Pathophysiology of Septic Shock

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LEADING ARTICLE

The last two decades have witnessed a remarkable expansion in the understanding of sepsis, its origins, consequences and outcomes: the pace of advancement in this field has been so great that articles and books are frequently out of date by the time they reach publication. As the various aspects of the septic cascade have been elucidated, we have begun to understand just how complex and involved this response is; as such, it is virtually impossible in any one article to describe each individual detail of each intricate pathway. Here we aim to draw together all the essential elements of the inflammatory response to sepsis, but the reader is encouraged to engage with the primary research papers. We concentrate on some of the most recent developments in this field and the ways in which these may impact on our clinical practice.

Definition and epidemiology

Septic shock is defined as acute circulatory failure occurring in the presence of severe infection. In essence, this circulatory shock represents an imbalance between the body's oxygen demands and the available oxygen supply, and is principally of the distributive type, although cardiogenic and hypovolemic components may also be involved. Classically, septic shock is associated with a normal or high cardiac output and a low systemic vascular resistance [1]. Generalized changes in capillary permeability result in edema formation with 'third spacing' and altered tissue function.

While traditionally associated with bacterial infection, fungi or even viruses can represent the infecting pathogen. Recent studies have indicated a swing in the predominant causative organisms from Gram-negative in favor of Gram-positive bacteria [2]. Sepsis can be the result of infection in many sites, but most commonly involved are the lungs, the abdomen, the urinary tract, and the skin. Pulmonary infection has become an increasingly common source of sepsis [2], perhaps as a result of the widespread, and often prolonged, use of mechanical ventilation, and also the better identification of abdominal sources of sepsis that can be rapidly eliminated.

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Interactions between bacterial products and the host

Septic shock is the end-result of the interaction between the invader (microorganisms and their products) and host factors released in response to that invasion (cytokines and other mediators). This host response is an innate mechanism developed to protect the organism from harm, but in septic shock, it seems to be stimulated to excess, with the resultant catastrophic effects leading to organ dysfunction and frequently to multiple organ failure and death.

Initiation

The invading threat and the stimulus for the host response may be the organism *per se,* or various products or features of the organism, such as endotoxin (Gram-negative), peptidoglycan, lipotiechoic acid (Gram-positive), or specific bacterial-produced toxins. These microbial products can stimulate a range of effects, including the release of cytokines, the generation of complement, the activation of coagulation, and platelet aggregation. While the activities and identities of many

of the mediators of sepsis (currently more than 150 mediators have been implicated in various aspects of the sepsis response) have been relatively well studied and defined, the means by which the microbial product effects the release of these mediators is only now becoming clear. In fact, microbial components are recognized by soluble or cell-bound pattern recognition molecules or receptors, such as CD14 and the Toll-like receptors (TLRs) [3,4]. The sequence of events for Gram-negative organisms is such that endotoxin (lipopolysaccharide [LPS]) binds to a specific LPS-binding protein (LPB) in the plasma. The LPS–LBP complex binds to a macrophage membrane receptor, CD14, which presents the LPS to a signal-transducing receptor in the membrane, TLR4. This binding activates nuclear factor-κB (NF-κB), causing macrophage activation with cytokine release. Proinflammatory mediator release attracts further macrophages and monocytes and the cycle repeats and grows. LPS–LBP can also bind to a soluble CD14 receptor present in the serum that promotes LPS binding to endothelial cells, again via TLRs.

For Gram-positive organisms, the sequence is probably similar, although is less clearly defined, with cell-wall components, such as lipoteichoic acid or peptidoglycan, binding to CD14, which then binds to TLR2, again stimulating cytokine release. Bacterial components can also act directly to stimulate the coagulation and complement cascades; the overall host response is thus a complex interaction between these multiple factors.

Cytokines

Cytokine is a generic term that 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. 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, tumor necrosis factor-α (TNF-α) and the interleukins (IL), particularly IL-1, have been most studied and been shown to play a key role in pathogenesis.

