The current consensus definitions of systemic inflammatory response syndrome (SIRS), sepsis and septic shock concentrate on clinical criteria in an attempt to improve homogeneity between putative treatment trials. There is no inclusion of any pathophysiological determinants of sepsis. As more knowledge is accrued concerning the control of the sepsis response and its relationships with the clinical situation, the relevance of pathophysiological criteria will increase. These will become important when investigating novel therapies and improving outcome in high-risk groups.

**Immune response to infection**

The overall host reaction to an infection relies on a complex combination of innate and acquired immune responses. Acquired immunity relies on the generation of a large repertoire of specific antigen receptors forged from the memory of previously encountered pathogens. Innate immunity describes a host response against specific molecular components of invading pathogens. These include lipopolysaccharide (LPS) and peptidoglycans of bacteria, glycolipids of mycobacteria and double-stranded RNA of viruses.

It is thought that the innate response plays the key role in signalling the presence of infection and the initiation of an immuno-inflammatory reaction. The innate response to Gram-negative infection (60% of sepsis cases in the ITU) is triggered by endotoxin (LPS). LPS complexed with a specific plasma protein (LBP) binds to a membrane receptor (CD14) on effector cells such as macrophages and endothelial cells. This initiates intracellular signal transduction via a specific receptor mechanism (Toll-like receptor, TLR). The response to Gram-positive infections (40% of cases in the ITU) occurs either secondary to the production of a specific exotoxin or, more commonly, due to the shedding of cell membrane fragments.

**Inflammatory response to infection**

Once the inflammatory response has been triggered, the vascular endothelium orchestrates the ensuing inflammatory process, directing cellular elements (primarily leukocytes) to the site of infection. Complex endothelial-leukocyte interactions are an essential precursor to sustaining an inflammatory response. These are regulated by a carefully timed sequence of molecular expression. The entire process is depicted in Figure 1.

**Leukocyte–endothelial adhesion and migration**

Initial leukocyte margination and rolling along the endothelial wall is regulated by the appearance of a group of glycoproteins known as selectins on the surface of both endothelial cells (P- and E-selectins) and leukocytes (L-selectin). This process is triggered by a variety of pro-inflammatory mediators including tumour necrosis factor (TNF-α), interleukin 1 (IL-1), histamine, complement, leukotrienes and oxygen free radicals. The resulting low-affinity interactions promote intermittent adhesion between leukocytes and endothelium and hence a rolling of the cells along the endothelium as bonds are made and broken. These are strengthened by the formation of high-affinity bonds regulated by a further group of corresponding endothelial and leukocyte adhesion molecules. The molecules on the endothelial cells include intercellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2), vascular cell adhesion molecule 1 (VCAM-1) and platelet-endothelial cell adhesion molecule 1 (PECAM-1). The leukocyte receptors include members of the β2-integrin family of adhesion molecules (e.g. CD11b and CD18).

Strong leukocyte-endothelial adhesion is followed by transmigration of leukocytes out of the blood vessel into the underlying tissue. This takes

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**Key points**

- The innate immune response triggers the reaction to infection
- The vascular endothelium directs the inflammatory process
- Nitric oxide is involved in mitochondrial dysfunction and cellular hypoxia in sepsis
- Microvascular intravascular coagulation is a key finding in sepsis
- All organ systems may be involved in sepsis

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place mainly across the wall of the post-capillary venules, although in some areas such as the lungs the process can also occur in the capillaries. The migration is facilitated by retraction of the endothelium resulting in gaps between the cells that also increase vascular permeability and local oedema.

**Endothelial and local tissue response**

The result of the endothelial–leukocyte interaction is injury to both the endothelial cell and to the underlying tissue. Pro-inflammatory cytokines and activated neutrophils produce endothelial cell injury. The cytokines are thought to induce apoptosis (programmed cell death) in the endothelial cells. Activated adherent neutrophils cause damage by a cascade of events which leads to the formation of oxygen free radicals $O_2^*$ and $OH^*$ within the endothelial cell.

If the whole process remains localised, it is viewed as being beneficial since it plays an important role in removing damaged and infected tissue. Various anti-inflammatory mediators counteract the pro-inflammatory reaction thereby localising the response. These include paracrine/autocrine substances such as nitric oxide (NO), adenosine, prostacyclin (PGI₂) and lipocortin-1 and endocrine substances such as glucocorticoids, secretory leukocyte protease inhibitor (SLPI) and IL-10 and IL-13. In sepsis, the inflammatory response breaks free from the anti-inflammatory checks and becomes wide-spread, causing systemic damage. The mechanism by which this occurs is likely to be multifactorial. However, a generalised dysfunction of cellular metabolism, related to abnormalities in NO production, is likely to play a pivotal pathophysiological role.

