pathophysiology of sepsis

host defence mechanisms

- Physical barriers
  - Skin and mucosal surfaces
  - Cilia
- Fever
- Lysozyme
- Lactoferrin
- Acute-phase proteins, e.g. C-reactive protein
- Fibronectin
- Mannose binding lectin
- Immune system, including secondary mediators
- Other mediators of inflammation
  - Kinins
  - Vasoactive amines
  - Coagulation system

definitions

Infection
Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms

Bacteraemia
The presence of viable bacteria in the blood

Systemic inflammatory response syndrome
The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:
- Temperature >38°C or <36°C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $Paco_2$ <4.3 kPa (<32 Torr)
- White blood cell count >12 000 cells/mm³, <4000 cells/mm³, or <10% immature (band) forms

Sepsis
The systemic response to infection. This systemic response is manifested by two or more of the following conditions as a result of infection:
- Temperature >38°C or <36°C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $Paco_2$ <4.3 kPa (<32 Torr)
- White blood cell count >12 000 cells/mm³, <4000 cells/mm³, or <10% immature (band) forms

Severe sepsis
Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status

Septic shock
Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time when perfusion abnormalities are measured

Hypotension
A systolic blood pressure of <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes for hypotension

Multiple organ dysfunction syndrome
Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

inflammatory mediators

Pro-inflammatory mediators and pathways	Anti-inflammatory mediators
Cytokines – TNF, IL-1, 6, 8, IFN-γ	Interleukin 4, 10, 11, 13
Contact system/coagulation pathways	Transforming growth factor β
Macrophages, monocytes, neutrophils	Colony stimulating factor
Endothelial cells, platelets	Soluble TNF receptors
Platelet activating factor	IL-1 receptor antagonist
Oxygen free radicals	Natural anticoagulants
Proteases	
Nitric oxide	

oxygen delivery in sepsis

- DO2 is supranormal in septic shock mainly as a result of the elevated cardiac output
- VO2 is also raised due to an increase in tissue metabolic activity
- supply dependency is observed over a wider range of DO2 values than usual
- sepsis-induced mitochondrial dysfunction may prevent oxygen utilisation at a cellular level

innate & acquired immunity

Innate	Acquired (adaptive)
Polymorphonuclear leukocyte	Complex, involving T and B cells and characterized by:
Natural antibodies, opsonins	memory
Macrophages	specificity
Dendritic cells	diversity
Natural killer cells (NKC)	
Complement system (alternative pathway)	
Coagulation system	

apoptosis in sepsis

Observation	Hypothesis	
Delayed neutrophil apoptosis	Beneficial	Enhanced function
		Prolonged function
	Detrimental	Prolonged elaboration of toxic metabolites
		May result in neutrophil necrosis
Increased lymphocyte apoptosis	Beneficial	Decreased autoreactive clones
		Decrease in effectors, which can perpetuate inflammation
	Detrimental	Immunosuppressive
Parenchymal apoptosis	Beneficial	Decreases burden of dying or senescent cells
		No bystander inflammation
	Detrimental	Decreases functional capacity of the organ