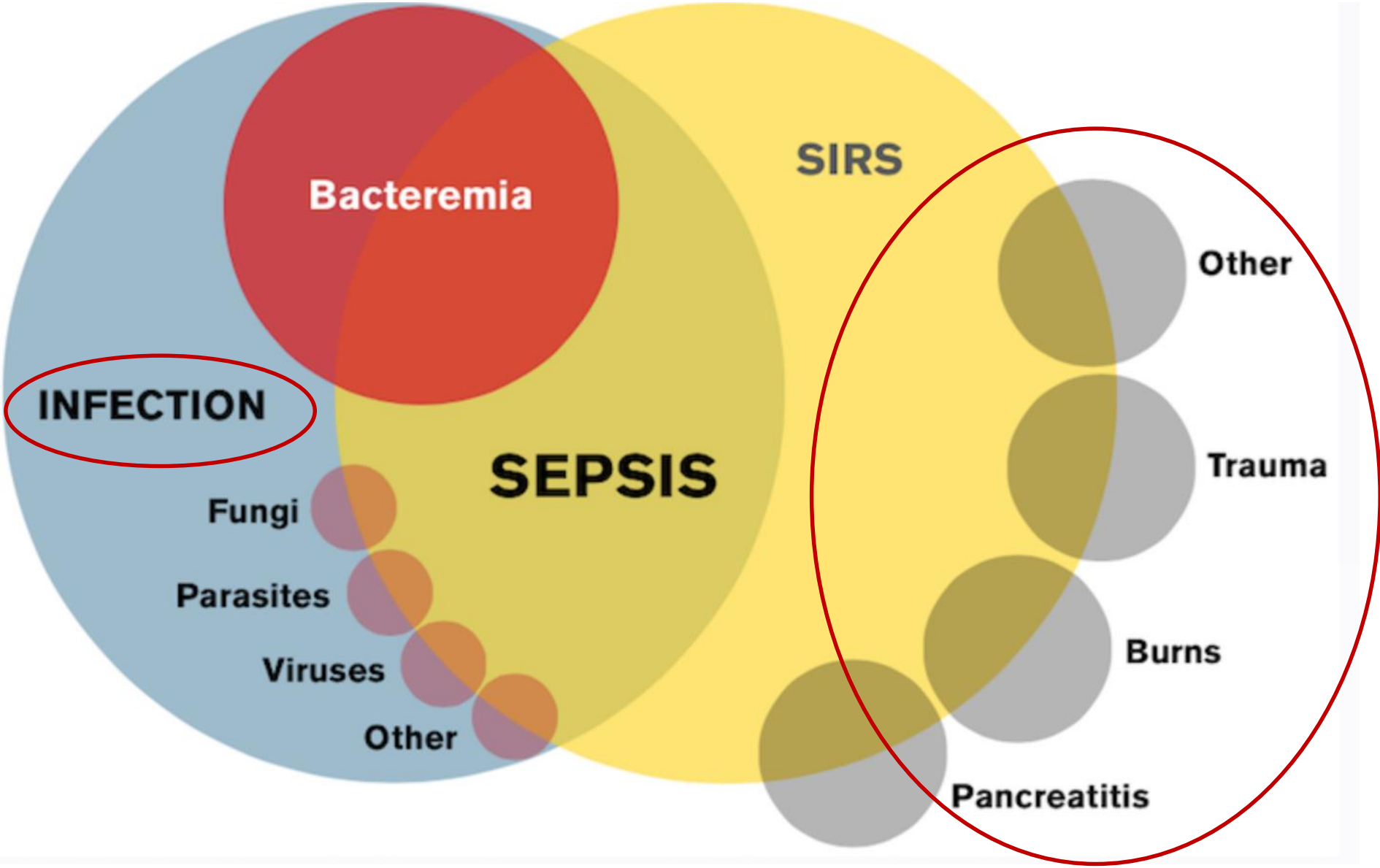
  (**colonization**: presence of microorganisms on an epithelial surface)

Systemic Inflammatory Response Syndrome (SIRS)

- The **systemic response** to a **wide range of stresses**

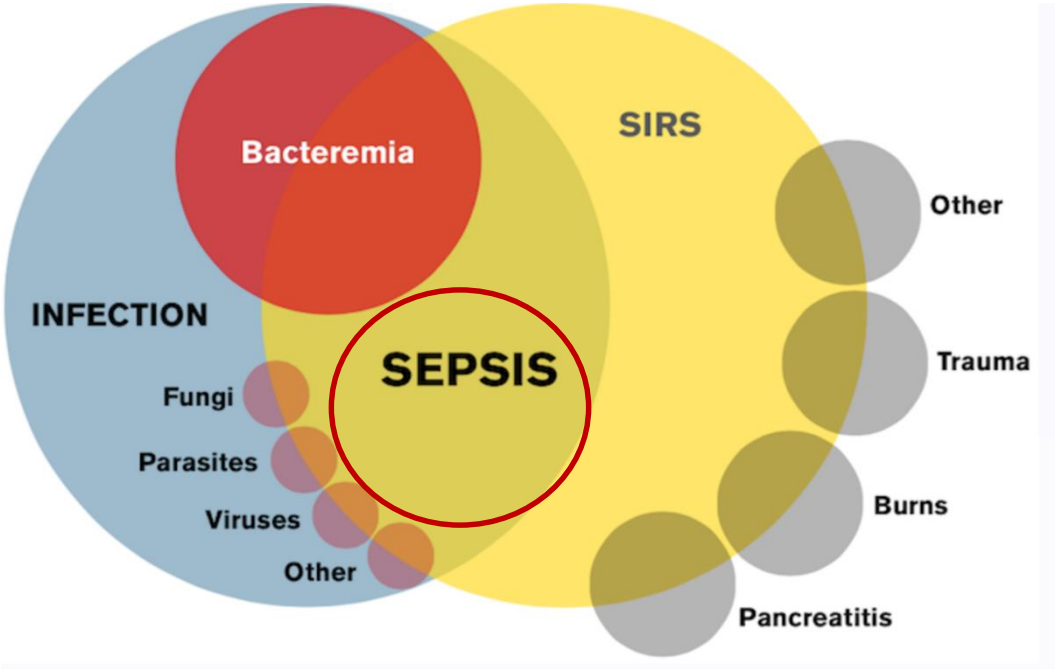
- Criteria include two or more of the following:
  - Temperature > 38°C or < 36°C
  - Heart rate > 90 beats/min
  - Respiratory rate
    - > 20 breaths/min or
    - $Paco_2$ < 32mmHg
  - WBC
    - > 12,000 cells/mm3 or
    - < 4,000 cells/mm3, or
    - > 10% immature (band) forms

SIRS


Bacteremia
SIRS
INFECTION
SEPSIS
Fungi
Parasites
Viruses
Other
Other
Trauma
Burns
Pancreatitis

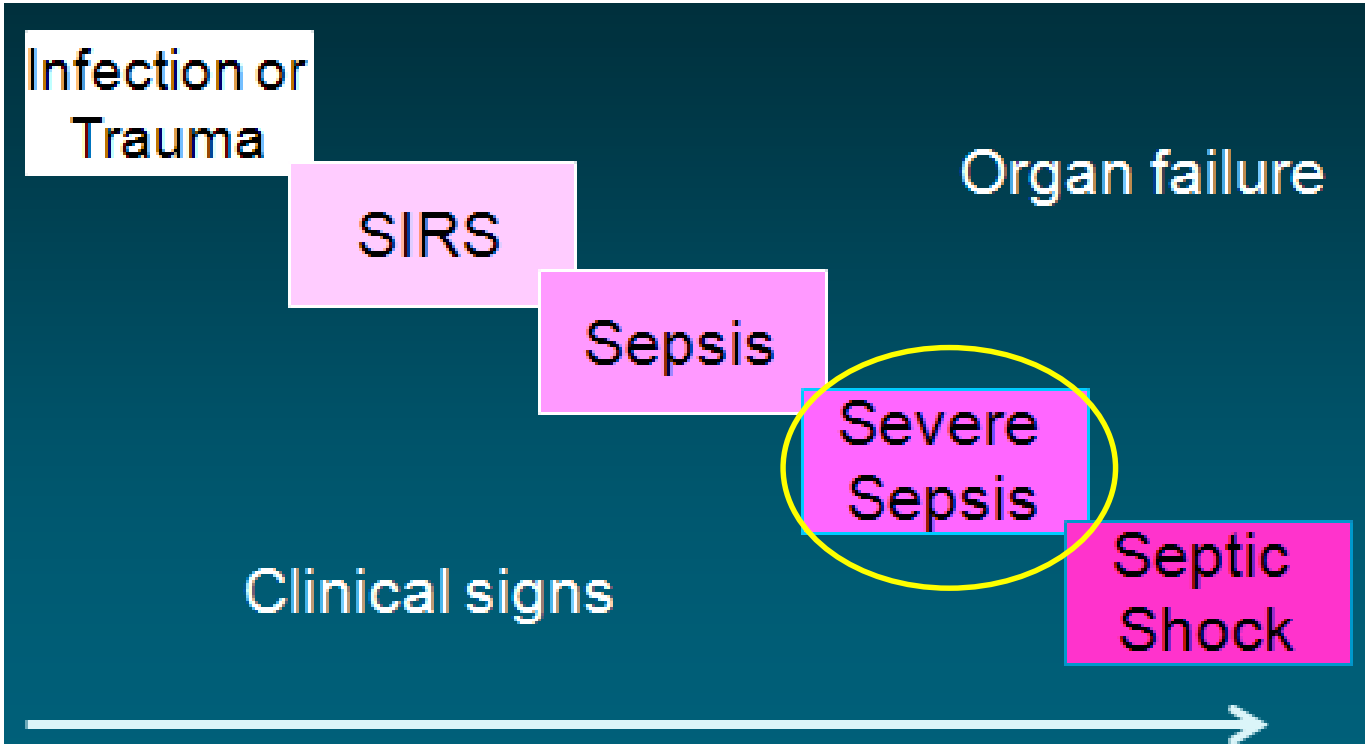
Sepsis

- The systemic response to infection.
- If associated with proven or clinically suspected **infection**, SIRS is called “sepsis.”

