Sepsis

Done by: Abdelhadi Okasha

Topics in this lecture

- 1- Definition
- 2- Epidemiology
- 3- Pathogenesis of sepsis
- 4- Treatment by immunomodulators

1- Definition

- 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.

- Notes on the following picture:
- Septic shock > severe sepsis > sepsis
- Septic shock is defined after measuring:
  1) Measuring arterial pressure
  2) Measuring serum lactate concentration

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}

Sequential organ failure assessment

*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].

→ Do not memorize anything, just take a general idea

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)

2- Epidemiology

- For 2017, it was estimated that it had affected 49 million individuals and was related to approximately 11 million potentially avoidable deaths worldwide. (More than 20%)
- Sepsis mortality is often related to:
  1) suboptimal quality of care
  2) an inadequate health infrastructure
  3) poor infection prevention measures in place
  4) late diagnosis
  5) inappropriate clinical management.
- Factors that complicates sepsis management:
  1) Antimicrobial resistance
  2) Presence of high-risk populations, such as neonates and patients in intensive care units (ICUs)

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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.

3- Pathogenesis of sepsis/ a- activation of immune system and cytokines secretion

- Sepsis is associated with a strong activation of the innate immune system that is mediated by the wide 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, and this shows that sepsis results from the strong immune response rather than the pathogenesis of the pathogen itself
- Pro-inflammatory cytokines implicated in sepsis pathogenesis include tumour necrosis factor (TNF), interleukin-1B (IL-1), IL-12 and IL-18; blocking or eliminating these cytokines confers protection in acute animal models of fulminant infection.
- Blocking one pathway of the immune response is not enough in preventing sepsis, at least this is a fact in humans

3- Pathogenesis of sepsis/b-Uncontrolled activation of complement

- Uncontrolled activation of complement is a major cause of damage to tissues and organ failure.
- Activation occurs in the three major pathways of complement, including the classical, lectin, alternative and terminal pathways can take place in sepsis.
- Severity of sepsis related to complement system is characterized by:
  1) Increase of C3b, C3a, C5a & C5b-9
  2) Decrease of C3 & C5
  3) Increase of sCD59 in the blood (Indicates its loss from the host cellular membranes)
- Blockade of C5a signaling improved the outcome of experimental sepsis in several animal models, including Escherichia coli sepsis in baboons and rats with polymicrobial abdominal sepsis

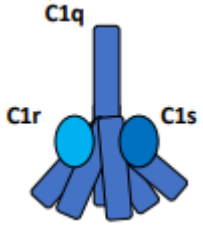
1

CRP & SAP

PAMPs & DAMPs

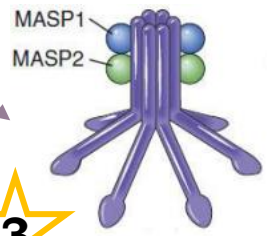
Immune complex

2 C1

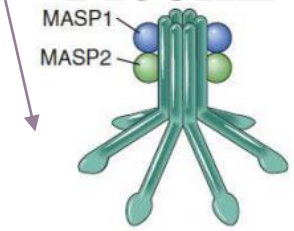


Classical pathway

MBL



3 Ficolin



Lectin pathway

Factor H

15

Alternative pathway

13

C3b Or iC3b

+ Factor b

+ Factor d

Join together forming:

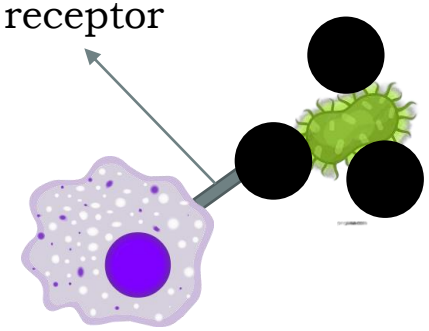
C3 convertase

Will act as the upper convertase

4

Cleaves C4 & C2

CR1 receptor



CD46

CD55

14

Inflammation

7 C3a

C4b & C2b forms:

