

# Shock: A Review of Pathophysiology and Management. Part II

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## ABSTRACT

**Objective:** To review pathophysiology and management of hypovolaemic, cardiogenic and septic shock in a two part presentation.

**Data sources:** Articles and published peer-review abstracts and a review of studies reported from 1994 to 1998 and identified through a MEDLINE search of the English language literature on septic shock, cardiogenic shock and hypovolaemic shock.

**Summary of review:** The pathophysiological effects of cardiogenic and hypovolaemic shock are related predominantly to a reduction in preload and myocardial contractility, respectively, whereas the pathophysiological effects of septic shock result largely from the overwhelming production of inflammatory mediators. The excessive inflammatory response results in haemodynamic compromise and widespread tissue injury. While the understanding of the acute inflammatory reaction has improved, therapies to modulate the chemical mediators responsible for the organ dysfunction associated with this reaction have not altered mortality, and in some instances may have increased it. Treatment of septic shock is still largely supportive, using intravenous fluids and inotropic agents to provide adequate tissue perfusion while the infective lesion is managed with antibiotic therapy and surgical drainage of septic focus.

**Conclusions:** Septic shock is provoked by an excessive acute inflammatory response to an infection. Management of the shock is supportive using fluids and inotropic agents, while antibiotic therapy and surgical drainage of the septic focus take effect. Immunomodulation of the acute inflammatory response causing septic shock has not improved mortality. (**Critical Care and Resuscitation 2000; 2: 66-84**)

**Key Words:** Shock, distributive shock, septic shock, sepsis, systemic inflammatory response syndrome

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Distributive shock is a name given to shock caused by the systemic inflammatory response syndrome, or shock provoked by the inhibition, or absence, of sympathetic tone (e.g. neurogenic shock).

The systemic inflammatory response syndrome (SIRS) is a clinical syndrome characterised by, but not limited to, two or more of the following:

1. a body temperature of  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$
2. a heart rate of  $> 90$  beats/min
3. respiratory rate  $> 20$  breaths/min or  $\text{PaCO}_2$  of  $< 32$  mmHg
4. a WBC count of  $> 12,000 /\text{mm}^3$  or  $< 4000 /\text{mm}^3$  or the presence of  $> 10\%$  immature neutrophils

and is caused by widespread inflammation due to infect-

ious (e.g. bacteria, fungi, viruses) and noninfectious (e.g. pancreatitis, multiple trauma, burns, infarction, biliary peritonitis, anaphylaxis) processes.

The definition of clinical syndromes due to infection include:<sup>1-5</sup>

- *sepsis* (i.e. SIRS caused by infection),
- *severe sepsis* (i.e. *sepsis* associated with organ dysfunction, hypoperfusion - including that which may be reflected by lactic acidosis, oliguria, altered mental status - or hypotension) and,
- *septic shock* (i.e. *sepsis* which is associated with hypotension and perfusion abnormalities despite adequate fluid resuscitation).

The differential diagnosis of septic shock, includes

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adrenal crisis, thyrotoxic crisis, delirium tremens, salicylate overdose, and malignant hyperpyrexia.

In this section the pathophysiology and management of septic shock will be presented.

#### CAUSES

Septic shock is usually provoked by exogenous agents (e.g. endotoxin, exotoxin, superantigens) leading to the excess production of endogenous inflammatory mediators. The mediators of septic shock are listed in Table 1.<sup>4,5</sup>

**Table 1. Mediators of septic shock**

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<i>Cytokines</i>
TNF- $\alpha$ , interleukins (e.g. IL-1, IL-6, IL-8) interferon- $\gamma$
<i>Platelet activating factor</i>
<i>Arachidonic acid metabolites (eicosanoids)</i>
prostaglandins (PGE <sub>2</sub> , PGI <sub>2</sub> ) leukotrienes (LB <sub>4</sub> , LC <sub>4</sub> , LD <sub>4</sub> , LE <sub>4</sub> ) thromboxanes (TxA <sub>2</sub> )
<i>Neutrophil-derived factors</i>
proteases: lysosomal enzymes, elastase, collagenase plasminogen activator free oxygen radicals
<i>Neuropeptides</i>
$\beta$ -endorphin, enkephalin
<i>Endothelium factors</i>
nitric oxide, endothelin-1
<i>Plasma proteases</i>
coagulation, fibrinolytic, kinins, complement
<i>Hormones</i>
glucagon, insulin, growth hormone, thyroxine, glucocorticoids
<i>Vasogenic amines</i>
histamine, serotonin, adrenaline, noradrenaline
<i>Other factors</i>
fibronectin depletion, myocardial depressant factors

