Immune Response to Bacterial Infection, Imunopathology of Sepsis

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Factors influencing the extent and severity of infection

- Pathogen factors
  - Dose
  - Virulence of organism
  - Route of entry
- Host factors
  - Integrity of non-specific defences
  - Competence of the immune system
  - Genetic influences
  - Previous exposure to antigen
  - Existence of co-infection

Immune mechanisms against bacterial infections

- **Non-specific immunity**
  - **Mechanical barriers**
  - **Phagocytosis**
  - **Complement system**
  - **Lysozyme**
  - **Defensins**

Immune mechanisms against bacterial infections

- **Specific immunity**
  - **Antibodies –**
    - **Opsonization,**
    - **Activation of complement system,**
    - **Neutralization of toxins (e.g. antiphagocytic toxins),**
    - **Receptor blocade**
    - **Agglutination of microbes (respiratory tract)**
  - **T-lymphocytes**
    - **Th1 lymphocytes- protection againts intracellular pathogens**
    - **Th2 lymphocytes – stimulation of antibody production**
    - **Th17 lymphocytes – pro-inflamatory effect**

Bacterial evasions of immune defences

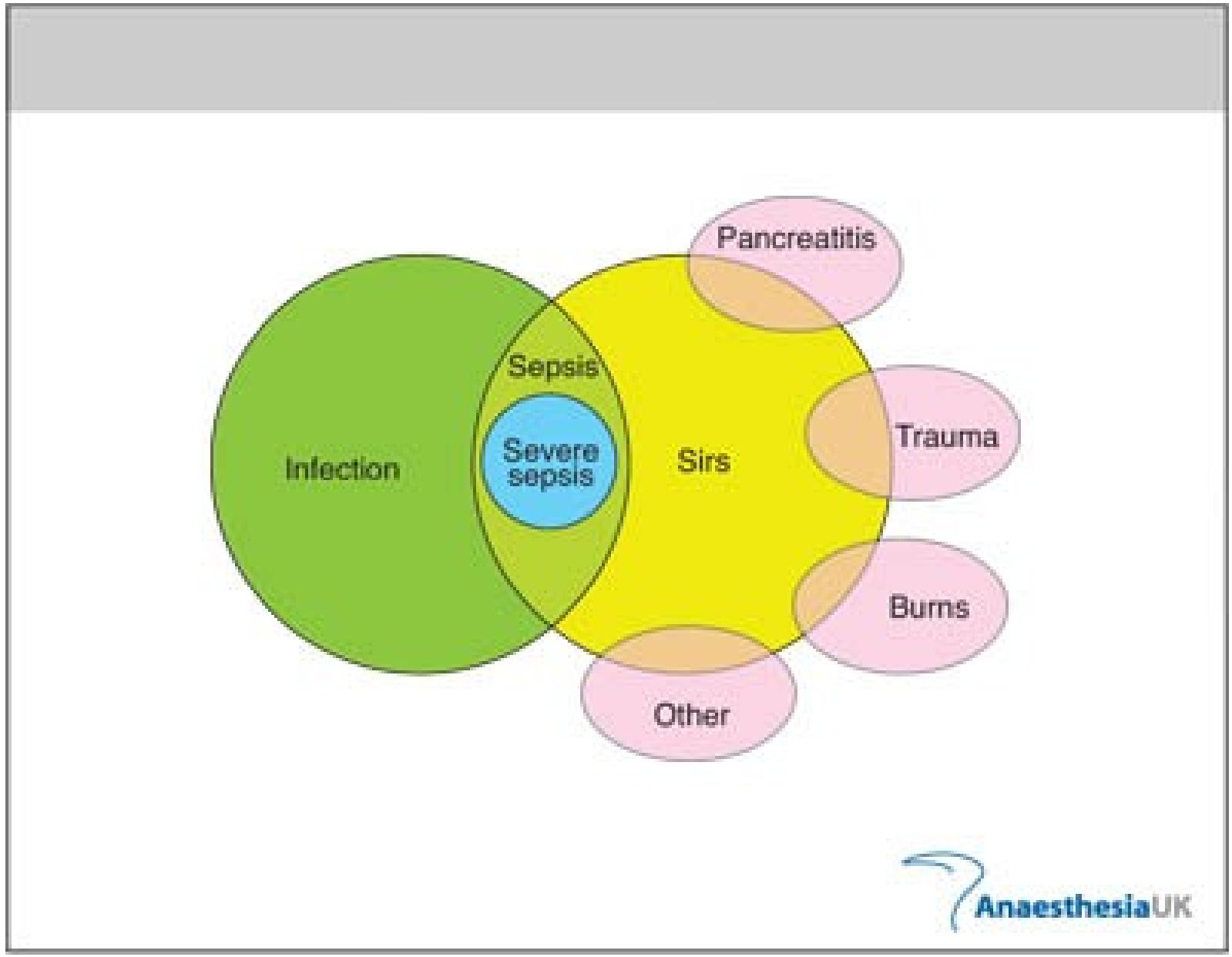
- Antiphagocytic machanisms: toxins, capsular polysaccharides
- Inhibition of the complement system: *Str. pyogenes, E. coli, N. meningitidis*
- Antigenic variations: *Borrelia recurrentis*
- Proteases lysing IgA - *Neisseria, Haemophilus*
- Sequestration in avascular regions- *Salmonella typhi* in the gall bladder and urinary tract
- Intracellular parasitism