Proinflammatory cytokines

TNF-α

The TNF family is primarily involved in the regulation of cell proliferation and apoptosis, but TNF-α has additional proinflammatory properties, recruiting and activating neutrophils, macrophages and lymphocytes, and stimulating the release of other proinflammatory cytokines and acute-phase proteins. TNF-α exerts its actions by binding to two distinct TNF receptors (TNFR1 and TNFR2), which trigger different cellular events: TNFR1 is believed to be primarily responsible for the proinflammatory properties of TNF-α, while TNFR2 seems to have little inflammatory properties of its own, but may act to potentiate TNFR1 activity. Three prime factors have contributed to the establishment of TNF-α as a primary role-player in sepsis:

- Elevated serum levels of TNF-α are found in patients with sepsis, and the degree of elevation is related directly to the severity of infection [5,6]; raised levels have been correlated with outcome [7,8]. In addition, systemic release of TNF-α occurs soon after the injection of endotoxin into healthy volunteers [9].
- The administration of TNF-α to animals reproduces the characteristics of septic shock (e.g. alterations in coagulation, non-hemodynamic pulmonary edema, renal failure) [10,11], and in human volunteers, TNF-α administration also results in the typical signs of sepsis (e.g. fever, hypotension, high cardiac output, myocardial depression) [12–14].
- The administration of anti-TNF-α antibodies prevents the complications associated with the administration of endotoxin in animal models [15,16]. In a recently completed randomized, controlled clinical trial of 2634 patients with severe sepsis, patients treated with afelimomab, an anti-TNF antibody fragment, had a 10% decrease in relative mortality risk compared with patients given placebo [17].

IL-1

IL-1 includes two related proteins, IL-1α and IL-1β, that activate the same receptors and thus have similar biological actions. IL-1's spectrum of activity is similar to that of TNF-α, although it generally produces a less severe effect. It acts in synergy with TNF to produce greater myocardial depression than either cytokine alone [18]. As with TNF, attempts to block the activity of IL-1 in endotoxic animal models, using an IL-1 receptor antagonist (IL-1ra), have resulted in improved survival [19,20], supporting the important role of this cytokine in the pathogenesis of septic shock. It is frustrating, however, that clinical studies have failed to show any positive benefit in outcome [21].

IL-6

This 185-residue protein is released largely under the influence of TNF-α and IL-1. It is involved in stimulating the release of acute-phase proteins, such as C-reactive protein (CRP) by the liver, and is thus frequently present in the serum of patients with septic shock. IL-6 levels

correlate more closely than other cytokines with the severity and outcome of septic shock [22], and IL-6 levels have thus been suggested as a possible indicator of the sepsis response.

IL-8
This small 8-kDa cytokine is again released predominantly on stimulation by TNF-α and IL-1. Its major role is in the recruitment and activation of leukocytes, and it may be of particular importance in mediating local organ dysfunction, such as that seen in acute respiratory distress syndrome (ARDS).

Granulocyte-colony stimulating factor
Granulocyte-colony stimulating factor is primarily responsible for the proliferation, differentiation, and activation of lymphocytes. While generally promoting ongoing inflammation, this can have anti-inflammatory effects in patients with neutropenia [23].

Anti-inflammatory cytokines
Alongside the proinflammatory cytokines, anti-inflammatory cytokines are released. These include:

IL-10
This could be said to be the 'perfect' anti-inflammatory cytokine because in macrophages stimulated by endotoxin, IL-10 inhibits the release of TNF, IL-1 and IL-6 [24]. In animal models, IL-10 administration prevents the mortality associated with sepsis [25].

TNF receptors
Soluble forms of TNF receptor are present in septic patients and bind to TNF, thus acting to limit TNF activity.

IL-1ra
This competitive inhibitor of the IL-1 receptor is produced by sepsis-activated monocytes and polymorphonuclear cells, and acts to reduce the proinflammatory effects of IL-1.

