

Causes and features of SEPSIS

By ROBIN OFFORD, MSc, MRPharms

The physiological changes that characterise sepsis and the mechanisms underlying them are discussed in the first part of this month's special feature

Sepsis is used to describe the overwhelming systemic disease that results from infection with a microbial pathogen. There is exaggerated stimulation of the normal host responses to the invading pathogen, leading to a widespread release of inflammatory mediators and vasodilation. This is initially compensated for by an increase in cardiac output, which helps to maintain a reasonable blood pressure and adequate organ perfusion. At this stage, the symptoms found in a septic patient are fever, tachypnoea and tachycardia.

As the syndrome progresses, the systemic vascular resistance decreases more pro-

foundly, with a concurrent fall in cardiac output. This is accompanied by an increase in the permeability of capillaries, loss of plasma water, and a relative hypovolaemic state. The end result is a fall in arterial blood pressure, inadequate organ perfusion and oxygenation, and eventually, multiple organ failure. The septic patient may have hypoxia, lactic acidosis and oliguria, with or without local signs of inflammation at the source of the infection. Admission to an intensive care or high dependency facility for appropriate supportive therapy is usually required at this stage.

At a consensus conference held in August 1991, the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) agreed on definitions for the various stages of disease within the sepsis

syndrome (see Table 1, p94).¹ These were designed to allow standardisation of entry criteria for sepsis trials, and provide some uniformity that had previously been lacking.

The term systemic inflammatory response syndrome (SIRS) was introduced to describe patients who exhibited a sepsis-like syndrome, but who were not infected. Some clinicians dislike the term because they believe that a diagnosis of SIRS would preclude the search for an infective source. However, when patients manifest such severe symptoms, debates about terminology are of much less consequence than the need to take appropriate action. SIRS may be precipitated by insults such as pancreatitis, burns or trauma, in addition to many conditions which are less common. Significant haemodynamic instability may also be present,

Mr Offord is senior intensive care unit pharmacist at Guy's and St Thomas' Hospitals NHS Trust, London

Table 1: ACCP/SCCM consensus definitions for sepsis and organ failure¹

Terminology	Definition
Infection	Inflammatory response to micro-organisms Invasion of normally sterile tissues
Systemic inflammatory response syndrome (SIRS)	Clinical response arising from a non-specific insult, including more than two of the following: <ol style="list-style-type: none"> 1 Temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$ 1 Tachycardia; heart rate ≥ 90 beats per minute 1 Tachypnoea; respiratory rate ≥ 20 /minute White blood cell count $\geq 12,000$ per mm^3 or $\leq 4,000$ per mm^3 or >10 per cent immature neutrophils
Sepsis	SIRS with a presumed or confirmed infectious process
Severe sepsis	Sepsis with more than one sign of acute organ dysfunction: <ol style="list-style-type: none"> 1 Renal 1 Respiratory 1 Hepatic 1 Haematological 1 Central nervous system 1 Unexplained metabolic acidosis
Septic shock	Severe sepsis with cardiovascular dysfunction, characterised by hypotension refractory to adequate volume resuscitation
Multiple organ dysfunction syndrome (MODS)	Altered organ function in an acutely ill patient Inability to maintain haemostasis without intervention

although this is not included in the standard definition.

— EPIDEMIOLOGY

Angus *et al*² conducted an observational cohort study across 847 hospitals in seven US states. By comparing data from over 6.5 million hospital discharge records with population and hospital records from the last US census, Centers for Disease Control and financing organisations, an estimate of the incidence, cost and outcome of severe sepsis in the US was produced. A projected 750,000 cases occur each year (three cases per 1,000 of the population and 2.25 cases per 100 hospital discharges), at a cost of \$22,100 per case, or \$16.7bn for all cases.

Severe sepsis is associated with a high mortality rate. The study by Angus *et al* predicts 215,000 deaths per year, equivalent to a mortality rate of 28.6 per cent.² In a subgroup analysis, patients with single organ dysfunction had a projected mortality rate of 21.1 per cent. The rate rises to 76.2 per cent for those in whom four or more organs are involved.