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#### Exogenous agents

**Endotoxin.** Bacterial toxins are either actively secreted (i.e. exotoxins), such as those responsible for tetanus, botulism or diphtheria; or are released on destruction of bacteria (e.g. endotoxin). Both Gram-positive and Gram-negative bacteria release toxins on breakdown. The cell wall of all Gram-negative bacteria contain a toxin known as endotoxin. The toxins released from Gram-positive bacterial destruction reside within

the cell protoplasm, largely as teichoic acids. The cell wall of Gram-positive bacteria is non toxic. Endotoxin is the lipopolysaccharide outer coat of Gram-negative organisms and consists of three main parts:<sup>6</sup>

- an outer branched chain polysaccharide portion (i.e. the O antigen),
- a mid portion R antigen polysaccharide core, and
- an inner toxic lipid A portion that is normally attached to the cell membrane of the bacterium (i.e. is concealed and therefore has low antigenicity).

The inner Lipid A portion is similar for many pathogenic Gram-negative bacteria and accounts for the majority of the toxicity of endotoxin. If the patient develops Gram-negative bacteraemia and possesses the appropriate IgM or IgG antibodies to the many possible O or R antigens of the outer and mid portion of the lipopolysaccharide coat, the opsonisation and phagocytosis of invading organisms will be sufficient to prevent the bacterium releasing lipid A. Endotoxaemia only occurs if there is disruption of the bacterium by complement or large doses of bactericidal antibiotics.<sup>7</sup> Levels of antibody to lipid A are normally very low, and removal of Lipid A occurs as a slow inactivation by  $\alpha$ -1-lipoprotein esterase, and reticuloendothelial system (RES) removal of platelet-bound and high density lipoprotein bound lipid A.<sup>8</sup> The limulus test has been used to assay endotoxin. However, its lack of sensitivity and specificity (i.e. numerous false positive and false negative results), has rendered the test of little clinical value.<sup>9</sup>

Endotoxin exerts its effects by binding to an acute phase reactant called lipopolysaccharide binding protein (LBP). This complex attaches to the host cell membrane CD14 receptor (which lacks an intracellular signaling domain), engages with, and activates, the Toll-like receptor 2 (which serves as a transmembrane signaling receptor) to activate a series of intracellular reactions.<sup>10</sup> Gram-positive bacteria (due to soluble peptidoglycan and lipoteichoic acid<sup>11</sup>) are also recognised by Toll-like receptor 2.<sup>12</sup> The intracellular response leads to transcription and release of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), interleukin-6, and platelet-activating factor (PAF) from macrophages and monocytes. Complement and the coagulation cascade are activated directly, all of which are necessary for an effective host defence but which may also lead to shock or death.<sup>4,5</sup>

Endotoxin is the most potent stimulus of TNF- $\alpha$  production known. After endotoxin is injected intravenously, TNF- $\alpha$  appears in the circulation within minutes, reaches a peak in 2 hr, and then rapidly declines. Plasma levels of IL-1 rise 3-4 hr after endotoxin injection and remain elevated for 24 hr.<sup>13</sup>

**Chemical mediators**

**Cytokines.** At low concentrations, cytokines (e.g. TNF- $\alpha$ , IL-1) are important 'communication proteins' which are essential for cell-to-cell signalling, transmitting information by binding to specific transmembrane receptors to regulate immunologic and physiologic events.<sup>14</sup> IL-1 and TNF- $\alpha$  mediate local phagocytic cell emigration and activation and release of lipid derived mediators (e.g. PGE<sub>2</sub>, thromboxane, PAF). IL-1 induces interleukin-8 (IL-8) synthesis, which in turn is a potent neutrophil and monocyte chemotactic factor and stimulates the release of enzymes from neutrophils. While the acute changes in hepatic protein synthesis (i.e. the acute phase response) can be induced by IL-1 and TNF- $\alpha$ , it is thought to be caused largely by interleukin-6 (IL-6).<sup>15</sup> TNF- $\alpha$ , IL-1, and IL-6 stimulate their own secretion; both TNF- $\alpha$  and IL-1 stimulate the secretion of IL-6, whereas IL-6 inhibits both IL-1 and TNF- $\alpha$  secretion.<sup>16</sup>