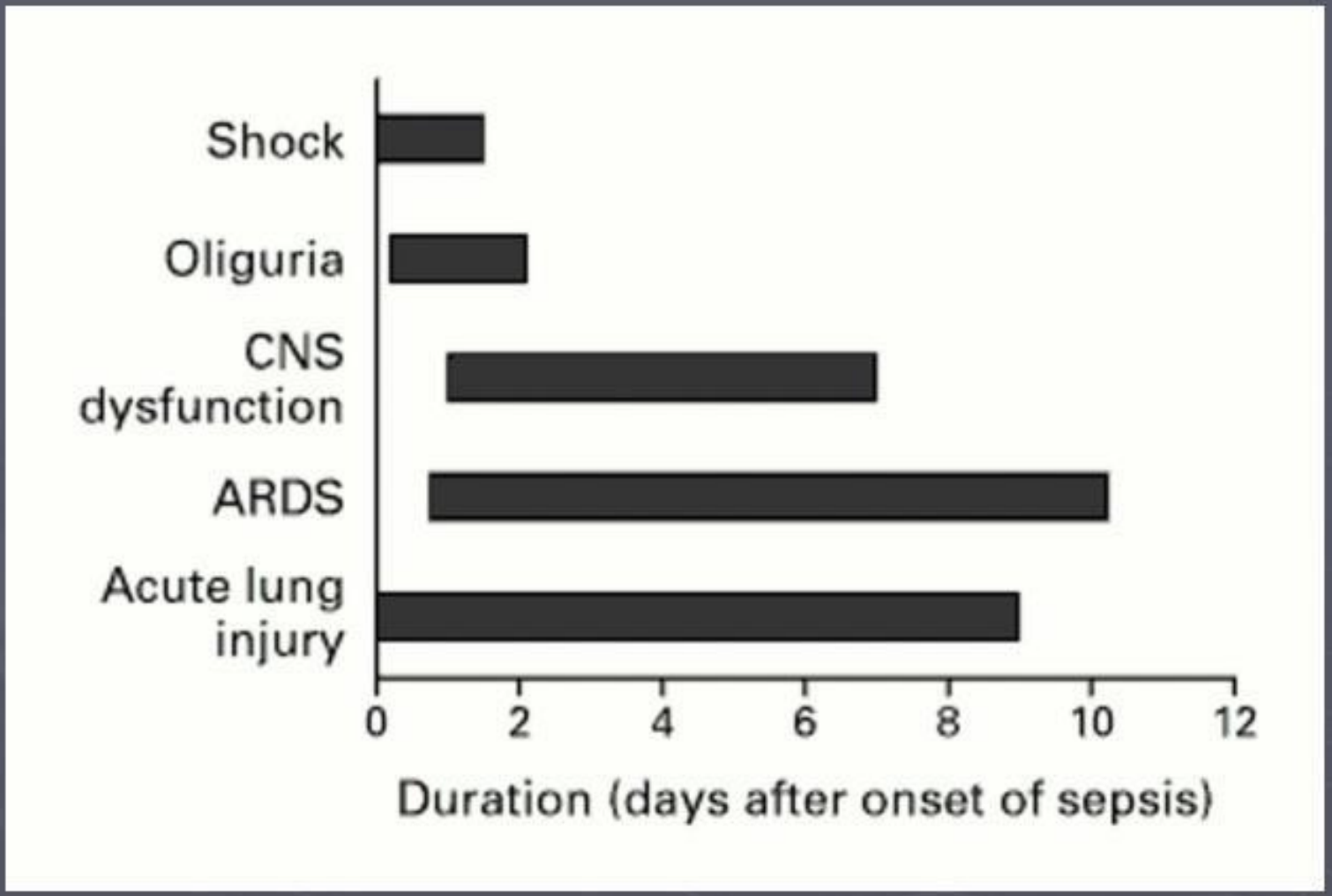


Severe sepsis

- Sepsis associated with **dysfunction** of organ(s) distant from the site of infection, **hypoperfusion**, or **hypotension**.