A prospective, multi-institutional, observational study examining the epidemiology of severe sepsis in eight US teaching hospitals found a 28-day mortality rate of 34 per cent.³ At five months, an additional 11 per cent of patients had died. A study of 11,828 consecutive admissions to adult intensive care units

(ICUs) in French public hospitals found a 28-day mortality rate of 56 per cent.⁴

— INITIATION OF SEPSIS

The source of the underlying infection resulting in sepsis is most frequently bacterial, although the incidence of fungal sepsis is increasing, and viruses may also be responsible.⁵ One study reported fungal isolates in 17 per cent of intensive care patients, and candidiasis accounted for around 10 per cent of all positive blood cultures.⁶ The proportion of pathogenic, as opposed to endogenous, isolates is not known, however.⁷

More recently, there has been a swing in the predominant infective organisms in sepsis, from Gram-negative to Gram-positive bacteria.⁸ The most common sites of infection are the lungs (40 per cent), abdomen (30 per cent) and urinary tract (10 per cent).⁹ The high rates of pulmonary infection may reflect the increasingly frequent and prolonged use of mechanical ventilation and the rising occurrence of nosocomial pathogens encountered in intensive care facilities.

Septic shock occurs as the end result of an interaction between an invader (micro-organisms and their products) and host factors released in response (cytokines and other mediators). The stimulus for the host response may be the organism itself, or various products and features of the organism, such as endotoxin in Gram-negative organisms, peptidoglycan and lipoteichoic acid in

Gram-positive organisms, or specific toxins produced by bacteria. A vast number of mediators involved in the host response have been identified and evaluated, although in many cases, it is not known exactly how the microbial product elicits production and release of the mediator. The response occurs as a method of protection. However, in sepsis, when these responses are profoundly stimulated, the outcome is often multiple organ failure and, potentially, death.

There are three factors that combine to precipitate organ failure. These are:

- 1 Systemic inflammation
- 2 Coagulation
- 3 Impaired fibrinolysis

— SYSTEMIC INFLAMMATION

Celsus first described the features of inflammation in 30 BC as *rubor* (redness), *calor* (heat), *dolor* (pain) and *tumor* (swelling).¹⁰ Inflammation occurs as a means of slowing blood flow through an affected area, allowing macrophage and neutrophil migration to infected sites. In sepsis, this process is so widespread that generalised haemodynamic instability results, with the predominant mediators being inflammatory cytokines.

The generic term, cytokine, refers to a diverse group of soluble proteins or peptides that act as humoral regulators, modulating the functional activities of, and interactions between, individual cells or tissues.⁵ Cytokines are produced by a variety of cell types under normal and pathological conditions, and can have systemic and local effects. Among the many cytokines so far implicated in septic shock, tumour necrosis factor-alpha (TNF-alpha) and the interleukins (IL), particularly IL-1 and IL-6, have been most studied and their key role in the pathogenesis of sepsis is established.

The plasma levels of implicated cytokines have been shown to be markedly elevated in patients with severe sepsis, and in many cases the degree of elevation correlates directly with patient outcome. Their administration to healthy volunteers may reproduce the characteristics of septic shock, and in animal models, the use of specific anti-cytokine drugs has been shown to reverse symptoms and improve survival.¹¹⁻¹⁴ Such agents include the anti-TNF-alpha antibody fragment, afelimomab, and an IL-1 receptor antagonist that has not yet been named. These positive results have not been achieved in clinical studies however, leading to the continued search for a targeted "magic bullet" in sepsis.¹⁴

Circulatory failure Shock can be described as acute circulatory failure due to a derangement of circulatory control or loss of circulating fluid. In septic shock, circulatory failure results primarily from vasodilation

secondary to the widespread release of inflammatory mediators. This is exacerbated by a decreased circulating volume when plasma water is lost through an increase in capillary permeability. Septic shock therefore induces hypotension, with a consequent poor perfusion of tissues.

The normal physiological response to a fall in tissue perfusion pressure would be peripheral vasoconstriction. Vasoconstriction increases arterial blood pressure and restores perfusion. Recent research has revealed that septic shock not only results in hypotension due to vasodilation, but also a failure of the vascular smooth muscle to respond to either endogenous or exogenous vasopressor agents.¹⁵ This finding is also supported by the failure of drugs targeted at inhibiting the mechanisms behind vasodilation to improve outcomes from septic shock.