At higher concentrations the proinflammatory cytokines (e.g. TNF- $\alpha$ , IL-1, IL-6, IL-8, interferon- $\gamma$ ) can exert potentially harmful biologic effects, ranging from tissue and organ dysfunction to a life threatening systemic reaction. Low concentrations of the counter-regulatory cytokines, for example interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-11 (IL-11) and interleukin-13 (IL-13) may also be detrimental.

**Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ):** TNF- $\alpha$  (or cachectin)<sup>17</sup> is a macrophage polypeptide hormone (that can also be produced by glial cells, Kupffer cells, mast cells, and natural killer T and B lymphocytes<sup>18</sup>) which binds with high affinity to muscle cells and adipocytes. Serum levels of TNF- $\alpha$  are usually undetectable during health and are increased during sepsis and critical illness by the many endogenous and exogenous stimulating factors produced by bacteria, viruses, tumours and cell damage.

TNF- $\alpha$  binds to at least two distinct membrane-associated receptors (i.e. TNF-R1 and TNF-R2) and TNF-binding proteins (i.e. soluble TNF receptors) and,

- induces release of IL-1, IL-6, IL-8 (which attracts and activates neutrophils), PAF, and the eicosanoids (i.e. leukotrienes, thromboxane A<sub>2</sub>, prostaglandins) by neutrophil and endothelial cells, and may even promote its own release,
- increases expression of the endothelial surface glycoproteins,<sup>19,20</sup> i.e.;
  - selectins (a group of structurally related glycoproteins that utilize protein-carbohydrate interaction to mediate cell adhesion and are important in the early transient neutrophil/endothelial adhesion phase, or 'rolling' phase, during inflammation),

- integrins (e.g. lymphocyte-function-associated-antigen-1 or LFA-1) and immunoglobulin superfamily (e.g. intracellular adhesion molecule 1 or ICAM-1, vascular cell adhesion molecule or VCAM) a family of glycoprotein cell surface adhesion receptors important in the neutrophil/endothelial adhesion phase of 'firm adherence' leading to enhanced adherence of neutrophils to the endothelium, and
- platelet endothelial-cell-adhesion molecule-1 or PECAM-1 (important in neutrophil transmigration),
- enhances polymorphonuclear leucocyte activity by stimulating phagocytic activity (it has only a weak effect on T cells),
- is directly toxic to endothelial cells, increasing capillary permeability, activating kinin and complement cascades, causing disseminated intravascular coagulation (DIC) and haemorrhagic necrosis, which in turn leads to gastrointestinal haemorrhage, acute renal failure, acute respiratory distress syndrome (ARDS) as well as cardiac failure (i.e. TNF- $\alpha$  has a negative inotropic action<sup>21</sup>) hepatic abnormalities, and pulmonary dysfunction,<sup>22</sup>
- induces fever through a direct effect on hypothalamic neurones and through IL-1 production, and,
- inhibits lipoprotein lipase activity reducing plasma clearance of lipids.

TNF- $\alpha$  is the first cytokine to appear in the circulation after experimental and clinical endotoxaemia (detected after 45 min, peaking after 90 min)<sup>23</sup> and, in man, has a half life of 20 min,<sup>18,24,25</sup> which increases in the absence of corticosteroids (e.g. up to 4 - 8 h in adrenalectomized animals<sup>18</sup>).

Recent studies indicate that the overstimulation of TNF- $\alpha$  biosynthesis in septicaemia is a critical step in triggering SIRS and causing septic shock and multiple organ dysfunction syndrome in septic patients, as mice, rabbits and baboons, immunised against TNF- $\alpha$  or treated with polyclonal antiserum directed against TNF- $\alpha$  are protected against the lethal effect of endotoxin.<sup>22</sup> Corticosteroids given before (but not after) an endotoxin infusion will inhibit TNF- $\alpha$  biosynthesis.

