Fever, Cytokines and Shock

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SUMMARY

Septic shock is a complex event with activation of many inflammatory pathways. Recent advances have begun to make some sense of the pathophysiological events. This review describes the historical background to the contemporary concepts and outlines the important role that cytokines probably have in the pathophysiology of septic shock.

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consequence of the changing understanding of septic shock is that new therapeutic interventions are becoming available.

**INTRODUCTION**

'Humanity has but three great enemies: fever, famine and war. Of these, by far the greatest, by far the most terrible, is fever'. Sir William Osler

This review will discuss the history of, and recent advances in, septic shock, an area which has seen major advances over the past few years which may soon lead to novel therapeutic measures.

In 1899 a young patient developed Gram-negative bacteraemia and died.\(^1\) This, probably the first reported case of Gram-negative septic shock\(^2\) had many of the features later recognised as typical of the syndrome. The condition was due to a Gram-negative organism, occurred in a hospitalised patient and proved fatal. Research into septic shock built upon interest in fever, infection and cardiovascular physiology.

Measurements of body temperature became available with the development of the calibrated, sealed mercury thermometer.\(^3\) By 1798 James Curries had suggested the use of the thermometer in clinical medicine\(^4\) and thermometry became sufficiently established for David Livingstone to take a thermometer on his travels, noting his temperature rising to 103°F during 'African fever'.\(^5\) Non-invasive measurement of blood pressure became practicable with the development of the mercury-in-glass sphymomanometer.\(^6\) In spite of extensive clinical observation in fever and the interest in cardiovascular physiology, no relationship between infection and hypotension was noted until the end of the nineteenth century. Studies of Gram-negative infection in the pre-antibiotic era did not comment on the cardiovascular status of the patients although most of the features of what came to be known as 'septic shock' were noted.\(^7\)

With the advent of antibiotics Gram-negative septicaemia and septic shock became more common, from 1951 to 1958 Gram-negative septicaemia increased from 0.75/1,000 hospital admissions to 4/1,000 in a US teaching hospital.\(^8\) Waisbren\(^9\) recognised three different syndromes amongst patients with Gram-negative septicaemia, some remained well, some were hot, dry and flushed, normotensive, with bounding pulses, whilst others were cold, clammy, lethargic and hypotensive. These frequently confirmed presentations are now known as 'warm shock' and 'cold shock'.

Recent studies\(^2,10\) of the cardiovascular abnormalities in septic shock show then to be different from those found in shock produced by other means. Patients with septic shock fall into two groups, those with a hyperdynamic and those with a hypodynamic circulation. Differences in cardiac output are important, those presenting with a high cardiac output being more likely to survive. Low cardiac output is associated with acidosis, suggesting poor tissue perfusion.

The initial event following Gram-negative septicaemia is probably peripheral vasodilatation. During this phase the skin is warm and dry (warm shock). It is not clear whether warm shock and cold shock are separate responses to an infection or the ends of a spectrum of possible responses. The transition from warm shock to cold shock may be due to the development of myocardial failure, the cardiac index falls as the heart can no longer compensate for the low peripheral resistance;\(^2,11\) if the skin becomes cold and clammy, hypotension and failure of organ perfusion develops. Myocardial depression and the presence of circulating myocardial depressant substances have been demonstrated in experimental animals, following injections of lipopolysaccharide (LPS), and in man during septic shock. Areas of abnormal myocardial contraction have been demonstrated in the hearts of patients with septicaemia.\(^12,13,14\)

**Role of Lipopolysaccharide:** The suggestion that organisms released a toxic substance was made following observations of serious illness, including shock and death, in patients even though organisms in their blood were known not to be viable.\(^15,16\) The toxic component of these bacterial was shown to be LPS. The lethal effect of dead bacterial had first been demonstrated in 1885\(^17\) when dead typhoid bacilli were shown to cause fever and death. Welch suggested that microbial agents cause fever by causing releasing 'ferments', possibly from white cells, a remarkable prescient suggestion. Bacterial LPS was identified as a probable cause of septic shock since when given intravenously to experimental animals they induce a syndrome similar to that seen with natural infection.\(^18,19\)
LPS consists of lipid A, core polysaccharide and ‘O’ chain polysaccharides. The lipid A and core polysaccharides which are responsible for the toxic properties, are common to all Gram-negative organisms; the O chain polysaccharides confer the antigenic differences between LPS. LPS, an integral part of the cell wall is released into the surrounding medium when the bacterium disintegrates, therefore organisms may produce similar pathophysiological changes. The terms endotoxin and lipopolysaccharide are frequently used interchangeably.

The observation that antibodies against the LPS core have a protective effect against the severe effects of Gram-negative bacteraemia has lead to the development of polyclonal and monoclonal antibodies raised against the core part of LPS. These antibodies should theoretically be active against a wide range of Gram-negative organisms. Trials of polyclonal antisera, and more recently monoclonal antibody have shown a reduction in mortality in some documented Gram-negative infection and shock, although it is as yet unclear how useful these antibodies will be in the clinical situation.

Mediators of Lipopolysaccharide Toxicity: Cytokines: Recent work suggests that LPS itself is not the cause of the events associated with it, but initiates the release of endogenous mediators. In mice a simple mutation can confer resistance to the effects of LPS, sensitivity can be restored by bone marrow ablation and reconstitution with cells from sensitive mice suggesting that sensitivity is conferred by marrow derived cells, sensitivity can also be reconstituted by the transfer of macrophages. Macrophages are known to take up LPS and are involved in the release of mediators which are effectors of LPS induced toxicity.