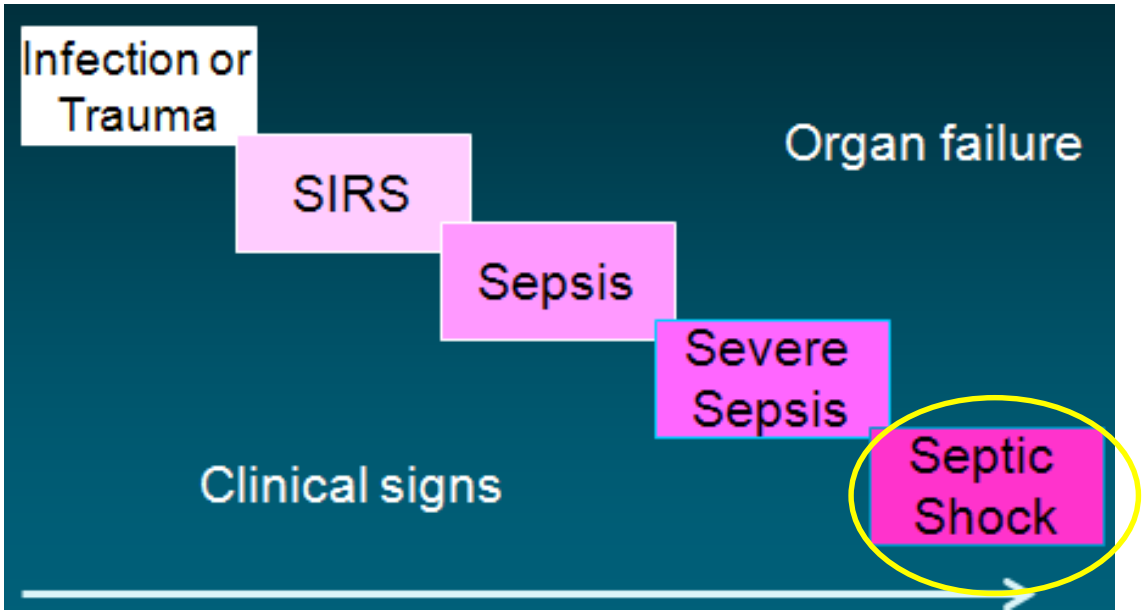


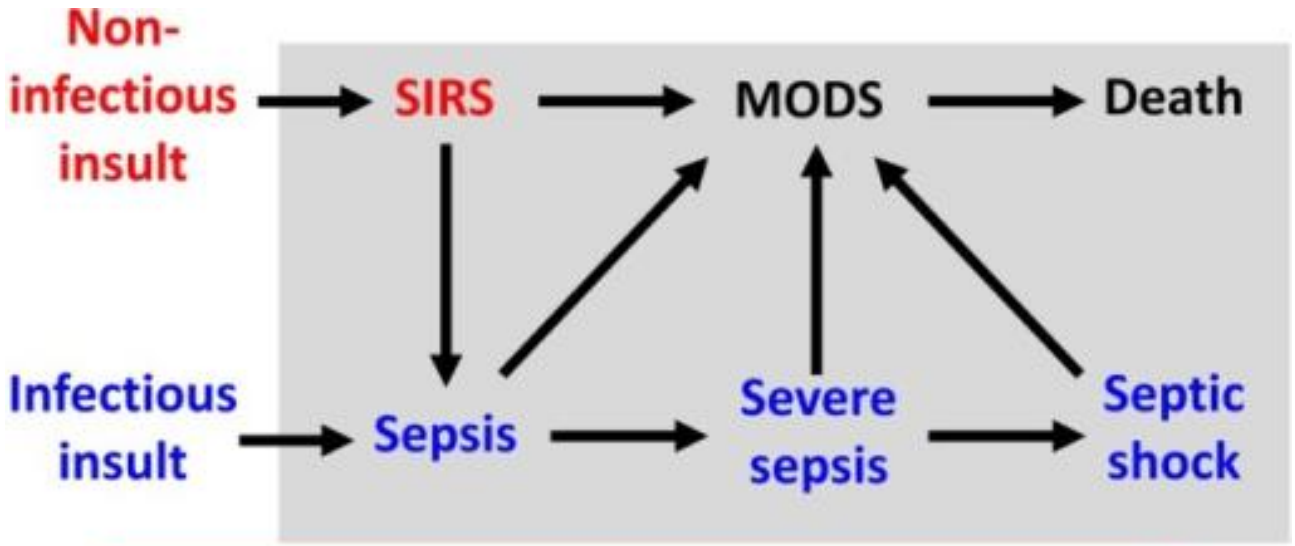
MODS

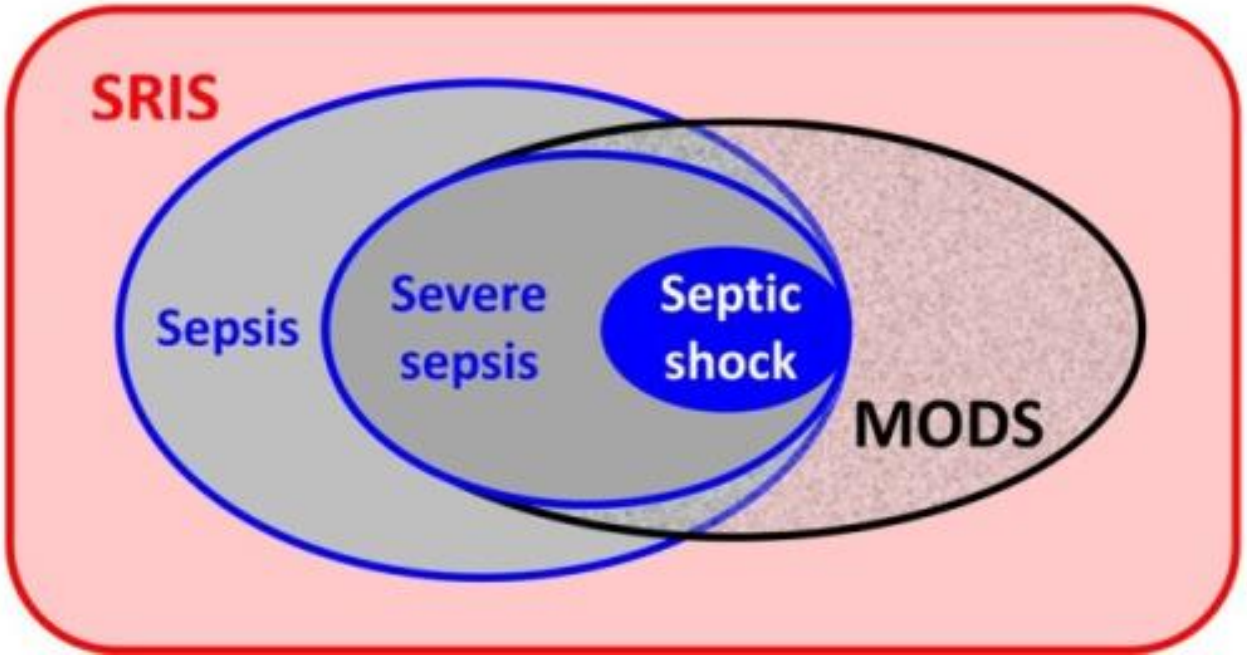

Shock
Oliguria
CNS dysfunction
ARDS
Acute lung injury
0
2
4
6
8
10
12
Duration (days after onset of sepsis)

Septic shock

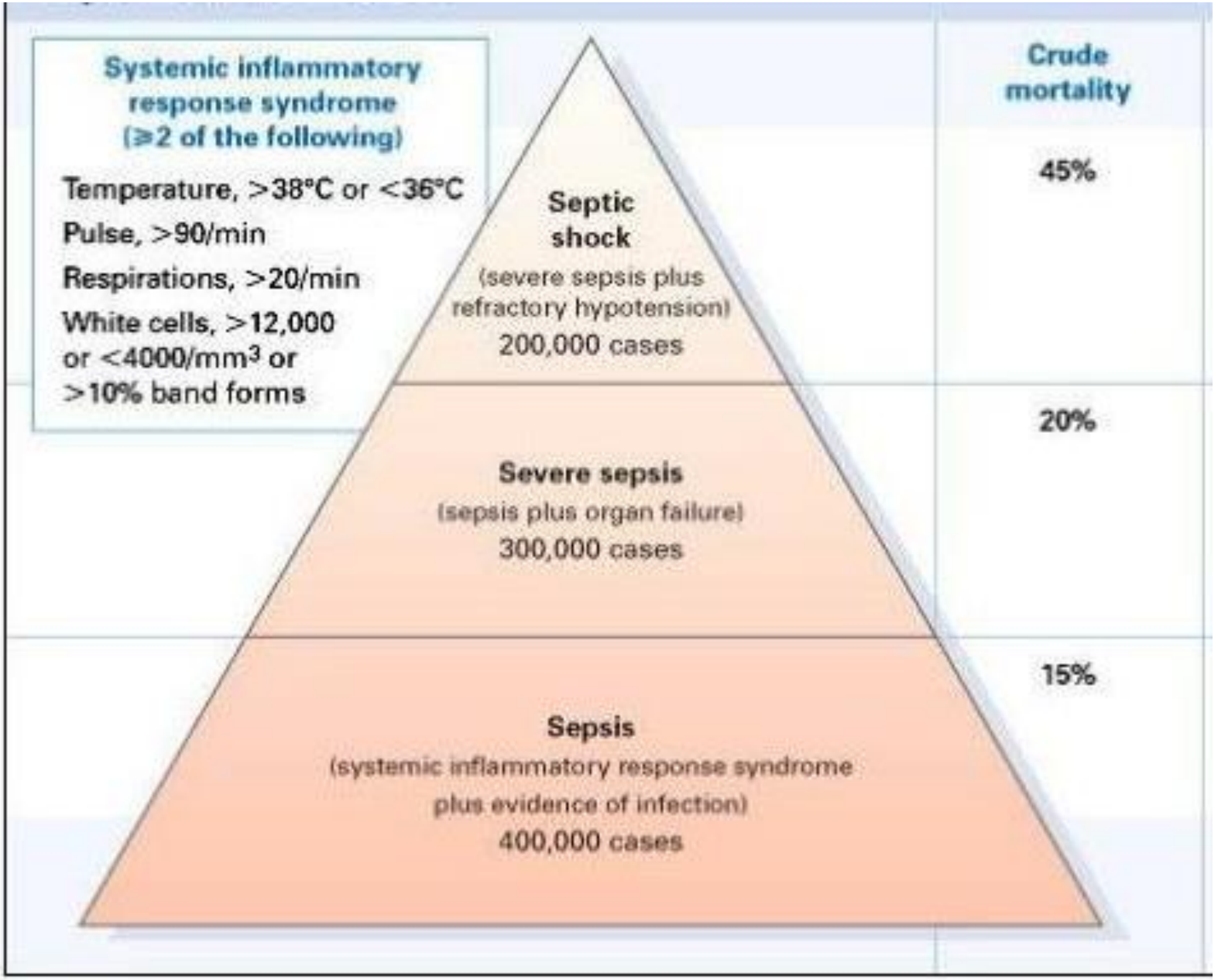
- Sepsis with **hypotension** that, despite **adequate fluid resuscitation**, requires **presser therapy**.
- In addition, there are perfusion abnormalities that may include lactic **acidosis, oliguria, altered mental status**, and acute **lung injury**