**Interleukin-1 (IL-1).** The IL-1 family consists of three structurally related polypeptides, two agonists (interleukin-1 $\alpha$  and interleukin-1 $\beta$ ) and an antagonist (interleukin-1-receptor antagonist).<sup>26</sup> While interleukin-1 $\alpha$  and interleukin-1 $\beta$  have different amino acid sequences, they are structurally related, and act through the same cell-surface receptors (i.e. share biologic activities).<sup>26</sup> Both interleukin-1 $\alpha$  and interleukin-1 $\beta$  are produced by monocytic phagocytes (e.g. monocytes,

tissue macrophages, phagocytic lining cells of the liver and spleen). Nearly all infections, immunologic reactions and inflammatory processes stimulate monocyte phagocytes to synthesise and liberate IL-1 into the circulation,<sup>27</sup> which,

- induces release of TNF- $\alpha$ , IL-6, IL-8, PAF, and the eicosanoids (i.e. leukotrienes, thromboxane A<sub>2</sub>, prostaglandins) by neutrophil and endothelial cells, and may even promote its own release,
- activates T lymphocytes, is chemotactic for T cells, and stimulates lymphocyte B-cell proliferation and antibody production,
- acts with TNF- $\alpha$  to promote adhesion of endothelial cells, polymorphonuclear cells, eosinophils, basophils, and monocytes,
- induces fever, by stimulating synthesis of prostaglandin E<sub>2</sub> in the anterior hypothalamus to elevate the hypothalamic temperature set level,
- increases the release of circulating neutrophils from the bone marrow and is chemotactic for neutrophils,
- increases hepatic production of acute phase reactants (e.g. complement, haptoglobin, ceruloplasmin, fibrinogen, plasminogen, C-reactive protein) and reduces albumin, prealbumin and transferrin production,
- increases skeletal muscle catabolism (by increasing prostaglandin E<sub>2</sub> production) and liberates amino acids for hepatic protein and inflammatory tissue production,
- induces slow-wave sleep, and
- reduces serum Fe and Zn.

The action of IL-1 is regulated through a cell membrane receptor, which has a natural inhibitor known as IL-1ra (interleukin-1 receptor antagonist) which inhibits the hypotension and leucocytosis induced by IL-1, and increases survival of animals injected with endotoxin.<sup>13</sup> Corticosteroids reduce the production of IL-1.

IL-1 and TNF- $\alpha$  are different compounds with similar biological actions (although IL-1 does not cause DIC or neutropenia, c.f. TNF- $\alpha$ ). During the inflammatory response they always appear together and always act synergistically.

**Arachidonic acid metabolites (eicosanoids).** The eicosanoids are a class of endogenous mediators derived from 20-carbon unsaturated fatty acid precursors, primarily eicosatetraenoic acid (arachidonic acid). Following the release of arachidonic acid from tissue stores (due to the action of phospholipase A<sub>2</sub> on phospholipid in cell membranes), it is transformed by the action of either cyclooxygenase (present in all cell

walls) into unstable endoperoxidases (PGG<sub>2</sub> PGH<sub>2</sub>) and then into a variety of vasoactive substances including prostaglandins (PGD<sub>2</sub> PGE<sub>2</sub> PGF<sub>2</sub> PGI<sub>2</sub>) and thromboxane (TXA<sub>2</sub>); or 5-lipoxygenase (found only in myeloid cells, i.e. monocytes, eosinophils, basophils, alveolar macrophages, and mast cells) in the presence of a nuclear membrane cofactor (5-lipoxygenase-activating protein or FLAP), to generate an unstable intermediate, 5-hydroperoxyl-eicosatetraenoic acid (5-HPETE). The latter converts to the unstable leukotriene A<sub>4</sub> (LTA<sub>4</sub>) which is rapidly converted to either LTB<sub>4</sub> or LTC<sub>4</sub>, the latter of which is transported extracellularly to be converted to LTD<sub>4</sub> and finally to LTE<sub>4</sub> (Figure 1). These compounds can increase vascular permeability, increase mucus secretion and can cause bronchospasm.<sup>28</sup>