5 C3 convertase

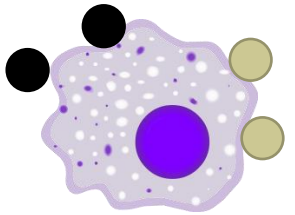
Cleaves C3 forming: C3a & C3b

6

C3b

Opsonize

8



C3 convertase join with properdin

9

C5 convertase

Cleaves C5 forming: C5a & C5b

10

Terminal pathway

Inflammation

C5a

11

C5b

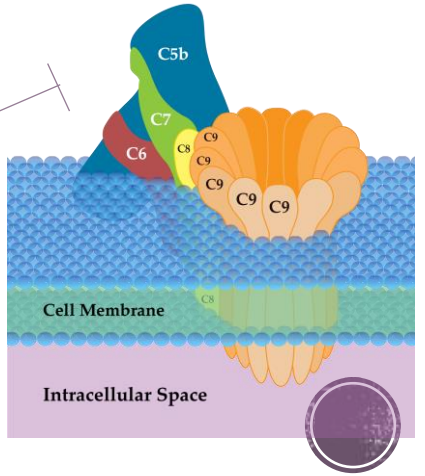
12

Forms MAC with (C 6-9)

16

CD59

Can inhibit the formation of MAC



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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.

3- Pathogenesis of sepsis/c- strong activation of the coagulation system

- Sepsis is associated with a strong activation of the coagulation system, and this can result in disseminated intravascular coagulation.
- Activation occurs because of:
  1) Tissue factor (It was found that Tissue factor inhibition prevents multiple organ failure and mortality in a model of other- wise lethal sepsis in baboons.)
  2) Platelets that induce thrombus formation
- disseminated intravascular coagulation is presented clinically by: thrombosis and hemorrhage (because factors that are used in thrombosis are consumed)

3- Pathogenesis of sepsis/d- vascular leakage

- 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 contributing to barrier incompetency

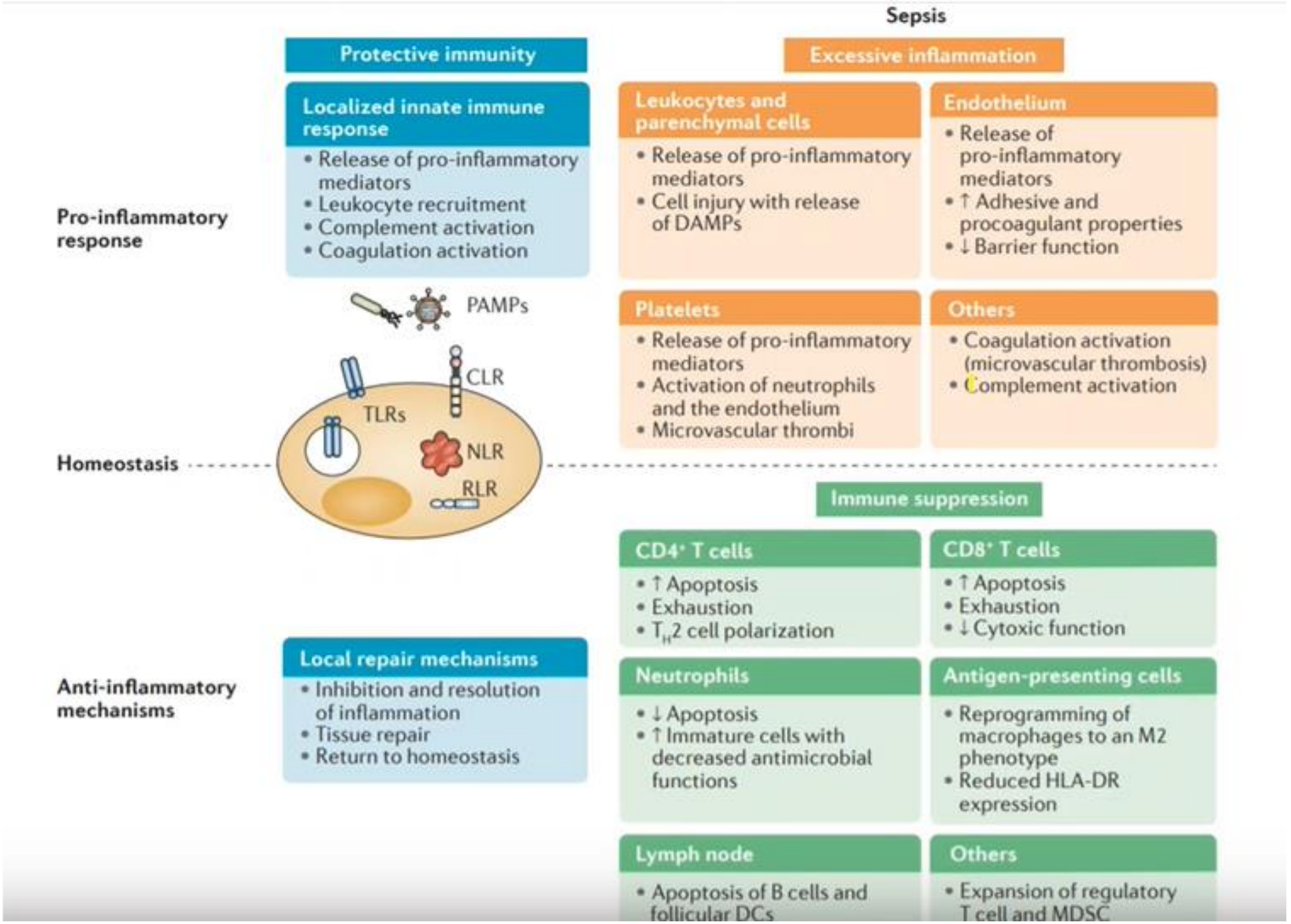
- A loss of barrier integrity causes the leakage of intravascular proteins and plasma into the extravascular space, tissue edema and reduced microvascular perfusion.