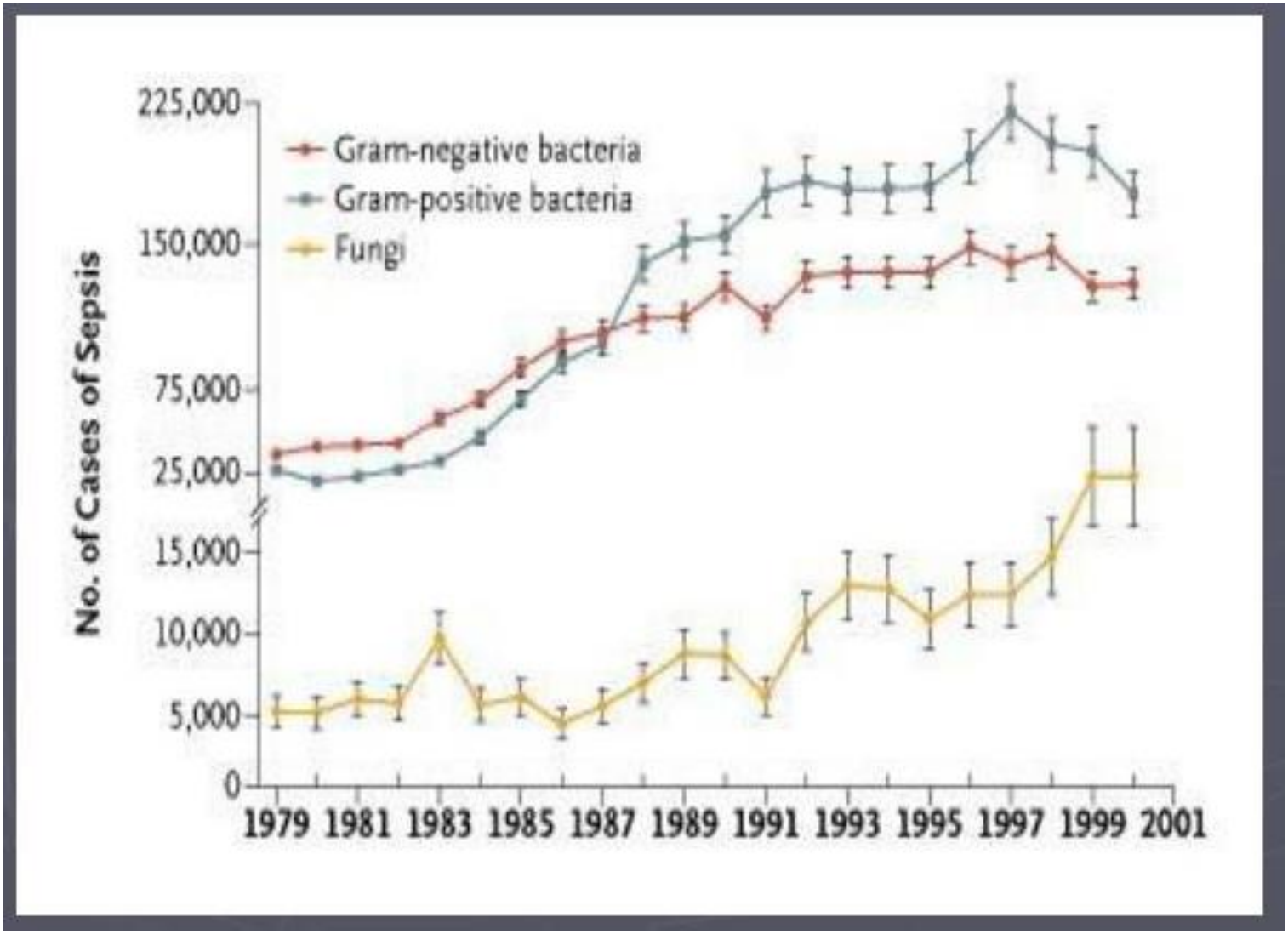

Non-
infectious
insult
SIRS
MODS
Death
Infectious
insult
Sepsis
Severe
sepsis
Septic
shock


SRIS
Sepsis
Severe
sepsis
Septic
shock
MODS

Mortality Rate



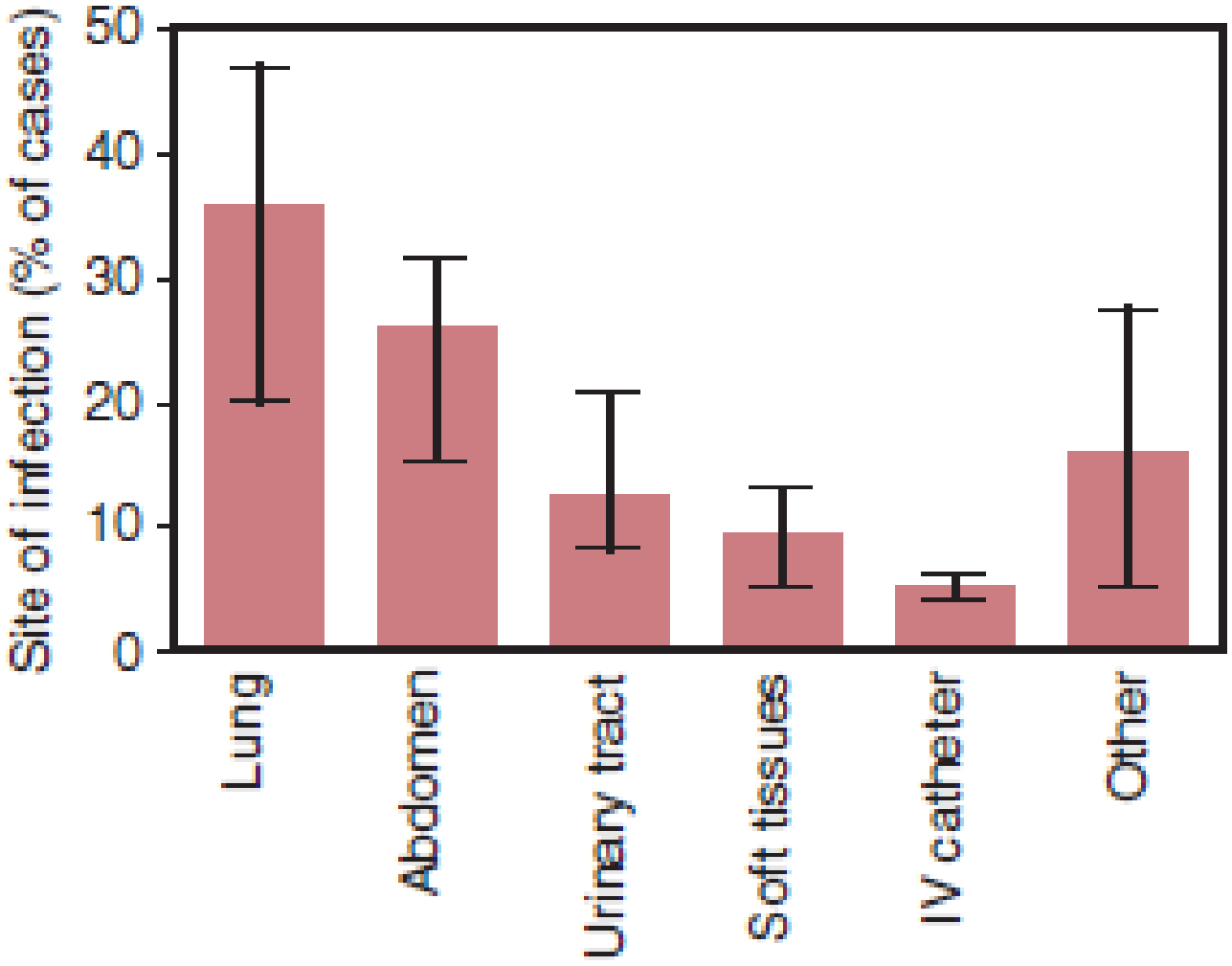
Epidemiology – Causative organisms



The site of infection

- The most common sites of infection in sepsis include the **lung**, the **abdomen**, and the **urinary tract**.
- In 20% to 30% of patients, the infection site is never determined

The site of infection



Presumed sites of infection in patients with culture-positive severe sepsis.

Initial recognition by innate mechanisms

Baseline innate mechanisms

- Epithelium and tight junctions
- Mucociliary ladder
- Defensins
- Cathelicidins
- Complement
- Neutrophils

Initial recognition by innate mechanisms

Pathogen recognition

- Virtually all ‘first responder’ cells in the mammalian body express pattern recognition receptors that can recognize and transduce signals on contact with bacterial components.

- Exposure to these bacterial ligands or pathogen-associated molecular patterns (PAMPs) triggers the signalling cascades that initiate the induced immune response, relevant to both innate and adaptive responses.

Recognition of individual ligands

- Bacterial components represent the key triggers to the immune response
  - Lipopolysaccharide
  - lipopeptides
  - Flagellin
  - Bacterial superantigens
  - Peptidoglycan
  - Bacterial DNA