Bystander damage caused by the immune response to bacterial infection

- **Autoimmune diseases**
  - **Cross-reactivity of bacterial and corporal antigens - rheumatic fever**
  - **Type-II hypersensitivity - autoimmune hemolytic anemia caused by *Mycoplasma* infection**
  - **Heat shock proteins**
  - **Superantigens (streptococcal, staphylococcal)**
- **Immunocomplex diseases**
- **Type IV hypersensitivity- cavitatoin in pulmonary tuberculosis**

Systemic Inflammatory Response Syndrome SIRS

- Systemic inflammatory response in a wide range of severe clinical situations.
- Characterized by at least 2 conditions:
  - Body temperature> 38 ° C or <36 ° C
  - Heart rate> 90 / min
  - Respiratory Frequency> 20 / min or PaCO2 <32mmHg
  - Leukocyte counts> 12 000 / mm^3, <4 000 / mm^3 or> 10% of immature form of granulocytes.


Pancreatitis
Sepsis
Infection
Severe sepsis
Sirs
Trauma
Burns
Other
AnaesthesiaUK

Sepsis: Systemic Inflammatory Response (SIRS) with proven infectious aetiology.

Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion or hypotension.

Septic shock: Sepsis induced hypotension despite adequate infusion therapy with abnormalities in organ perfusion.

Sepsis 3
The Third International Consensus Definition for Sepsis and Septic Shock (2016)

- Sepsis - A life-threatening organ dysfunction caused by the dysregulation of host responses to infection.

- ("Severe sepsis" was omitted)

Pathological immune consequences of sepsis

- Severe inflammatory response
- Secondary immunosuppression

Organ dysfunction in severe sepsis

- **Cardiovascular system**: hypotension, metabolic acidosis, rise in lactate, oliguria
- **Respiratory system**: decrease in Pa02, the rise of PaCO2 Hematologic abnormalities: decreased platelet count, DIC, leukocytosis, leukopenia
- **Nerve system**: coma
- **Renal**: increased creatinine
- **Hepatic**: increased bilirubin, ALT

Lipopolysaccharides (LPS) of G-bacteria - Endotoxins,

- Are composed of lipid A (responsible for the biological activity), the cortex and the lateral polysaccharide chains.
- Through the LPS-binding protein (LBP) binds to CD14 and TLT-4 on monocytes and macrophages and activates them.
- A similar mechanism activates macrophages and peptidoglycan and teichoic acid of G+ of bacteria.

Inflammatory response in sepsis

- Formation of pro-inflammatory cytokines as a response to the stimulaci PAMPs (Pathogen-Associated Molecular Pattern) and DAMP (Damage Associated Molecular Pattern – alarmins).
- Activation of the complement system formation of C3a, C4a.
- Activation of the coagulation system, platelets.
- Activation of endothelial cells leads to endothelial dysfunction with increased permeability.
- NET(Neutrophil extracellular traps)osis of granulocytes

Major mediators involved in the pathophysiology of sepsis

Proinflammatory: TNF-α, IL-1, IL-6, IL-8, PAF, IL-4, complement activation products

Anti-inflammatory: IL-1RA, IL-10

The main effect outside the immune system: NO (hypotension, myocardial depression)

Tumor necrosis factor-α (TNF-α) in the pathophysiology of sepsis

- Produced primarily by cell of the monocyto-macrophage lineages after endotoxin stimulation, GM-CSF, IFN-g
- Causes a decrease of blood pressure, leukopenia with subsequent leukocytosis. Induces the formation of IL-1, IL-6, IL-8, subsequently NO (hypotension, pulmonary hypertension), acute phase proteins.
- But: Complete blockade of TNF-α production leads to high animal mortality in experimental infection. In people treated with anti-TNF-α MP for rheumatoid arthritis, there was a clinical manifestation of tuberculosis.

Interleukin-1
in the pathophysiology of sepsis

Produced by monocyto-macrophage cell lineage.

The inductors of production are endotoxin, TNF-α. IL-1

KO mice are resistant to the effect of endotoxin.

Induces production of cytokines of an inflammatory response.

IL-6 in the pathophysiology of sepsis

Produced by monocytes, macrophages, T-lymphocytes, fibroblasts, endothelial cells.

It is a differentiation factor of B lymphocytes and a T lymphocyte activation factor.