Elevated levels of prostacyclin (PGI<sub>2</sub>) occur 1-6 hr after the onset of septic shock and causes vasodilation, inhibits platelet activation, and disperses platelet aggregates. Prostaglandin-E<sub>2</sub> (PGE<sub>2</sub>) dilates bronchi and blood vessels while prostaglandin-F<sub>2 $\alpha$</sub>  (PGF<sub>2 $\alpha$</sub> ) constricts them. Thromboxane (TXA<sub>2</sub>) is a potent vasoconstrictor.<sup>29</sup>

**Platelet activating factor (PAF).** Platelet activating factor is a potent phospholipid mediator that leads to amplification of cytokine release. It causes vasoconstriction and bronchoconstriction, but in very low doses induces vasodilation and increased venular permeability with a potency 100-10 000 times greater than histamine. It also causes increased leukocyte adhesion to the endothelium (by enhancing integrin binding), chemotaxis, degranulation and oxidative 'bursts' (i.e. all of the cardinal features of acute inflammation).<sup>30</sup> The chemical structure of PAF is acetyl-glycerol-ether-phosphorylcholine. It mediates its effects by a single G protein-coupled receptor, and its effects are regulated by a family of inactivating PAF acetylhydrolases.

**Neutrophil derived factors.** The neutrophil derived factors released during shock consist of:

**Lysosomal enzymes and neutrophil proteases:** these are proteolytic enzymes released from monocytes and polymorphonuclear leucocytes. In the presence of hypoxia and acidosis these enzymes destroy structural proteins, and activate coagulation, complement and kinase systems and can cause myocardial depression and coronary vasoconstriction.

**Free oxygen radicals:** superoxide and other free oxygen radicals released by aggregated leucocytes have been implicated in damaging endothelium and producing increase in capillary permeability and capillary disruption.

