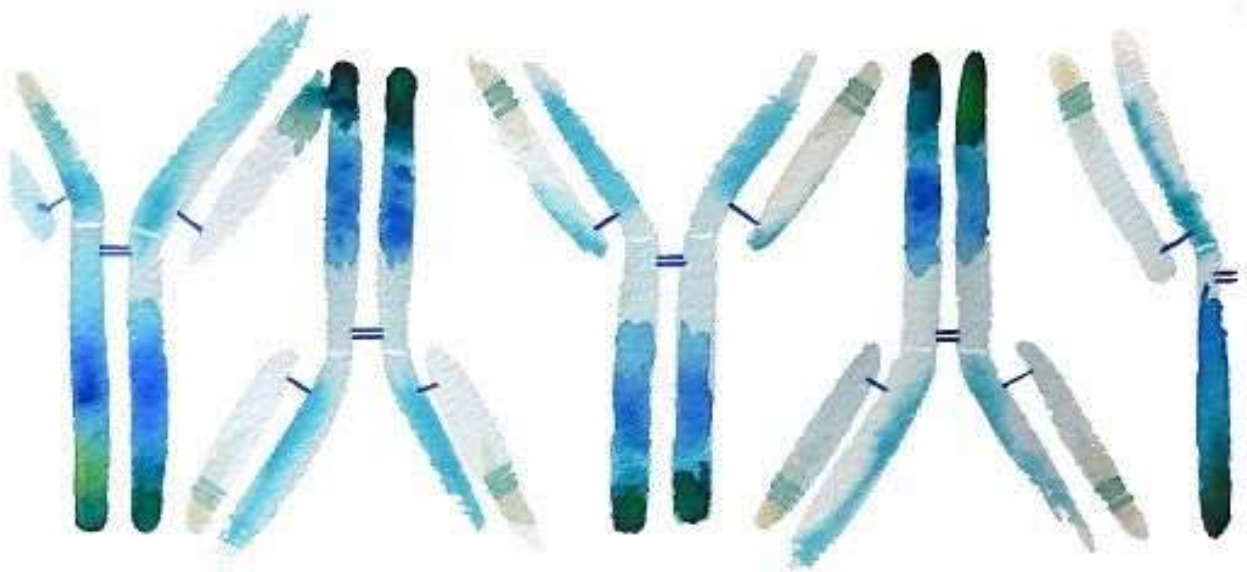
Medical Immunology



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Sepsis

In this lecture we will discuss:

- The epidemiology and definition of sepsis
- The immunopathology of sepsis

Sepsis/overview

- Sepsis is a highly heterogeneous syndrome that is caused by an unbalanced host response to an infection.

- Sepsis was not clinically defined until the early 1990s when a group of key opinion leaders released the first consensus definition of sepsis. Since then the definition was updated several times.

- The definition of sepsis matters in the **prognostication** of patients since those labelled as having sepsis are expected to have a **difficult clinical course and poor outcome** compared to those without sepsis.

- For many years, a disproportionate inflammatory response to invasive infection was considered to be central to the pathogenesis of sepsis, but it is now clear that the host response is disturbed in a much more complex way, involving both sustained **excessive inflammation** and **immune suppression**, and a **failure to return to normal homeostasis**

Sepsis/overview

Box 1 | **Sepsis definitions**

1991 Consensus Conference[2]

Diagnosis	Signs and symptoms
Systemic inflammatory response syndrome	Patients experiencing at least two of the following symptoms: • Body temperature >38 °C or <36 °C • Heart rate >90 beats per minute • Respiratory rate >20 breaths per minute or arterial CO_2 <32 mmHg • White blood cell count >12 × 10^9 l^{-1} or <4 × 10^9 l^{-1}, or >10% immature forms
Sepsis	Systemic inflammatory response syndrome and proven or suspected infection
Severe sepsis	Sepsis and acute organ dysfunction
Septic shock	Sepsis and persistent hypotension after fluid resuscitation

2001 International Sepsis Definitions Conference[145]

The 2001 definitions of sepsis were very similar to the definitions stated in 1991. Of note, in 2001 it was acknowledged that the signs and symptoms of sepsis are more varied than described in the 1991 definition, and this resulted in the addition of a list of these signs and symptoms for the diagnosis of sepsis.