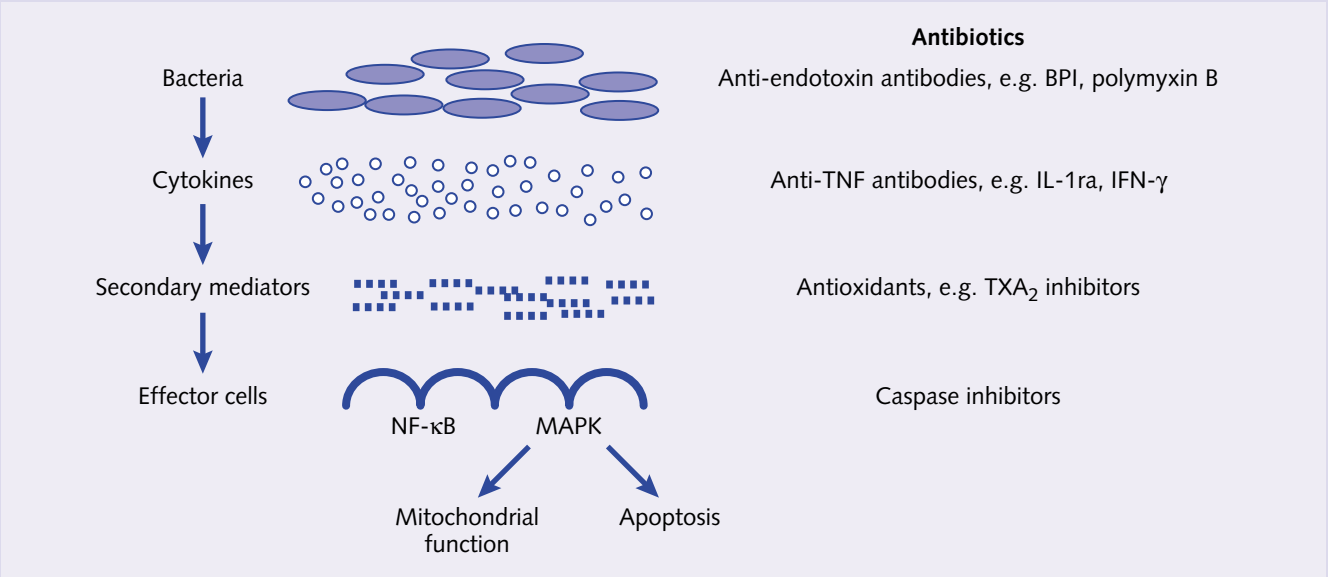
Other mediators
Coagulation system
Perhaps one of the most exciting areas of current research in the field of sepsis, activation of the coagulation system, is a key feature in the pathogenesis of septic shock. Tissue factor, exposed on the surface of endothelial cells after stimulation by endotoxin or certain proinflammatory mediators including IL-1, TNF, and platelet-activating factor (PAF) [26,27], activates the extrinsic coagulation pathway, resulting in the release of thrombin and the conversion of fibrinogen to fibrin. Inhibitory mechanisms of coagulation are simultaneously downregulated with a resultant procoagulant state. A recombinant human version of Activated Protein C (drotrecogin alfa [activated]), an endogenous protein that promotes fibrinolysis and inhibits thrombin production, has recently been shown to reduce the relative risk of death by 19% in a randomized clinical trial involving 1690 patients with severe sepsis [28]. Trials with tissue factor pathway inhibitor have also given encouraging results, and a Phase 3 study is ongoing.

Complement system
Bacterial products, including endotoxin, can activate the classical and alternative complement pathways — an important part of the normal host defense mechanism aimed at facilitating bacterial clearance. However, complement activation causes an increased release of IL-1 and TNF, and other inflammatory mediators, thus sustaining the sepsis response. C5a is perhaps one of the more important complement factors in the pathogenesis of sepsis, stimulating the adhesion and degranulation of polymorphonuclear lymphocytes. Degranulation results in the release of reactive oxygen species and proteases causing endothelial damage. This sequence is seen particularly in the lung and could be of importance to the pathogenesis of ARDS. In animal models, anti-C5a agents improve survival [29].

Contact system
The contact system is activated by various factors during sepsis, including endotoxin-stimulated Factor XII. The resultant conversion of prekallikrein to kallikrein and subsequent cleavage of kininogen to release bradykinin has been implicated in the hypotension seen in septic shock, since bradykinin is a potent vasodilator. A randomized trial of a bradykinin antagonist, although suggesting a possible improvement in survival in the subgroup of patients with Gram-negative septic shock, however, showed no significant effect on overall 28-day mortality rates [30].