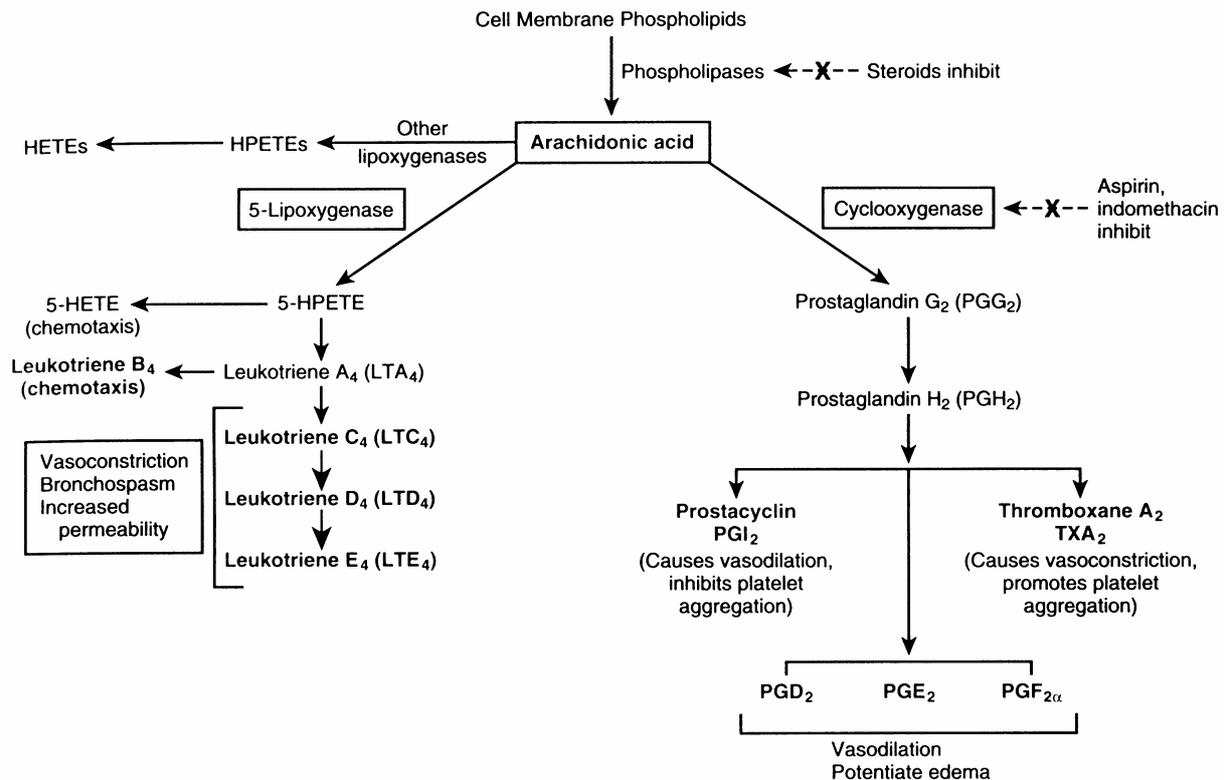


Figure 1. Arachidonic acid metabolites and their role in inflammation.

**Neuropeptides (e.g. endorphins).**  $\beta$ -endorphin and adrenocorticotrophic hormone (ACTH) are derived from the common precursor pro-opiomelanocortin and are released in equimolar amounts from the anterior pituitary in response to stress or endotoxin. It is thought that pituitary endorphins enter the central nervous system to react with specific opiate receptors, to enhance vagal-cholinergic tone, reducing cardiac output and mean arterial blood pressure.<sup>31</sup> It has been suggested, however, that at least part of the effect involves alteration of the efferent sympathetic nervous system.<sup>32</sup>

#### Endothelial factors

**Nitric oxide.** Nitric oxide is thought to be the mediator largely responsible for the sustained vasodilation in septic shock.<sup>33,34</sup> It is also thought to be the mediator responsible largely for reduced myocardial contractility,<sup>35</sup> hepatic damage, microvascular hyperpermeability and intestinal barrier dysfunction in septic shock.<sup>36</sup> Endotoxin and other proinflammatory agents induce a release of PAF, TNF- $\alpha$ , IL-1, and interferon-gamma, and enhance the synthesis of nitric oxide by endothelial constitutive nitric oxide synthase (in the early phase of septic shock) and vascular smooth muscle cell inducible nitric oxide synthase (in the later phase of septic shock).<sup>37</sup>

**Endothelin-1.** Endothelin-1 is a 21 amino acid peptide which is synthesised de novo by the endothelium, from preproendothelin-1, which undergoes an initial processing to form the 38 amino acid peptide, proendothelin-1, which is in turn cleaved by an endothelin converting enzyme (ECE), forming endothelin-1.<sup>38</sup> Endothelin-1 acts on surface receptors of vascular smooth muscle (endothelin A receptor) activating phospholipase C and producing the secondary messengers inositol 1,4,5-triphosphate (which releases Ca<sup>2+</sup> from the sarcoplasmic reticulum) and diacylglycerol (which activates protein kinase C), causing contraction of the smooth muscle cell.<sup>38</sup> In addition, endothelin-1 potentiates the effects of other vasoconstrictor hormones (e.g. noradrenaline, serotonin) and stimulates proliferation of smooth muscle cells. It is usually produced in response to hypoxia, ischaemia and shear stress.<sup>39</sup>

**Plasma proteases (e.g. kinin, coagulation and complement activation).** The activation of pre-kallikrein forms proteolytic enzymes of bradykinin, causing peripheral vasodilation, myocardial depression, DIC, complement activation and increased capillary permeability.

**Vasogenic amines.** Histamine released from mast cells in response to complement activation, increases capillary permeability and vasodilation. Serotonin (which is also released) causes arteriolar vasoconstriction.

#### Other factors

**Fibronectin.** Depletion of this opsonic glycoprotein occurs in septic shock, reducing the ability of the reticuloendothelial system to remove protein particulate matter from the circulation, causing prolongation of sepsis and DIC.

**Myocardial depressant factor.** Early studies concluded that up to 9 polypeptides with molecular weights ranging between 250-1000 were released from lysosomal enzyme fragmentation of cellular proteins of the gastrointestinal tract and pancreas, to appear in the plasma of patients who had splanchnic ischaemia and were responsible for the myocardial depression associated with shock.<sup>40</sup> Subsequently the myocardial depressant factor was found to be due to the synergistic effect of TNF- $\alpha$  and IL-1,<sup>41,42</sup> (via a nitric oxide mediated mechanism).<sup>43</sup>

#### CLINICAL FEATURES

The clinical features of septic shock include those features that are characteristic of the underlying disorder (e.g. peritonitis, pyelonephritis, pneumonia, etc.) as well as the features included in the definition of shock and the systemic inflammatory response syndrome.