2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[3]

Diagnosis	Signs
Sepsis*	• 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 of ≥2 points‡
Septic shock	• Sepsis in which the underlying circulatory and cellular and/or metabolic abnormalities are marked enough to substantially increase mortality • Clinically defined as sepsis with persisting hypotension that requires vasopressors to maintain the mean arterial pressure at ≥65 mmHg and with a serum lactate concentration >2 mmol l^{-1}

*Of note, the presence of organ dysfunction is central and required in the new 2016 consensus sepsis definition. Until then, organ dysfunction was part of the definition of 'severe' sepsis, a term that was abandoned in the Sepsis-3 definition. ‡The sequential organ failure assessment (SOFA) score is based on six different scores (each classified from 1 to 4 according to increasing abnormality and/or severity), one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems[146].

Sepsis/overview

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg)	> 400	301–400	201–300	101–200	≤ 100
(kPa)	> 5.3)	(4.1–5.3)	(2.8–4.0)	(1.4–2.7)	≤ 1.3)
Coagulation					
Platelets ($x10^3/mm^3$)	> 150	101–150	51–100	21–50	≤ 20
Liver					
Bilirubin (mg/dl)	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥ 12.0
(μmol/l)	< 20)	(20–32)	(33–101)	(102–204)	≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl)	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	> 5.0
(μmol/l)	< 110)	(110–170)	(171–299)	(300–440)	> 440)
or urine output				< 500 ml/day	< 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in μg/kg/min)

Sepsis/epidemiology

- For 2017, it was estimated that it had affected 49 million individuals and was related to approximately 11 million potentially avoidable deaths worldwide.

- Sepsis mortality is often related to suboptimal quality of care, an inadequate health infrastructure, poor infection prevention measures in place, late diagnosis, and inappropriate clinical management.

- **Antimicrobial resistance** further **complicates sepsis management** across all settings, particularly in high-risk populations, such as **neonates** and patients in **intensive care units** (ICUs)

- **One in four cases of sepsis in hospitals** and **one in two cases of sepsis in ICUs** result from **health care-associated infections**.

Sepsis/epidemiology

Characteristics of Adult Sepsis Patients in the Intensive Care Units in a Tertiary Hospital in Jordan: An Observational Study

Anas H. A. Abu-Humaidan,[1] Fatima M. Ahmad,[1,2] Maysaa' A. Al-Binni,[2] Amjad Bani Hani,[3] and Mahmoud Abu Abeeleh[3]

All adult patients admitted to the adult ICUs between June 2020 and January 2021 were included in the study. Patients' clinical and demographic data, comorbidities, ICU length of stay (LOS), medical interventions, microbiological findings, and mortality rate were studied.

We observed 194 ICU patients during the study period; 45 patients **(23.3%) were diagnosed with sepsis using the Sepsis-3 criteria.**

Mortality rate and median ICU LOS in patients who had sepsis were **significantly higher** than those in other ICU patients (mortality rate, **57.8%** vs. 6.0%, value < 0.001, resp., and LOS 7 days vs. 4 days, value < 0.001, resp.).

Additionally, sepsis patients had **a higher combined number of comorbidities**. The use of **mechanical ventilation**, **endotracheal intubation**, and **blood transfusions** were all significantly more common among sepsis patients.

Sepsis/The initiation of inflammation

- Sepsis is associated with a strong activation of the **innate immune system** that is mediated by the activation **of PRRs** by **PAMPs** and **DAMPs**

- There is similarity between the inflammatory reactions induced by different pathogens and those elicited by different types of injury, either infectious or non-infectious.

- Pro-inflammatory cytokines implicated in sepsis pathogenesis include **tumour necrosis factor (TNF), interleukin-1β (IL-1β), IL-12 and IL-18**; blocking or eliminating these cytokines confers protection in acute animal models of fulminant infection.

Sepsis/Complement activation

- Although complement activation is an essential component of protective immunity, the uncontrolled activation of complement can cause **damage to tissues and organ failure**.

- **Activation of the three major pathways of complement**, including the **classical**, **lectin**, and **alternative** pathways can take place in sepsis.