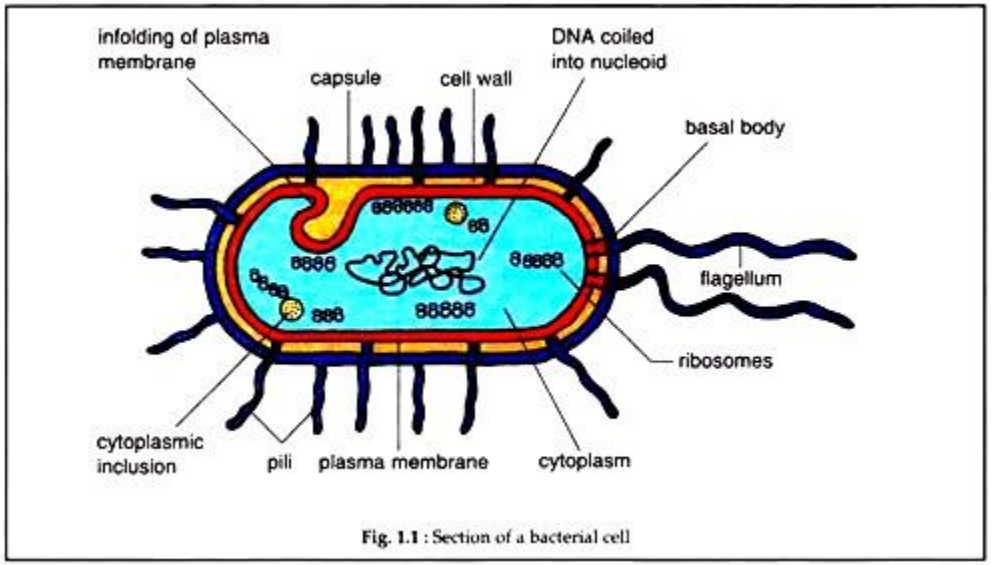
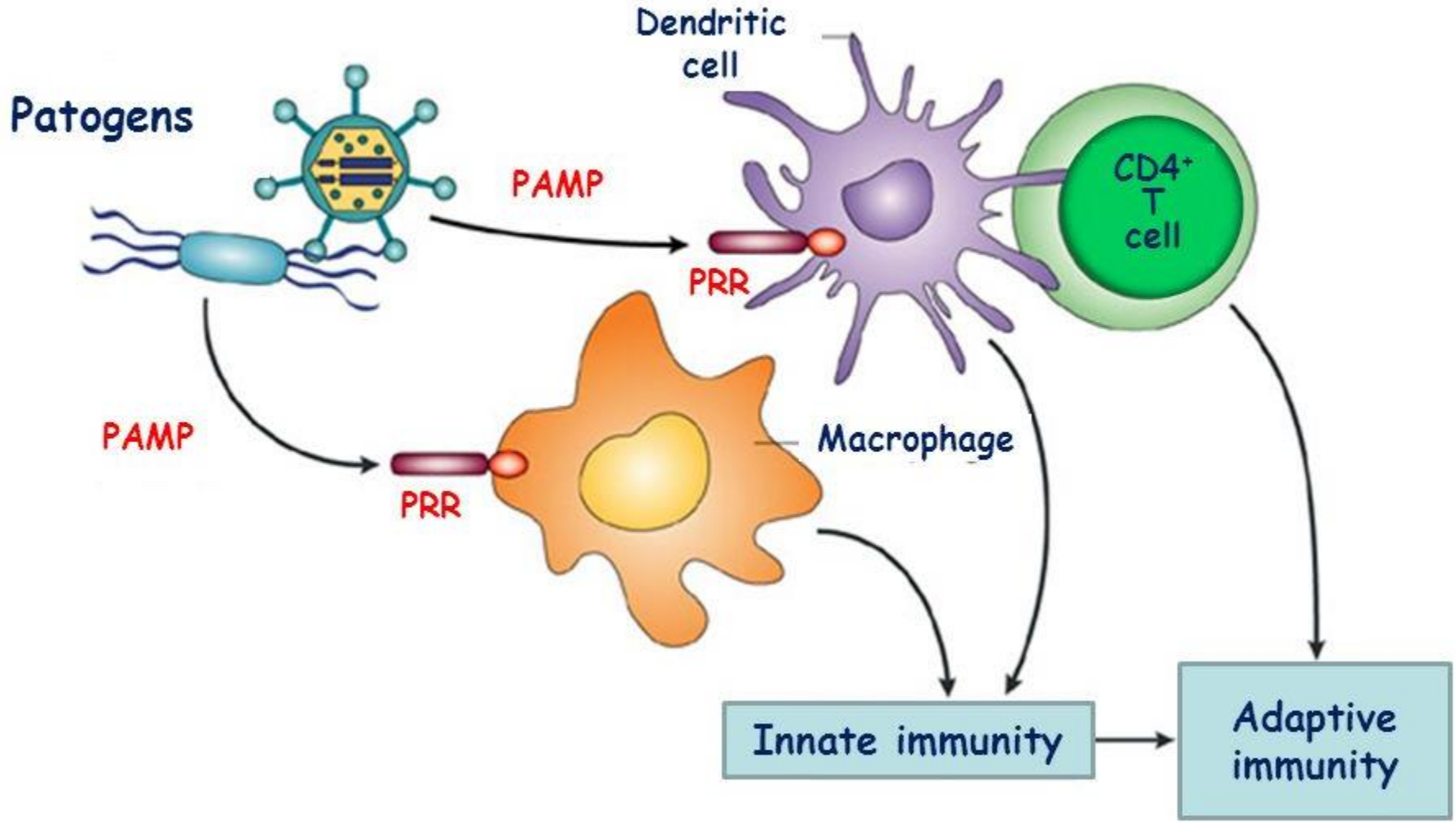


Fig. 1.1 : Section of a bacterial cell

Initial recognition by innate mechanisms



Pro-inflammatory cytokines

- The primary role of sepsis-associated inflammatory mediator release is to enhance leukocyte infiltration from blood vessels to the site of infection.

Immunology of sepsis

INFECTION triggers inflammation:

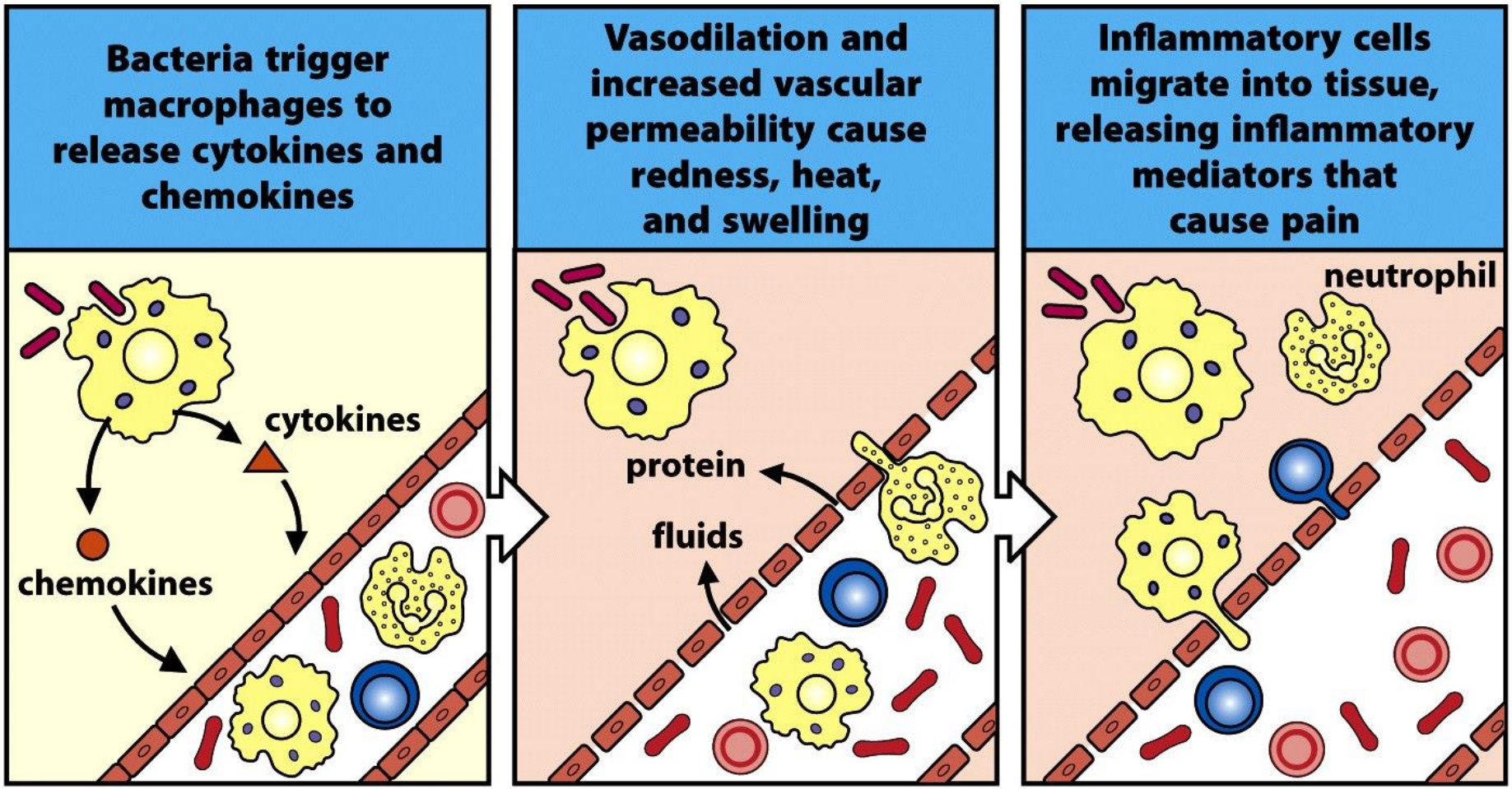


Figure 1-8 Immunobiology, 7ed. (© Garland Science 2008)

Inflammatory mediators in sepsis

- Cytokines
- Chemokines
- Nitric oxide
- Acute phase response

Pro-inflammatory cytokines----

- Triggering through **TLRs by bacterial ligands**
- initiates signalling cascades for transcription of a range of important pro-inflammatory cytokine and chemokine genes eg:

TNFα, IL-1, IL-6, IL-12 and IL-8

Pro-inflammatory cytokines----

- Activation of TLR4 by LPS additionally leads to production of **type 1 interferons**, which can result in production of inducible nitric oxide synthase (iNOS) in both immune cells and vascular tissue, leading to production of nitric oxide (**NO**)

Pro-inflammatory cytokines----

- In either Gram-positive or Gram-negative sepsis, **NO-induced local vasodilatation** allows slowing of blood flow, permitting **tethering** of **neutrophils** to the vessel wall.

Pro-inflammatory cytokines----

- **Neutrophils pass through the vessel wall** accompanied by a significant amount of **intravascular fluid**, partly explaining the profound **peripheral tissue oedema** observed in cases of severe sepsis.

Pro-inflammatory cytokines----

- Significant **damage may occur in organs** such as the lung, where release of proinflammatory granules and enzymes result in catastrophic damage.

Pro-inflammatory cytokines----

- Simultaneously, **TNFα, IL-1 and IL-6** coordinate initiation of the acute phase response.

The acute phase response

- Pathogen recognition triggers an **acute phase response**, resulting in transcriptional upregulation of a vast array of proteins.