#### Cardiorespiratory changes of septic shock

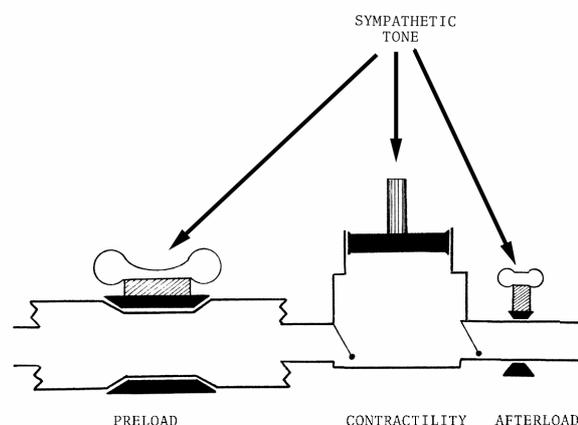
**Vascular changes.** The vascular response is usually characterised by:

1. an early vasodilated phase (i.e. warm shock), with warm extremities, low systemic resistance, high or normal cardiac output, normal or low blood pressure and increased pulse pressure. Some studies have shown that nutrient capillary blood flow during this phase is often greater than normal,<sup>44</sup> and that the defect may be an inability to extract and utilise the oxygen and substrate delivered to the cells.<sup>45</sup> There is also an increase in capillary permeability with loss of fluid from the vascular to the interstitial space (normally albumin leaves the circulation at 8% per hour, in septic patients albumin leaves the circulation at 20% per hour<sup>46</sup>).

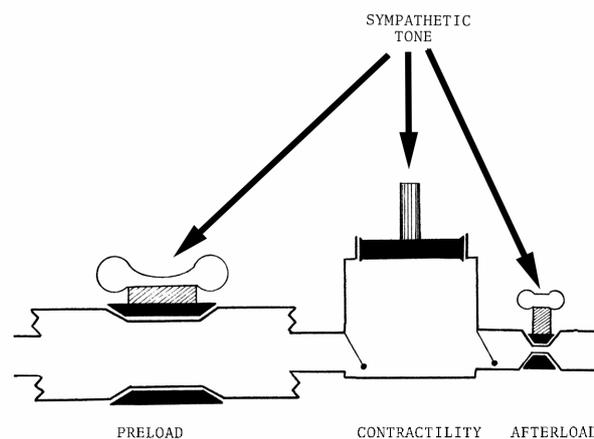
The haemodynamic defect during this phase is caused by peripheral vasodilation and a loss of intravascular fluid (Figure 2).

2. a later vasoconstricted phase (i.e. cold shock), with cold extremities, hypotension, small pulse pressure, low cardiac output and normal or high systemic resistance. The haemodynamic defect during this phase is caused by a reduction in myocardial

contractility, loss of intravascular fluid and peripheral vasoconstriction (Figure 3).



**Figure 2.** A model characterising the early haemodynamic changes found in septic shock, with a reduction in intravascular volume (preload), contractility, and peripheral resistance (afterload), with an overall increase in sympathetic tone (c.f. Figure 1 part I).



**Figure 3.** A model characterising the late haemodynamic changes found in septic shock, with a reduction in contractility, intravascular volume (preload), and increase in peripheral resistance (afterload), with an overall increase in sympathetic tone.