- Moreover, some studies reported a **correlation between levels of complement activation fragments such as C3b and C5a to sepsis severity**. Complement activation can culminate in activation of the terminal pathway, through cleavage of C5 to form C5a, a potent anaphylatoxin, and C5b, which initiates formation of the pore forming complex C5b-9 on cellular membranes.

- **Blockade of C5a signalling improved the outcome of experimental sepsis** in several animal models, including Escherichia coli sepsis in baboons and rats with polymicrobial abdominal sepsis

Sepsis/Complement activation

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ORIGINAL RESEARCH

Complement Terminal Pathway Activation is Associated with Organ Failure in Sepsis Patients

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Conclusion: In sepsis patients, levels of **C5** and **sCD59**, but not sC5b-9, correlated to the **severity of organ damage measured by SOFA**. A similar correlation was not found in non sepsis patients. **This indicated that organ damage associated with sepsis led to a more pronounced terminal pathway activation than in non-sepsis patients**, it also indicated the potential of using C5 and sCD59 to reflect sepsis severity.

Sepsis/Coagulation, endothelial cell activation and vascular leakage

- Sepsis is associated with a **strong activation of the coagulation system**, and this can result in disseminated intravascular coagulation, which clinically can be associated with microvascular thrombosis and haemorrhage, the latter being due to the consumption of clotting factors and platelets. **Tissue factor** is the main driver of coagulation activation in sepsis. In addition, tissue factor inhibition prevents multiple organ failure and mortality in a model of other- wise lethal sepsis in baboons.

- In response to localized infection, **leukocytes and platelets adhere to the endothelial surface and migrate to the sites at which bacteria are multiplying**. In **sepsis**, exaggerated inflammation augments these processes, thereby con- tributing to barrier incompetency

- A loss of barrier integrity causes the **leakage of intravascular proteins and plasma into the extravascular space**, tissue oedema and reduced microvascular perfusion.

Sepsis/Other immune mechanisms

- **Neutrophil extracellular traps.** NETs can entrap pathogens and thereby contribute to pathogen elimination. However, NETs can also contribute to collateral tissue damage and thrombosis. Patients with sepsis have **increased NET levels** in their circulation, and this feature is associated with organ dysfunction.

- **The role of platelets. Excessive platelet activation** has been implicated in organ injury during sepsis through several mechanisms, including the augmentation of immune cell recruitment and inflammation, the facilitation of the formation of vaso-occlusive thrombi in capillary vascular beds and direct cell toxic effects mediated by platelet derived microparticles.

- The role of B cells. A subset of B cells, the so-called **innate response activator B cells**, is important for bacterial eradication as well as for the attenuation of proinflammatory cytokine release. Innate response activator B cells can produce IL-3, which in the context of sepsis increases inflammation and the production of myeloid mononuclear cells.