PAF
Produced by the degradation of membrane phospholipids from various cells, PAF stimulates G-protein coupled receptors to activate phospholipases. PAF is a potent vasodilator in most vascular beds, but causes vasoconstriction in the pulmonary, renal, and coronary beds. In addition, PAF increases vascular permeability, and stimulates platelet aggregation and activation with the release of histamine and serotonin. PAF also encourages

Figure 1. Possible sites in sepsis at which immunomodulatory interventions could be targeted.



BPI: bactericidal permeability-increasing protein; IFN: interferon; IL-1ra: interleukin-1 receptor antagonist; MAPK: mitogen-activated protein kinase; NF: nuclear factor; TNF: tumour necrosis factor; TXA_2: thromboxane A_2.

neutrophil aggregation, and degranulation with the release of leukotrienes and the production of superoxide. It has been implicated in the hypotension and myocardial depression of septic shock, and a recent trial suggests a decreased incidence of organ dysfunction in septic patients treated with a PAF antagonist, although no improvement in outcome was noted [31].

Arachidonic acid metabolites

Arachidonic acid is released from cellular phospholipids and enters either the cyclooxygenase pathway, resulting in the formation of prostaglandins (PG) or thromboxane (TX), or the lipoxygenase pathway, resulting in the formation of leukotrienes. Also termed eicosanoids, these locally acting metabolites are potent agents with various functions in different organs. PGE_2 is a vasodilator and may thus contribute to the hypotension seen in septic shock, but it also inhibits platelet aggregation, and as such may have a protective effect on capillary patency. TXA_2 causes vasoconstriction in the pulmonary vasculature and induces platelet aggregation. Leukotriene B_4 is a potent chemotactic and activating agent for polymorphonuclear neutrophils (PMNs), resulting in the production of superoxide.

Reactive oxygen species

Reactive oxygen species (ROS) are produced by various mechanisms during sepsis, including PMN degranulation and eicosanoid metabolism. ROS cause cell membrane damage by degrading lipids and proteins, including DNA. In the erythrocyte, this can result in red cell deformation, encouraging microcirculatory perfusion deficits. In the endothelium, ROS-induced increased permeability promotes edema formation.

Nitric oxide

Nitric oxide (NO) is produced in large amounts during sepsis by stimulation of inducible NO synthase and clearly has both protective and potentially harmful effects during septic shock [32]. NO has been implicated in the hypotension and myocardial depression of sepsis. NO combines with superoxide to form peroxynitrate, which has toxic effects, including inhibiting mitochondrial respiration. However, by combining with ROS, NO may protect against ROS-induced cellular damage.

The septic response: Friend or foe?

The production and release of the proinflammatory mediators discussed above is an essential mechanism evolved to protect the body against an invading microorganism. However, in septic shock, this mechanism is clearly no longer beneficial to the patient. In fact, there exists an 'inflammatory' balance, with an excessive proinflammatory response tipping the scales in favor of severe circulatory failure and multiple organ failure, and an insufficient inflammatory response resulting in immunosuppression. The position at which the scales rest

is critical to the patient. This is also an important factor for the physician, as it may determine which treatment should be given. For example, a patient with a predominantly proinflammatory reaction may benefit from anti-inflammatory therapies, for example, anti-TNF-antibodies, to restore the balance, while a patient with a predominant anti-inflammatory reaction may be more likely to respond to an immune stimulatory treatment, for example, interferon-γ [33]. Importantly, cellular responses appear to be deactivated early in sepsis, such that a patient may already be in a state of so-called immunoparalysis on admission [34]. Strategies to evaluate the degree of immune activation need to be developed to enable potential new immunomodulatory therapies to be appropriately targeted.

Conclusion

In this brief review, we have discussed the basic events associated with the development of septic shock and some of the key mediators involved. The potential for immunomodulation is vast, with multiple possible sites to target (Fig. 1). Great advances have been, and are being, made in this field and all intensivists are excited that, finally, we seem to be seeing positive results from clinical trials using immunomodulatory therapies. After many years of discouraging results, we are at the edge of a new era in sepsis management, and able to offer our septic patients a brighter prognosis.

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