3- Pathogenesis of sepsis/ other mechanisms

- E- Neutrophil extracellular traps: 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.
- F- platelets: Excessive platelet activation has been implicated in organ injury during sepsis through several mechanisms
- G- innate response activator B cells (B1-B cells): Innate response activator B cells can produce IL-3, which in the context of sepsis increases inflammation and the production of myeloid mononuclear cells.

3- Pathogenesis of sepsis/ h- immunosuppression

- Uncontrolled immune suppression occurs after uncontrolled activation of immune system in sepsis, it increases the probability of acquiring a secondary infection
- Such mechanisms of immunosuppression are:
  1) lymphocyte exhaustion
  2) depletion of CD4+ and CD8+ T cells, B cells and dendritic cells (DCs) as a result of apoptosis
  3) Th2 cell polarization
  4) reduced expression of HLA-DR on blood monocytes


Sepsis
Protective immunity
Excessive inflammation
Localized innate immune response
• Release of pro-inflammatory mediators
• Leukocyte recruitment
• Complement activation
• Coagulation activation
Leukocytes and parenchymal cells
• Release of pro-inflammatory mediators
• Cell injury with release of DAMPs
Endothelium
• Release of pro-inflammatory mediators
• ↑ Adhesive and procoagulant properties
• ↓ Barrier function
Pro-inflammatory response
PAMPs
CLR
TLRs
NLR
RLR
Platelets
• Release of pro-inflammatory mediators
• Activation of neutrophils and the endothelium
• Microvascular thrombi
Others
• Coagulation activation (microvascular thrombosis)
• Complement activation
Homeostasis
Immune suppression
CD4+ T cells
• ↑ Apoptosis
• Exhaustion
• T_H2 cell polarization
CD8+ T cells
• ↑ Apoptosis
• Exhaustion
• ↓ Cytoxic function
Local repair mechanisms
• Inhibition and resolution of inflammation
• Tissue repair
• Return to homeostasis
Anti-inflammatory mechanisms
Neutrophils
• ↓ Apoptosis
• ↑ Immature cells with decreased antimicrobial functions
Antigen-presenting cells
• Reprogramming of macrophages to an M2 phenotype
• Reduced HLA-DR expression
Lymph node
• Apoptosis of B cells and follicular DCs
Others
• Expansion of regulatory T cell and MDSC

4- Treatment by immunomodulators

- 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.
- Some treatment mechanisms:
  1) Immune suppression through inhibition of complement or coagulation (examples, C5a-specific monoclonal antibody, recombinant human thrombomodulin)
  2) Blood purification techniques have been proposed as a method of removing PAMPs and inflammatory mediators from the circulation of patients.
  3) Immune stimulation. There are several drugs that could potentially reverse immune suppression in sepsis. One approach is to use immune-stimulating cytokines, such as IFNy and some interleukins.