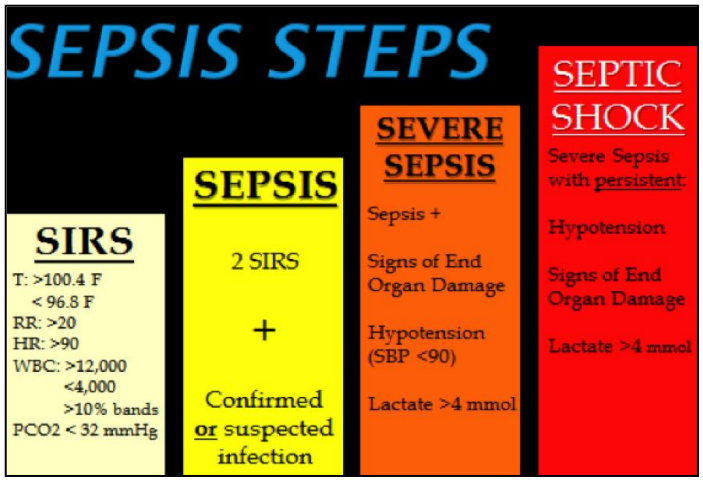
Problem 6 – Unit 6 – Pathology: Sepsis

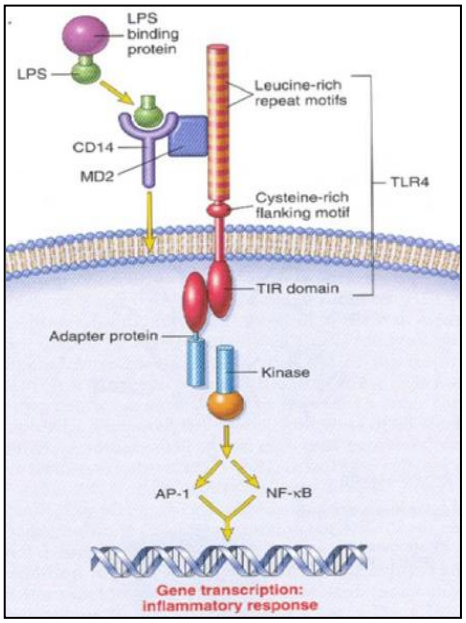
- **Infection**: is the inflammatory response to a microorganism or the invasion of normally sterile host by these organisms.
- **SIRS (Systemic Inflammatory Response Syndrome):**
  - This may occur following an infection (therefore it will also be called sepsis), pancreatitis, multiple trauma, tissue injury, hemorrhagic shock or immune-mediated organ injury.
  - **SIRS is characterized by the presence of 2 or more of the following criteria:**
    - ✓ Body temperature greater than 38C or less than 36C.
    - ✓ Heart rate greater than 90 beats/min (tachycardia).
    - ✓ Respiratory rate greater than 20 breaths/min (tachypnea) or pCO_2 less than 32 mmHg.
    - ✓ WBC count greater than 12,000 cells/µL or less than 4,000 cell/µL or greater than 10% band forms.
- **Severe sepsis:**
  - **It is associated with organ dysfunction with perfusion abnormalities:**
    - ✓ *Lactic acidosis* (because there will be reduced delivery of oxygen to the tissue thus glycolysis will be shifted to the anaerobic pathway resulting in the production of lactic acid > 4mmol).
    - ✓ *Oliguria* (because of the reduction in the blood flow to kidneys resulting in decreased GFR and urine formation).
    - ✓ *Coma*.
- **Septic shock:**
  - It is defined as sepsis with hypotension (in which the BP is less than 90 mmHg) despite adequate fluid resuscitation.
  - Shock will occur when there is failure of the circulatory system (either in the cardiac output or in the blood volume) resulting in severe impairment of tissue perfusion and thus leading to tissue ischemia and multi-organ failure.
  - Septic shock causes a mortality rate of 25-50% and it is considered among the most important causes of mortality in intensive care units (ICU).



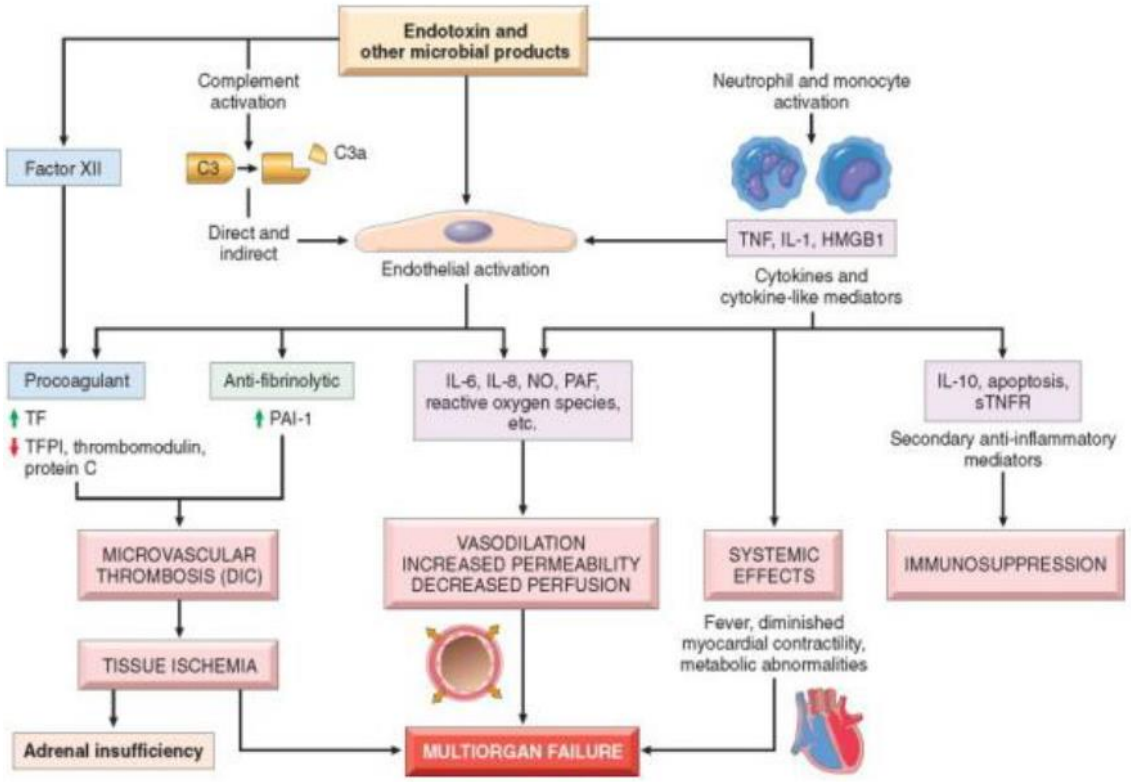
- **Causes of septic shock include:**
  - ✓ Commonly by Gram (+) bacteria (secreting exotoxins to initiate sepsis).
  - ✓ Second most common causes are Gram (-) bacteria (secreting LPS to initiate sepsis) and fungi.