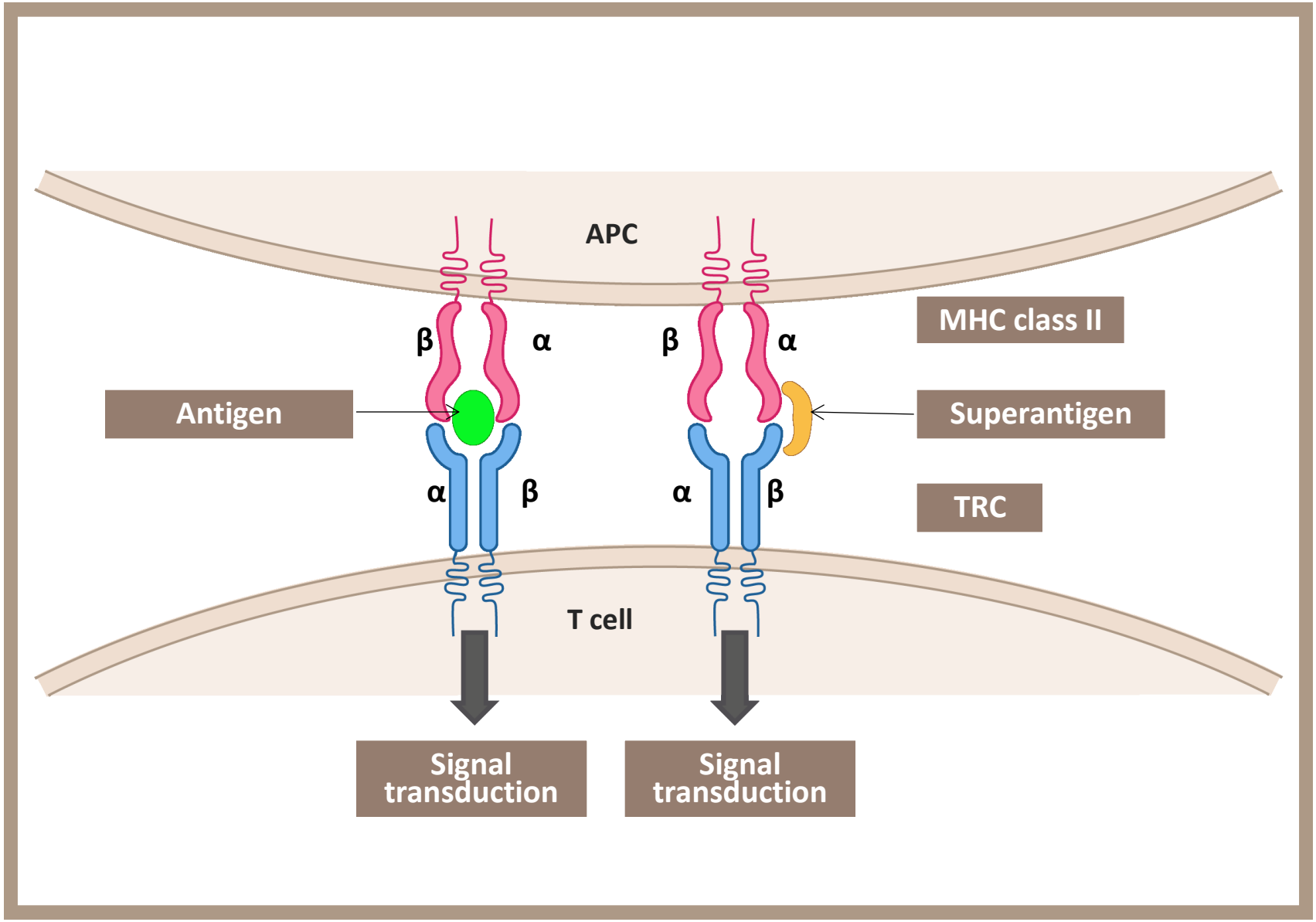
It acts pyrogenically, induces the formation of acute phase proteins.

In some studies, IL-6 levels correlated with patients mortality.

Secondary immunodeficiency in sepsis (formerly Compensatory Anti-Inflammatory Response Syndrome-CARS)

- Some patients in sepsis pass from the "hyperinflammatory" phase to a state of low immune response (immunoparalysis).
- Anti-inflammatory responses include IL-4, IL-10, IL-11, IL-13.
- Changes in antigen-presenting cells of low expression of HLA-DR on monocytes.
- Decrease in T-cell count is due to increased apoptosis.
- Lymphocytic exhaustion occurs. Th2 predominance.
- High PD1 (Programmed Cell Death) expression on lymphocytes and its ligands (PD1L) on macrophages and granulocytes.
- The production of proinflammatory cytokines TNF-α, IL-1, IL-6, IL-8 is reduced.

Activation of TCR by antigen and superantigen



The most important superantigens

- S. aureus: Enterotoxin and toxin toxic shock syndrome
- Str. pyogenes: pyrogenic (erythrogenic) toxins, M protein
- Clostridium perfringens: enterotoxin
- superantigens of mycoplasma, Pseudomonas, Yersinia enterocolitica, Mycobacterium tuberculosis

The toxic shock syndrome

- The toxic shock syndrome can most often occur in people infected with staphylococci.
- The superantigen toxic shock toxin (TSST-1 - Toxic Shock Syndrome Toxin-1) is crucial in the pathogenesis.
- Massive production of cytokines in particular leads to the development of shock and multi-organ failure.