Sepsis/ Immune suppression in sepsis

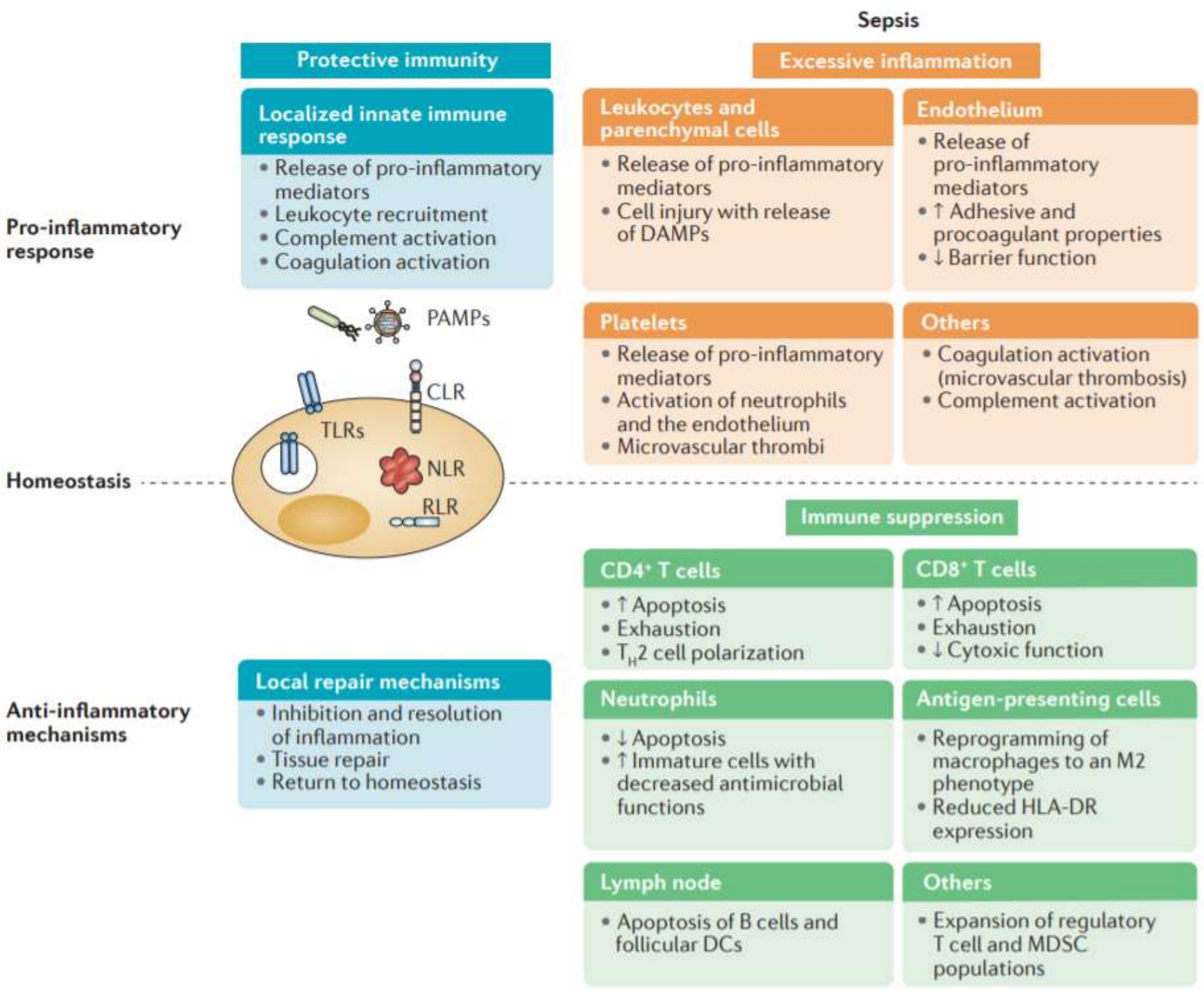
- Sepsis is associated with **immune suppression** that is characterized by **lymphocyte exhaustion** and the **reprogramming of antigen-presenting cells**.

- Sepsis is associated with a strong **depletion** of CD4+ and CD8+ T cells, B cells and dendritic cells (DCs) as a result of apoptosis

- Immune suppression in sepsis is characterized by the **reduced expression of HLA-DR** on blood monocytes, and by the diminished capacity of monocytes and macrophages to release pro-inflammatory cytokines upon stimulation.

- The immune suppression **increases the risk of secondary infections**. A recent observational study indicated that secondary infections are responsible for only 10.9% of overall sepsis mortality in the ICU.

Sepsis/ Overview



Sepsis/ Immunomodulation as a treatment for sepsis

- How the host response should be manipulated in patients with sepsis is controversial. The immune disturbances are complex and require targeting more than one pathway/ mechanism.

- **Immune suppression** through inhibition of complement or coagulation (examples, C5a-specific monoclonal antibody, recombinant human thrombomodulin)

- **Blood purification techniques** have been **proposed** as a method of removing PAMPs and inflammatory mediators from the circulation of patients. Recently, a blood-cleansing device that removes multiple pathogens and toxins from the blood via magnetic nanobeads coated with an engineered form of the human opsonin mannose-binding lectin (also known as MBPC) was described, and it is currently being evaluated in preclinical studies

- **Immune stimulation**. There are several drugs that could potentially reverse immune suppression in sepsis. One approach is to use immune-stimulating cytokines, such as IFNγ, IL-7 and IL-15.

Further reading:

- The immunopathology of sepsis and potential therapeutic targets.

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