    Note: other membrane component which can initiate sepsis is peptidoglycans.
  - LPS will bind to LPS-binding protein (LBP) → this complex will bind to CD14 on monocytes → leading to their activation → pathogen-associated molecular patterns (microbial antigens) will bind to Toll-like receptors on cells → this will lead to activation of transcription factors (mostly NFkB) → which will encode proteins such as:
    - ✓ Cytokines (TNF,IL-1) → stimulating T-cells and NK-cells.
    - ✓ Endothelial adhesion molecule (E-selectin).
    - ✓ Proteins involved in microbial killing.

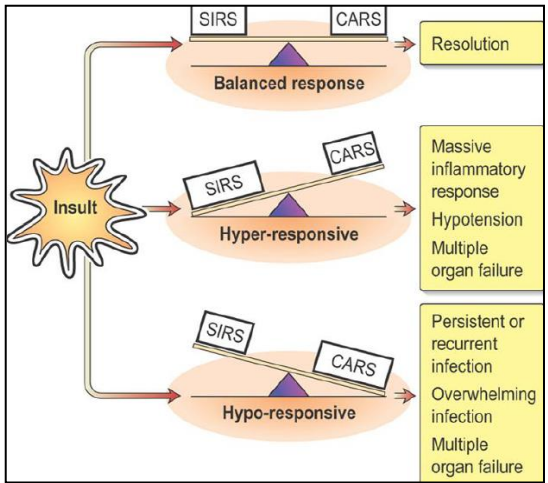
    Note: this process of septic shock will also lead to increased activity of iNOS and increased synthesis of nitric oxide (NO) in endothelial cells of blood vessels thus leading to vasodilation.



- **Main events occurring in septic shock (look to the figure below):**
  - ✓ LPS from the cell wall of gram (-) bacteria will activate macrophages and lead to the release of cytokines such as (TNF & IL-1). These cytokines will lead to the activation of endothelial cells of the blood vessels resulting in expression of adhesion molecules, a procoagulant phenotype and secondary waves of cytokine production.
  - ✓ LPS will also activate the complement cascade releasing C5a (which is a chemotaxic fragment).
  - ✓ A procoagulant state will be favored by increasing tissue factor (TF) production and decreasing anticoagulant factors such as (tissue factor pathway inhibitor, thrombomodulin & protein C). Also, there will be anti-fibrinolytic state by increasing the levels of PAI. All of these actions will lead to microvascular thrombosis (DIC) which will result is tissue ischemia.
  - ✓ Inflammatory mediators such as IL-6, IL-8, NO, PAF & ROS will lead to relaxation of vascular smooth muscle cells (vasodilation) resulting in hypotension. They will also cause the adhesion molecule VE-cadherin to be displaced from the tight junctions of endothelial cells resulting in increased vascular permeability and therefore tissue edema.
  - ✓ There will also be metabolic abnormalities such as insulin resistance & hyperglycemia (which will decrease the bactericidal activity of neutrophils), in addition to adrenal insufficiency caused by frank adrenal necrosis due to DIC.



- Factors which affect the pathogenesis of septic shock:
  - ✓ Those which are related to the pathogen include: virulence and the dose.
  - ✓ Those which are related to the host include: age, nutrition, associated diseases & genetic.
- Bacteremia/ongoing infection may not be present in septic shock.



- **CARS (Compensatory Anti-inflammatory Response Syndrome):**
  - **The process of inflammation is derived by**: cytokines (TNF, IL-1), compliment factors, coagulation factors and cellular activation & interaction.

- **CARS is derived by**: cytokine antagonists (such as IL-10), shedding of receptors (TNF-R, IL1-R), hormonal control and cell death (apoptosis).

- **Potential complications of septic shock include:**
  - Acute Respiratory Distress Syndrome (ARDS).
  - Renal failure.
  - GI bleeding and stress gastritis.
  - Anemia.
  - Deep Vein Thrombosis (DVT).
  - Intravenous catheter-related bacteremia.
  - Electrolyte abnormalities.
  - Hyperglycemia.
  - Disseminated Intravascular Coagulation (DIC).