**Nitric oxide and its potential effects on cell respiration in sepsis**

NO is produced from L-arginine by the action of the enzyme nitric oxide synthase (NOS). There are three isoforms of NOS: (i) eNOS found in the endothelium; (ii) nNOS in neurones; and (iii) iNOS, an inducible form found in a number of locations (e.g. macrophages, smooth muscle and endothelium).

eNOS and nNOS are constitutive enzymes and are sometimes grouped under the title cNOS. In contrast, the expression of iNOS is induced by several stimuli associated with inflammation and iNOS produces much greater amounts of NO than eNOS. Its activation is often sustained for several days. Recently, exciting insights have been gained into the role of NO in regulating cell respiration. Physiological levels of NO regulate cell respiration by acting on the mitochondrial cytochrome c oxidase (complex IV) to reduce oxygen utilisation. Since NO can be displaced by $O_2$ in a competitive process, the interaction between $O_2$ and physiological levels of NO protects the cell by reducing $O_2$ consumption when $O_2$ levels become low. However, in sepsis, pro-inflammatory stimuli lead to the induction of iNOS over a period of several hours, thereby causing excessive production of NO. In this circumstance, there is insufficient $O_2$ to displace NO from complex IV. Consequently, the respiratory chain becomes reduced and $O_2^*$ is formed in the mitochondria. The $O_2^*$, in turn, reacts with free NO to form the peroxynitrite anion (ONOO$^\cdot$). In contrast to the reversible effects of NO on complex IV, ONOO$^\cdot$ causes irreversible damage to complexes I and III, ultimately leading to an initiation of events which cause apoptosis. There is now evidence of mitochondrial dysfunction in a number of tissues during sepsis, including monocytes, intestinal mucosa, liver and skeletal muscle. The degree of dysfunction appears to be related to the severity of sepsis and to some extent outcome. A consensus opinion is that, in the early phase of sepsis, there may be increased mitochondrial function, which gives way to a depression of activity later.

**Organ dysfunction**

Whatever the mechanism of disordered cellular metabolism seen in sepsis, the overall result is of generalised organ system dysfunction. The mechanisms whereby the inflammatory process affects multiple organs with different degrees of severity are not known. In clinical terms, our understanding of individual organ dysfunction is biased by our ability to investigate a given system. As an example, the pulmonary response to sepsis has been extensively investigated, whereas the hepatic response, although known to play a key role in the sepsis process, has not been so well delineated. With this in mind, in the next section, we will review individual system dysfunction in the septic individual.
Cardiovascular

In addition to disrupting oxygen consumption at the cellular/mitochondrial level, sepsis is also associated with gross disturbance of cardiovascular function.

Impairment of vasomotor control

Sepsis is associated with wide-spread vasodilatation and loss of reactivity to catecholamines. Much of this is related to the disruption in NO regulation (described above). NO plays a key role in endothelium vasomotor regulation and hence microvascular haemodynamics. Under normal physiological conditions, there is a basal synthesis and release of NO by endothelial cells. NO then diffuses to the underlying smooth muscle cells where it activates guanylate cyclase leading to an elevation of guanosine 3',5'-cyclic monophosphate (cGMP). This triggers an intracellular cascade culminating in falls in free calcium concentrations and muscle relaxation. During sepsis, the excessive production of NO causes extensive systemic vasodilatation, which may be detrimental to regional oxygen delivery by causing regional blood flow mismatching.

Cardiac dysfunction

There is evidence that myocardial function is depressed as a response to sepsis resulting in a reduction in the rate of cardiac contraction and relaxation. This may relate to problems with Ca^{2+} uptake/release from the sarcoplasmic reticulum via voltage-gated Ca^{2+} channels in the sarcolemma, sometimes known as the ryanodine receptor. A decrease in the number of these receptors in the hypodynamic phase of sepsis reduces the rate of Ca^{2+} release from the sarcoplasmic reticulum, hence limiting the interaction with the myocardial contractile proteins during systole. There is also a decrease in the rate of reuptake into the sarcoplasmic reticulum which delays the onset of relaxation and hence diastole. The mechanism underlying the reduction in the number of these Ca^{2+} channels may relate to mediators such as TNF-α and NO, which can interfere with Ca^{2+} release via the ryanodine receptor.

Haematological

Sepsis causes an acute disseminated intravascular coagulation with low platelets, prolonged clotting times and hypofibrinogenaemia leading to both haemorrhagic and thrombotic complications. Wide-spread microvascular thrombosis, due to impairment of the anticoagulant systems (antithrombin III and thrombomodulin) and cytokine induction of the extrinsic coagulation systems, exaggerates the deficiency in cellular oxygen delivery/utilisation. Endogenous activated protein C, which promotes fibrinolysis and inhibits thrombosis and inflammation, is decreased in sepsis. The administration of activated protein C has been shown to reduce mortality in some septic patients and is undergoing further clinical trials. The mechanisms are shown in Figure 2.