Interleukin-1 (IL-1) and tumour necrosis factor (TNF), polypeptide cytokines which are known to be pyrogens, are released by macrophages after stimulation with LPS. Interleukin-1 was first described as ‘endogenous pyrogen’. Beeion showed that peritoneal exudate cells released a fever producing substance that was not LPS. Later studies showed that this substance could induce a fever in animals made tolerant to bacterial pyrogen, and that the property of fever induction in whole blood incubated with LPS resided in the white cells. Endogenous pyrogen has been shown to be the same substance as leucocytic endogenous mediator (LEM), a mediator, produced by white cells which initiates events of the acute phase response such as hypoferaemia. EP/LEM is now known as Interleukin-1 and is known to be a macrophage product. IL-1 has been purified and cloned and comprises two different molecules IL-1 and IL-β which have similar physiological actions. IL-1 is now known to be synthesised by a wide variety of cells. The biological effects are widespread and similar to those described to endogenous pyrogen. Recombinant IL-1 produces fever and stimulated prostaglandin synthesis. Many of the features of the acute phase response, synthesis of serum amyloid A, alpha-1 antitrypsin and neutrophilia are seen (see ref 29 for review).

In the late nineteenth century, following an observation that some patients with spontaneous regression from advanced cancers had had concurrent bacterial infections, Dr William Coley began to treat some of his patients with killed preparations of Gram-negative bacterial. Some of the patients made dramatic improvements and in 1934 the American Medical Association stated the Coley’s toxins were the only known systematic therapy for cancer. Serum from animals injected with LPS was shown to cause necrosis of tumours, this factor was further characterised and found to be a macrophage product. Meanwhile an endogenous cachexia producing factor (cachectin) had been identified in chronically infected rabbits. Subsequent purification, cloning and sequencing of TNF and cachectic showed that they are identical. TNF and IL-1 have similar properties as mediators of the inflammatory response.

IL-1 and TNF are involved in many of the phenomena associated with inflammation, which occur following LPS injection. LPS induces production of both of these cytokines and, macrophage released cytokines are though to be important in the pathophysiology of Gram-negative sepsis. TNF is released by macrophages upon stimulation by LPS, it is toxic in normal animals and produces pathology similar to that seen following septic shock. Neutralisation of TNF is elevated in man during severe infection, extremely high levels being reported in meningococcaemia, high levels being associated with poor outcome. A similar association has been shown in cerebral malaria.
Experimental animals infused with lethal numbers of Gram-negative organisms have high TNF levels. The evidence is such that TNF has been called the mediator of septic shock. However, TNF is unlikely to be the sole mediator involved. Evidence from germ free animals and on the synergistic interaction between cytokines, interferons and LPS suggest that other mediators are probably involved. IL-1 receptor blockade interferes with the effects of LPS, suggesting that TNF alone is not responsible for the development of septic shock. IL-1 has also been shown to be hypotensive.

The interactions between the cytokines and LPS as well as interactions with other bacterial products such as Staphylococcal toxic shock syndrome toxin-1 (TSST-1) are important in our understanding of clinical septic shock. Products of Gram-positive organisms are known to stimulate TNF production and to sensitize animals to the effects of LPS. The demonstration of synergy between LPS and TNF suggests that hypotension may develop in the presence of levels of these substances which alone would not be toxic.

Leukotrienes, Prostaglandins and PAF: LPS stimulates the release of a large number of vasoactive mediators which have a role to play in the pathogenesis of septic shock. Lipid-1 and the polysaccharide part of LPS activate complement by the classical and alternate pathways; C3a and C5b vasodialatory anaphylatoxins are released. Platelet activating factor (PAF) rises after LPS infusion and PAF antagonists prevent death in one model of endotoxin shock. Products of arachidonic acid metabolism via both the cyclo-oxygenase (prostaglandins) and lipoxygenase (leucotrienes) pathways appear in septic shock. Phospholipase A2 (PLA2) causes the release of arachidonic acid from membrane bound phospholipids; PLA2 is hypotensive in a rabbit model, PLA2 levels rise following injections of LPS and that there is a relationship between the levels of PLA2 and the fall in mean blood pressure. Pretreatment of the animals with systemic glucocorticoids prevents the rise in PLA2 following LPS and hypotension. Glucocorticoids are known to induce an inhibitor of PLA2 activity (lipocortin).

If TNF and IL-1 are proximal mediators of endotoxin shock they should activate these pathways which are believed to be involved in the pathogenesis of endotoxin shock, there is evidence that they do. TNF induces eicosanoid synthesis, and increases PLA2 activity. The involvement of the cytokines in the synthesis of products of arachidonic acid metabolism may explain the action of non-steroidal anti inflammatory agents in blocking the action of IL-1 and TNF.

The role of IL-1 and TNF in the normal response to infection is uncertain. There is evidence that fever is a beneficial adaptive response and that the other components of the acute phase response, such as hypoferraemia confer some protection against infection. Whilst it is unknown that IL-1 and TNF are endogenous pyrogens and trigger the acute phase response raised levels of these cytokines have not been demonstrated in patients with fever who are otherwise well.

The difference between the person who develops a fever and remains cardiovascularly normal and the person who develops septic shock is terms of their levels of LPS, IL-1 and TNF remains uncertain, although detectable of any of these are associated with the development of shock. Prospective studies of the levels of cytokines in patients at risk of developing septic shock, in conjunction with trials of anticytokine therapy have started.

CONCLUSION

The developing understanding of the roles of the cytokines, in particular TNF and IL-1 in the pathogenesis of septic shock helps to explain why a wide variety of stimuli can produce a similar final pathway. The complex response of interacting cytokines released following infection or exposure to bacterial products is a potential area for therapeutic intervention. Septic shock is a severe condition with high mortality and it is likely that antibodies to these mediators as well as anti-LPS antibodies will become important in the treatment of septic shock in the near future.

REFERENCES