Three mechanisms have so far been implicated in the vasodilation seen in septic shock, and the poor response of vascular smooth muscle to vasopressor agents. These are activation of adenosine triphosphate (ATP)-sensitive potassium channels, increased nitric oxide synthesis, and the depletion of vasopressin.

Activating ATP-sensitive potassium channels

Vasoconstriction is dependent upon the action of feedback agents such as angiotensin II and noradrenaline, whose production is increased in states of low tissue perfusion pressure. These agents bind to receptors upon the surface of vascular smooth muscle cells, and through secondary messengers, increase the influx of calcium through voltage-gated calcium channels, along with calcium release from intracellular stores. Through formation of a calmodulin-calcium complex, and subsequent activation of a kinase enzyme which phosphorylates myosin, cycling of myosin cross-bridges along actin filaments occurs, and muscle contraction results. Endogenous vasodilators, such as atrial natriuretic peptide (ANP) and nitric oxide, have the reverse effect and prevent muscle contraction through a kinase enzyme that dephosphorylates myosin.

The second crucial factor for changes in smooth muscle tone has recently been found to be the membrane potential. The usual resting membrane potential for vascular smooth muscle is between -30mV and -60mV , depending on the cell type. A shift to a more positive potential (depolarisation) results in the opening of voltage-gated calcium channels, an increase in the cytosolic calcium concentration and the resultant vasoconstriction. A more negative potential (hyperpolarisation) results in closure of the calcium channels, inducing relaxation. More importantly, vasoconstriction is prevented, even in the presence of vasoconstrictor ligands.¹⁶ The channels contributing most significantly to the membrane potential are the potassium

channels, of which there are four, the most understood being ATP-sensitive potassium channels (K_{ATP}).

The opening of K_{ATP} channels allows an outflow of potassium ions, leading to membrane hyperpolarisation and inhibition of calcium entry into the cell, again preventing vasoconstriction. This effect may be induced pharmacologically by K_{ATP} channel activating drugs such as diazoxide. The K_{ATP} channels are activated physiologically by decreases in intracellular ATP, or increases in intracellular hydrogen ion or lactate concentrations.^{17,18} As lactate is produced as a by-product of anaerobic metabolism in underperfused, hypoxic tissues, the vasodilation would appear to be self-perpetuating. In such circumstances, the sulphonylureas, which produce their insulin-secreting effects through the closure of ATP-sensitive potassium channels, also have the same effect on K_{ATP} channels in vascular smooth muscle, and may reverse this vasodilation.¹⁹

Increased synthesis of nitric oxide Nitric oxide is known to be a potent vasodilator, with high plasma levels of its metabolites found in septic shock patients. Production of nitric oxide is increased in septic shock through increased expression of the inducible form of the enzyme nitric oxide synthase (iNOS). It is currently thought that a number of inflammatory cytokines, such as IL-1 β , IL-6, TNF- α , interferon- γ , are involved in this process.

In addition to its action on the dephosphorylation of myosin mentioned above, it seems likely that nitric oxide also activates potassium channels on the plasma membrane of vascular smooth muscle cells.¹⁹⁻²² During normal vasoconstriction, induced by high levels of cytosolic calcium, calcium-sensitive potassium (K_{Ca}) channels are activated. This allows an efflux of calcium ions and subsequent hyperpolarisation, which again prevents further vasoconstriction. Nitric oxide is able to activate these K_{Ca} channels, and therefore causes vasodilation, as well as resistance to vasopressors. Animal studies have confirmed that lack of responsiveness to noradrenaline can be at least partially reversed by the use of K_{Ca} -channel inhibitors.²³

Depletion of vasopressin The antidiuretic hormone vasopressin regulates the permeability of the renal collecting ducts to water, and is secreted in hyperosmotic states. Vasopressin may also be produced under baroreflex control in states of cardiovascular instability, where it has a potent constrictor effect on vascular smooth muscle if present in high enough concentrations. A number of actions underlie this highly potent vasoconstrictor effect in septic shock. They are:

- 1 High receptor availability due to low

circulating levels of vasopressin. Levels of endogenous vasopressors such as noradrenaline and angiotensin II are raised due to a lack of constrictor effect, with receptors subsequently becoming down-regulated

- 1 Potentiation of noradrenaline
- 1 Direct inactivation of K_{ATP} channels in vascular smooth muscle
- 1 Inhibition of the cyclic guanosine monophosphate (cGMP) production that is induced by nitric oxide and ANP
- 1 Decreased synthesis of iNOS caused by bacterial endotoxins

In contrast to normal physiological conditions where vasopressin has only a minor role in arterial pressure regulation, septic shock results in high plasma concentrations of the hormone, following release from the posterior pituitary gland. Levels then rapidly fall if hypotension persists, probably due to depletion of stores of vasopressin. Correction of these inappropriately low levels of vasopressin (by infusing exogenous vasopressin) leads to rapid increases in arterial pressure (approximately 25–50mmHg).²⁴⁻²⁶

— COAGULATION

Studies have demonstrated that in sepsis, tissue factor becomes exposed on the endothelial cell surface after activation by endotoxin or a number of inflammatory mediators, such as IL-1, TNF- α and PAF (see below), resulting in activation of the extrinsic coagulation system.^{27,28} This leads to the release of thrombin and the conversion of fibrinogen to fibrin. Thrombin generation induces the production of endogenous inhibitors of coagulation, such as protein C, antithrombin and tissue factor pathway inhibitor (TFPI) as a natural feedback mechanism.

In addition to its anticoagulant properties, the active form of protein C has also been found to have significant anti-inflammatory properties, mainly through a decrease in cytokine production, and inhibition of leukocyte adherence to the endothelium.²⁹ Levels of these circulating anticoagulants rapidly begin to decline as coagulation activation continues, and there is evidence of a down-regulation in their production in septic states.

In parallel with activation of the coagulation system, a number of factors induce platelet activation and aggregation. Arachidonic acid is released in sepsis from liberated cellular phospholipids, and enters the cyclooxygenase pathway. Metabolites may contribute to coagulation (by means of platelet activation) and vasodilation (through their effects upon thromboxane activation and prostacyclin generation).

PAF is produced by the degradation of membrane phospholipids from a variety of cells, and was originally known as platelet

activating factor due to its coagulation properties. It is now also known to be a potent vasodilator in most vascular beds, but a vasoconstrictor in the coronary, renal and pulmonary circulation. Its haemodynamic actions are thought to be due to liberation of histamine and serotonin from platelets, accompanied by neutrophil activation and degranulation, resulting in the release of leukotrienes and production of superoxide.

Although the resulting clinical picture resembles disseminated intravascular coagulation (DIC), there are some distinct differences in the coagulopathies encountered in septic syndromes. It is not a common occurrence for the degree of thrombocytopenia, or elevation of international normalised ratio (INR) and activated partial thromboplastin time ratio, to meet the diagnostic criteria for DIC. Additionally, clinical bleeding occurs relatively infrequently.

— IMPAIRED FIBRINOLYSIS

Fibrinolysis is known to be impaired in septic states. In a study of 48 patients with septic shock admitted to a general ICU, low plasminogen and plasminogen/alpha₂-antiplasmin ratios were found in survivors and non-survivors, although there was a trend towards normalisation in the survivor group.³⁰ Plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (t-PA) concentrations were high in both groups. The rise in PAI-1 was thought to be the main contributory factor to impairment of fibrinolysis, and a subsequent poor outcome.

— CONCLUSION

Although the understanding of sepsis has increased greatly in recent years, sepsis remains the leading cause of death in intensive care settings, and the 11th leading cause of death in the US.^{3,31} In comparison with other major diseases, such as the acquired immune deficiency syndrome, cardiac failure, and colon and breast cancers, sepsis has attracted minimal research funding despite the fact that it has both a greater incidence and greater associated mortality. Sepsis remains misunderstood by many clinicians, and a low index of suspicion often results in a diagnosis being missed or delayed.

However, the tide appears to be turning, and with an increased knowledge of the pathophysiology of sepsis, researchers have identified a number of possible targets for therapeutic agents that may halt the sepsis

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