- Cause fever, **neutrophilia**, increased **gluconeogenesis**, **muscle catabolism**, altered lipid metabolism and **activation** of both **complement** and **coagulation** pathways

The acute phase response

- Broadly, there are two types of acute-phase proteins; those induced by IL-1 , TNFα and IL-6.

- **IL-1 , TNFα** induces major acute phase proteins that are enhanced by up to 1000-fold, such as **C-reactive protein** and serum **amyloid A,** which play a major role in antibacterial immunity

Pro-inflammatory cytokines----

- **TNFα** and **IL-1** exert profound effects on the vasculature and endothelium, and participating in **activation of the coagulation cascade**

Immunology of sepsis - hypercoagulation

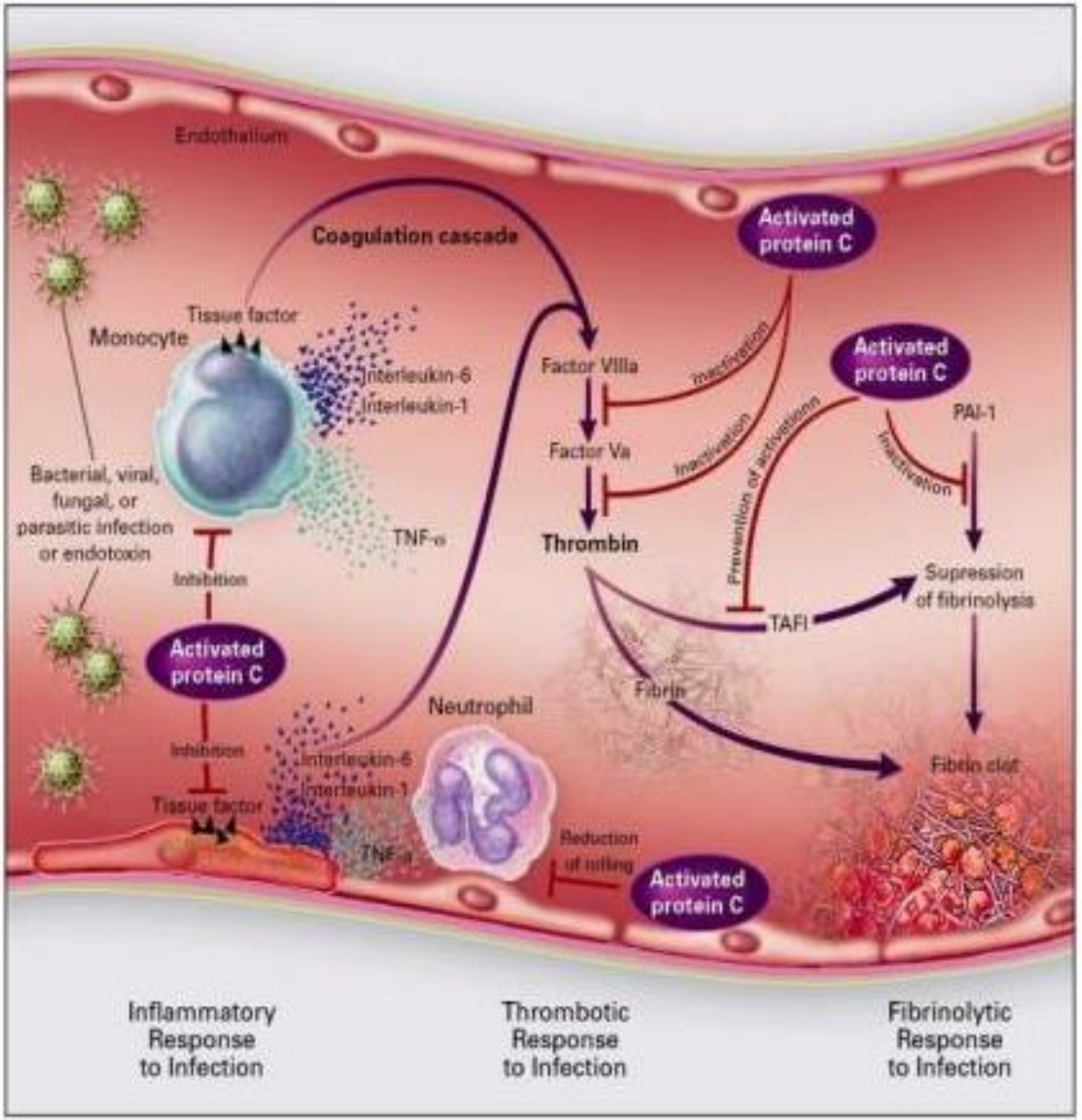
- Overstimulation of **proinflammatory compounds**, such as the cytokines tumor necrosis factor (TNF), **interleukin-1, and interleukin-8**, may alter vascular hemostasis and tilt it in the **direction** of **hypercoagulation** associated with sepsis, severe sepsis, and septic shock.

Immunology of sepsis - hypercoagulation

- Normally, the procoagulation cascade is balanced by anticoagulant mechanisms and complexes

  (antithrombin III, protease inhibitor, protein C) which cleave tissue factors involved in procoagulation process.

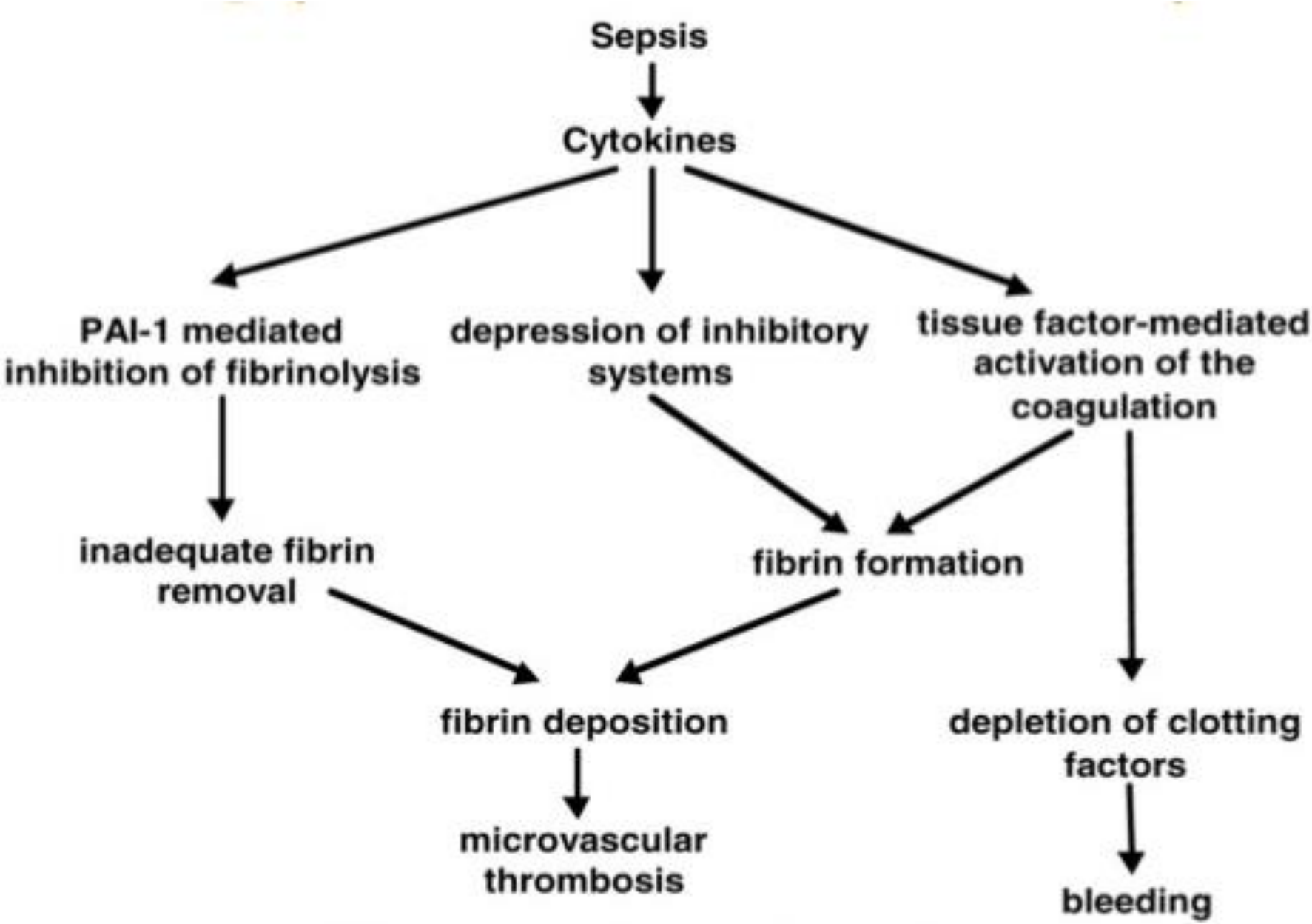
- In **sepsis**, these **anticoagulant systems** tend to be **depleted** or **consumed**


Endothelium
Coagulation cascade
Activated protein C
Tissue factor
Monocyte
Interleukin-6
Interleukin-1
Factor VIIIa
Inactivation
Activated protein C
Factor Va
Inactivation
PAI-1
Bacterial, viral, fungal, or parasitic infection or endotoxin
TNF-α
Thrombin
Prevention of activation
Inactivation
Supression of fibrinolysis
Inhibition
TAFI
Activated protein C
Fibrin
Neutrophil
Inhibition
Interleukin-6
Interleukin-1
Fibrin clot
Tissue factor
TNF-α
Reduction of rolling
Activated protein C
Inflammatory Response to Infection
Thrombotic Response to Infection
Fibrinolytic Response to Infection

Immunology of sepsis - hypercoagulation

- In sepsis, **tissue factor activation along with a reduction in a number of natural anticoagulant** mechanisms results in a tilting of the hemostatic balance toward coagulation.