Hepatic

Liver dysfunction, when defined as low-grade hyperbilirubinaemia and mild liver enzyme rise, is as common in sepsis as pulmonary and renal failure. In sepsis, increased hepatic oxygen demand is only partially met by an increase in hepatosplanchnic blood flow, commensurate with an overall increase in cardiac output. Hepatic impairment occurs if hepatic blood flow is insufficient for the increased regional oxygen demand or hepatic dysfunction is not flow-dependent. The presence of normal liver function prior to the development of sepsis has a beneficial impact on prognosis.

Pulmonary

Acute lung injury or acute respiratory distress syndrome (ARDS) is involved in 60% of septic patients. Endothelial dysfunction caused by neutrophil infiltration is the primary process that leads to protein-rich fluid extravasation into the pulmonary interstitium and alveolar spaces. Pathophysiological sequelae include alveolar collapse, pulmonary shunting, hypoxaemia, decreased compliance and functional residual capacity and increased work of breathing. IL-8 produced by the abundant alveolar macrophage population is related to pulmonary injury and has been associated with patient outcome.

Renal

Renal hypoperfusion in sepsis results primarily from systemic vasodilatation and the relative hypovolaemic state. Other neurohumeral factors including endothelin and thromboxane A_{2} and an influx of cellular material (e.g. neutrophils and coagulation factors)
are also important and lead to varying degrees of renal impairment through to acute renal failure. Although oliguria is the usual clinical outcome, polyuric renal failure can be caused by a poorly understood specific tubular dysfunction.

**Metabolic**
Metabolic changes occurring during sepsis are related to the hyperdynamic state and co-existing nutritional deficiencies, leading to exaggerations of the normal reaction to stress and/or starvation. The metabolic response seen in sepsis is also a result of impaired oxygen utilisation, which alters substrate metabolism at the cellular level. The impact of these changes is related to the stage of sepsis.

**Glucose**
During the hypermetabolic state, glucose production is accelerated. This is due to elevations of counter regulatory hormones (e.g. glucagon, catecholamines). However, in sepsis, high plasma glucose concentrations are often associated with raised plasma insulin. This state may be explained by the specific induction of functional insulin resistance by the depression of key mitochondrial glycolytic enzymes (glucokinase and pyruvate dehydrogenase) or by effects on the insulin receptor itself.

**Protein**
Where glucose utilisation is impaired, energy demands are met by protein breakdown, especially from skeletal muscle. The metabolism of alanine usually creates an important gluconeogenic substrate in the form of glutamine. Unfortunately, sepsis directly impairs the intracellular conversion of glutamine to glucose by reducing the activity of the rate-limiting enzymes (e.g. glutaminase). In addition, whilst glutamine is at a premium for glucose production, the gut wall is at risk of disruption, since the integrity of some parts of the gastrointestinal (GI) tract mucosa are directly influenced by the availability of glutamine. Hence, glutamine supplementation during sepsis may be GI protective and is likely to be important in preventing the progression of sepsis to multiple organ failure.

**Lipid metabolism**
In the early septic state, catabolic stimuli predominate and lipids are broken down into free fatty acids (FFA). These are available both for use as an energy source for skeletal muscle and as a precursor for ketone body production used by peripheral cells. In the later stages of sepsis, there is impairment of FFA utilisation which contributes indirectly to inhibition of glucose production, glycolysis and ketogenesis.

**Lactate**
Cellular anaerobic metabolism and microvascular tissue hypoxia/ischaemia will both lead to lactate formation. Lactate production during anaerobic metabolism is beneficial because it allows high-energy phosphate bonds to be formed without the inhibitory effect of pyruvate accumulation. In this instance, the lactate/pyruvate ratio remains in equilibrium. During cellular hypoxia/ischaemia, pyruvate production falls causing a decrease in the lactate/pyruvate ratio. By looking at the lactate/pyruvate ratio rather than lactate concentrations in isolation, it is often possible to distinguish between compensatory anaerobic metabolism and cellular hypoxia/ischaemia. Unfortunately, in the context of sepsis, an elevated lactate concentration is also related to increased lactate production, reduced lactate clearance and alterations in lipid pathways, which may render mitochondrial enzymes unable to utilise oxidative pathways. Thus in sepsis, hyperlactataemia or an increased lactate/pyruvate ratio does not always reflect tissue hypoxia.

**Summary**
The pathophysiological mechanisms of sepsis are likely to become more important in the future definition of the sepsis syndrome. Infection promotes a complex immuno-inflammatory response which, if localised, serves to protect the individual and promote healing. Systemic sepsis causes wide-spread vascular damage leading to microvascular thrombosis and a generalised dysfunction of cellular oxygen metabolism. Abnormalities in NO production are likely to play a pivotal pathophysiological role to the ensuing multisystem organ dysfunction. Future strategies of therapy will require specific targeting of such mechanisms to improve patient outcome.

**Key references**
Special issue. Sepsis (a series of reviews). Crit Care Med 2001; 29 (Suppl 7)
See multiple choice questions 9–11.