Immunology of sepsis - hypercoagulation



Robust activation of complement in Sepsis

- Early in sepsis, robust activation of complement occurs, generating **C5a**

- **C5aR** and **C5L2** are expressed in large amounts by **neutrophils**, and at lower levels in macrophages and monocytes and nonmyeloid cells

- Systemic inflammatory response syndrome (SIRS) progress to multiorgan failure (MOF), septic shock, and lethality.

Sepsis

Excessive production and systemic appearance of C5a

Neutrophil

Paralysis of MAPK signalling pathway

Defective translocation of $p47^{phox}$

Inability to assemble NADPH oxidase

Loss of O_2-dependent killing of bacteria

Lethal bacteraemia

Macrophage

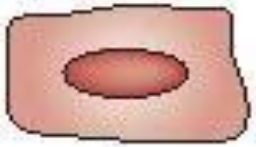
Enhanced production of cytokines/chemokines

Cytokine/chemokine storm

Uncontrolled inflammation

Multi-organ failure

Endothelial cell

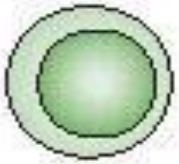


Production of tissue factor; imbalance in the regulation of coagulation

Disseminated intravascular coagulation

Death

Thymocyte



Increased expression of C5aR

C5a

Activation of caspases 3, 4 and 6

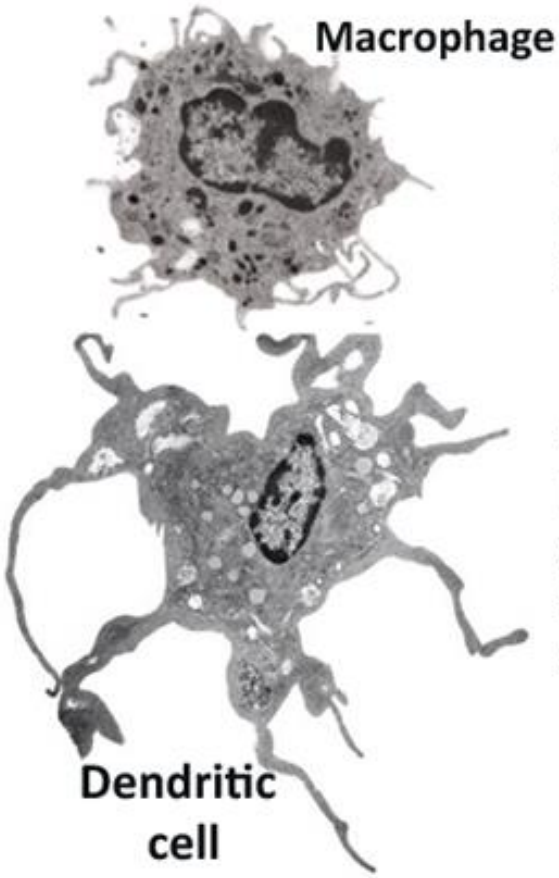
Apoptosis

Immunodeficiency

Sepsis-induced immunosuppression and defective phagocytes

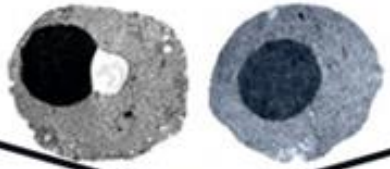
- Caused by
  - depletion or functional deficiencies in **macrophages** and **dendritic cells**
  - **apoptosis of T and B cells**
  - tissue **expression of inhibitory ligands** and receptors that **suppress immune responses**
- **Immunosuppression** and **defective phagocyte function**, leads to **failure to contain commensal** and invading bacteria and fungi

Sepsis-induced immunosuppression and defective phagocytes



Sepsis

apoptosis of T and B cells



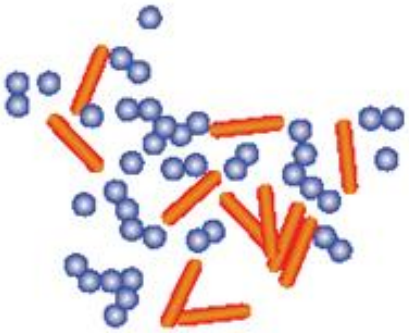
Defective phagocytes and DCs

Expression of anti-immune receptors and ligands

Defective innate & adaptive immune responses

Immunosuppression

Defective ability to deal with commensal and invading bacteria/fungus



MOF

Lethality

a Effects of protracted sepsis on the innate immune system

Follicular dendritic cell

- ↑ Apoptosis
- ↓ Antigen presentation to B cells

Dendritic cell

- ↑ Apoptosis
- ↓ Antigen presentation to T cells
- ↓ Cytokine secretion

Macrophage

- ↑ Anti-inflammatory cytokine secretion
- ↓ HLA-DR expression
- ↓ Pro-inflammatory cytokine secretion
- ↓ Pathogen killing

NK cell

- ↑ Apoptosis
- ↓ Cytotoxic function
- ↓ Cytokine secretion

Neutrophil

- ↑ Release of immature neutrophils
- ↑ IL-10 secretion
- ↓ Apoptosis
- ↓ Reactive oxygen species release
- ↓ Nitric oxide release
- ↓ Expression of adhesion markers

MDSC

- ↑ Apoptosis
- ↓ Cytotoxic function
- ↓ Cytokine secretion

b Effects of protracted sepsis on the adaptive immune system

$CD4^+$ T cell

- • Cell exhaustion
- ↑ Apoptosis
- ↑ T_H2 cell polarization
- ↓ Adhesion molecule expression
- ↓ CD28 expression
- ↓ TCR diversity

$CD8^+$ T cell

- • Cell exhaustion
- ↑ Apoptosis
- ↓ Cytotoxic function
- ↓ Cytokine secretion
- ↓ TCR diversity

T_{Reg} cell

- • Resistance to apoptosis
- ↑ Suppressive activities

B cell

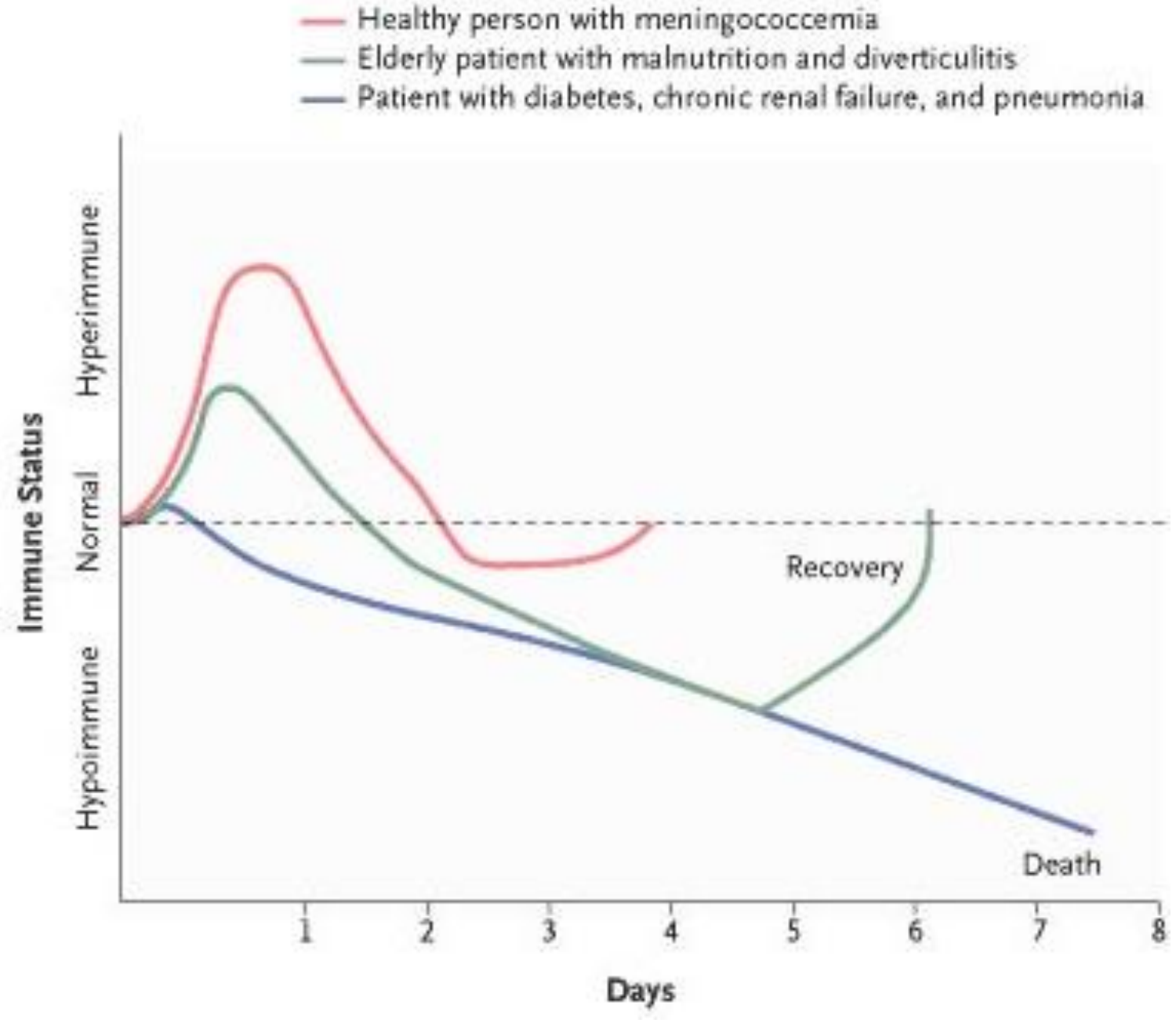
- ↑ Apoptosis
- ↓ Antigen-specific antibody production

Immunomodulation

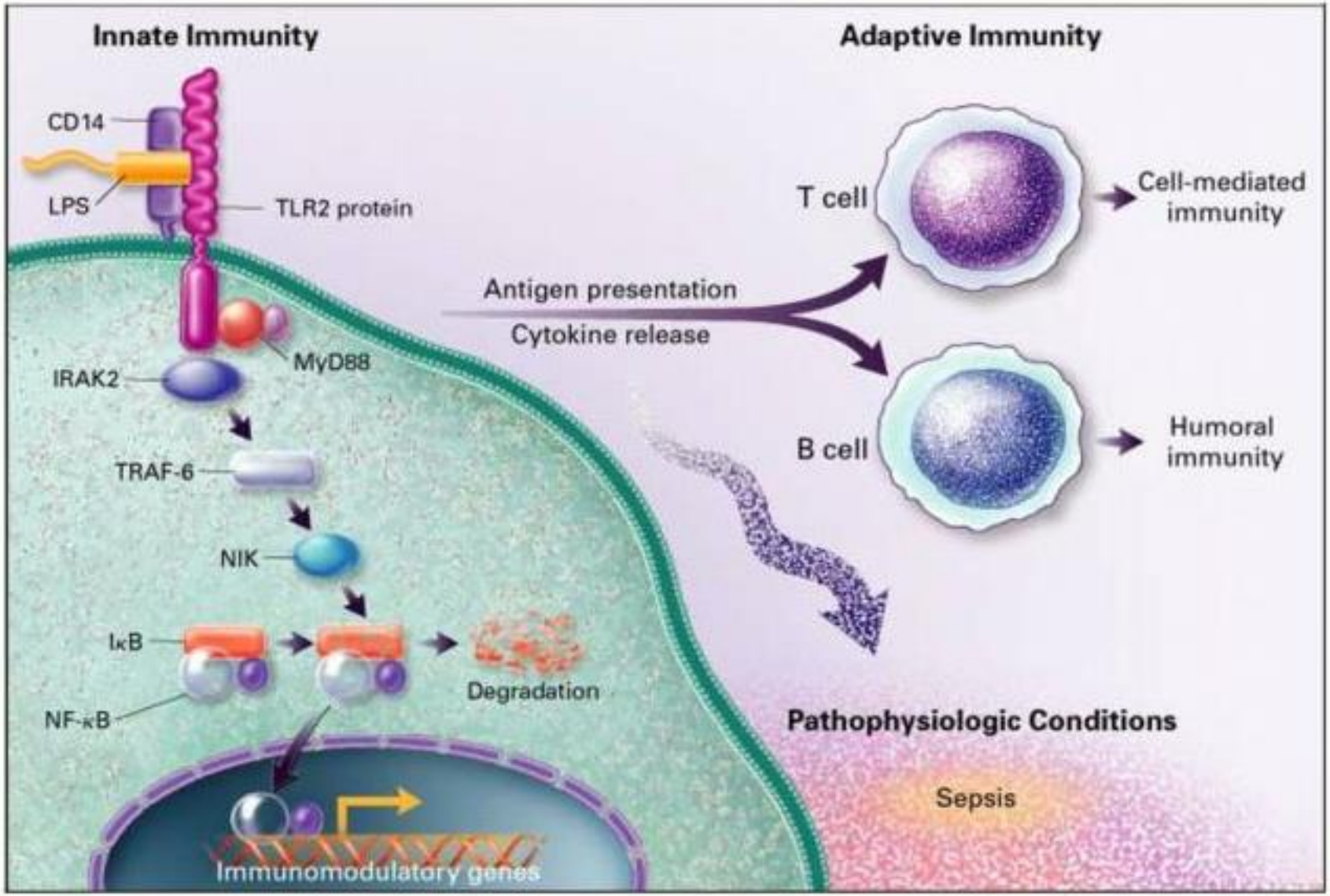
- Alongside the inflammatory response, the host produces counter-balancing **anti-inflammatory mediators**, including **IL-10** and numerous soluble **cytokine receptors**, including **sTNFR**

- Profound **lymphopaenia** in both the spleen and peripheral circulation is seen

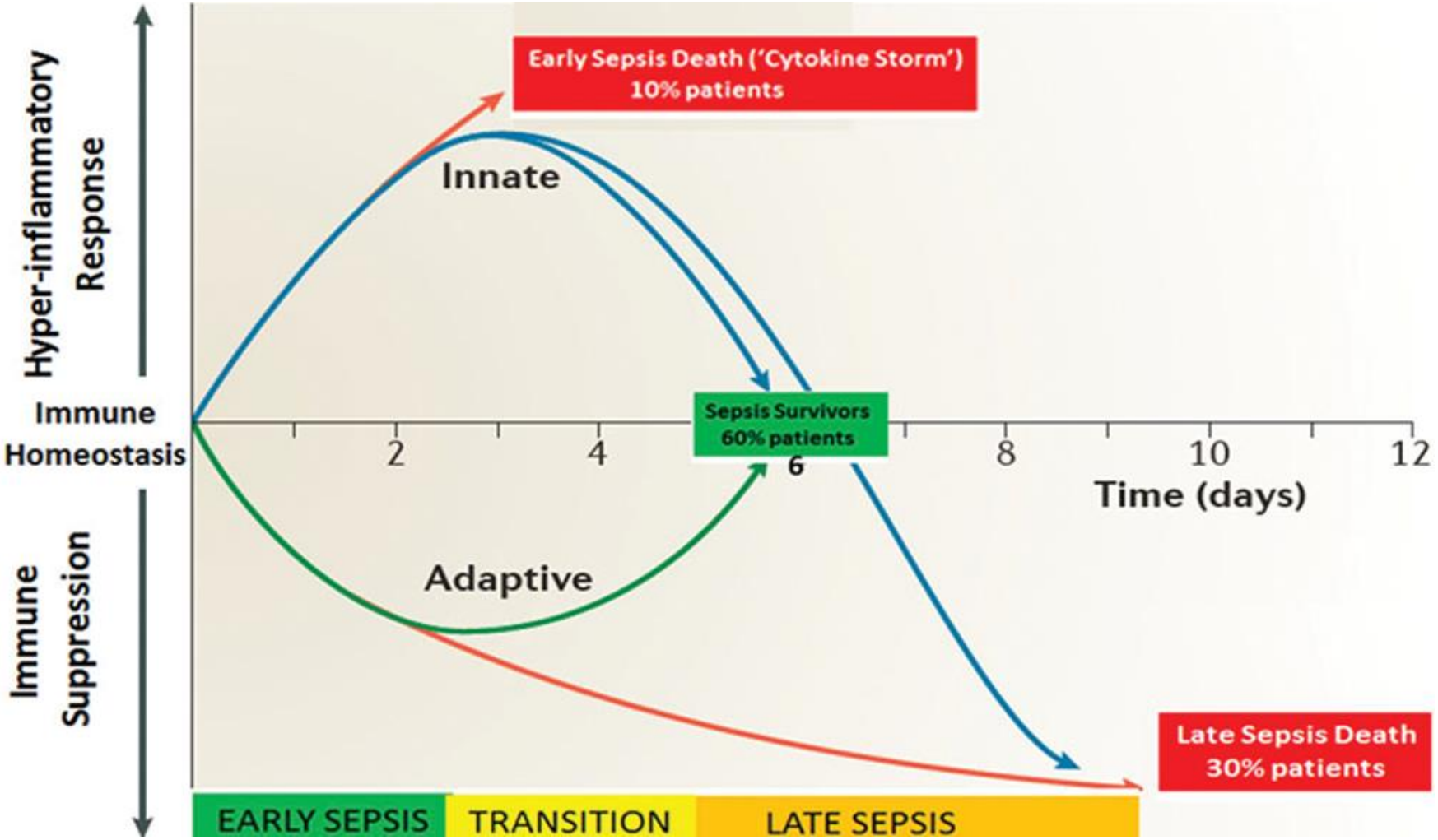
Immune activation and immunosuppression in sepsis



The adaptive and innate host immune responses to sepsis



The adaptive and innate host immune responses to sepsis



Management of patients in the early phase of sepsis