**Myocardial changes.** Myocardial depression associated with septic shock is manifest by ventricular dilation and reduction in the ejection fraction (a reduction in ventricular compliance may also occur<sup>47</sup>), which is completely reversible 7-10 days after the episode of septic shock has resolved.<sup>48,49</sup> The myocardial defect is not caused by a reduction in coronary perfusion,<sup>50</sup> or the associated metabolic derangement (e.g. changes in pH, nutrient or oxygen availability<sup>51</sup>), and is believed to be caused by endogenously produced circulating myocardial toxic factors<sup>52,53</sup>

TNF- $\alpha$  depresses myocardial function and may play a key role in directly producing the myocardial depression in septic shock.<sup>54</sup> In isolation, IL-1 does not depress myocardial function whereas IL-2 and endotoxin do.<sup>55</sup> In one study, intravenous endotoxin in normal subjects caused an increase in plasma TNF- $\alpha$  levels after 1 hr, which then returned to normal before a progressive depression of myocardial contractility occurred, indicating that either TNF- $\alpha$  had a delayed effect on cardiac function or other cardiovascular depressant mediators were produced following the endotoxaemia.<sup>55</sup> The vasodilation and reduction in cardiac contractility caused by TNF- $\alpha$  may be caused by an associated increase in intracellular cGMP<sup>56</sup> (caused by TNF- $\alpha$  activation of inducible nitric oxide synthase, increasing nitric oxide production which in turn increases intracellular cGMP<sup>57</sup>). Downregulation or dysfunction of  $\beta$ -adrenergic receptors may also be responsible for some of the haemodynamic effects associated with sepsis.<sup>58-60</sup>

Currently it is believed that the myocardial depression is predominantly due to the synergistic effect of TNF- $\alpha$  and IL-1, via a nitric oxide mediated mechanism.<sup>41-43</sup>

#### Oxygen utilisation in septic shock

A reduction in peripheral oxygen extraction has been reported in septic shock where an otherwise more than adequate oxygen supply exists.<sup>61</sup> Some studies have also demonstrated that an increase in oxygen delivery is associated with an improvement in tissue oxygen extraction, indicating that oxygen consumption may be delivery-dependent in patients with septic shock.<sup>62,63</sup> The oxygen extraction defect has been suggested to be due to either an elevation in the anaerobic threshold of oxygen delivery or peripheral AV shunting.<sup>61</sup>

Other studies, however, have failed to demonstrate the cardiac output dependent oxygen extraction in sepsis and believe that the increase in oxygen extraction with increase in oxygen delivery may be due to an increase in myocardial oxygen extraction with increase in cardiac output<sup>64</sup> or is artifactual (e.g. due to mathematical coupling).<sup>65,66</sup> At comparable increases of cardiac index and oxygen delivery, there is no significant difference in the increase in oxygen consumption between hypovolaemic shock and septic shock patients,<sup>67</sup> supporting the experimental findings that the mitochondrial oxygen utilisation in septic shock is probably unaltered<sup>68</sup> and that the observation of a delivery dependent oxygen consumption in septic shock is probably artifactual.

#### INVESTIGATIONS

Apart from culturing various fluids (i.e. pus, blood sputum, urine, etc), investigations of patients with septic shock are largely centred on diagnosing the cause, (e.g. pneumonia, endocarditis, peritonitis, pyelonephritis, cholangitis, etc).

Elevation of acute phase reactants (e.g. C-reactive protein), proinflammatory cytokines (e.g. TNF- $\alpha$ , IL-1, IL-6), nitric oxide production markers (e.g. plasma methemoglobin, nitrite/nitrate concentrations<sup>69</sup>) and non-specific markers of septic shock (e.g. procalcitonin),<sup>70</sup> have been used to diagnose the presence and monitor the treatment of sepsis. However, they are of little help in diagnosing its cause. Moreover, many cytokines are released sporadically and have a very short plasma half-life (i.e. low sensitivity for the diagnosis of sepsis) with only IL-6 and IL-8 having any utility in the estimation of presence, severity and outcome of sepsis.<sup>71</sup>

#### TREATMENT

Management of septic shock usually includes treatment of the septic focus (e.g. drainage of abscess, antibiotics), management of the haemodynamic disorder and organ failures (e.g. renal failure, respiratory failure, hepatic failure, etc), with immunotherapy in experimental studies revealing the possibility of new treatments (Table 2).

#### Haemodynamic therapy

This commonly focuses upon methods to improve tissue perfusion, which may be achieved by optimising preload, contractility and afterload, although the correct circulatory distribution to each organ is the desired goal.

In the animal model, appropriate antibiotics and cardiovascular support have a synergistic effect in reducing the mortality associated with septic shock, although the effect of cardiovascular support is due largely to the intravenous fluid administered rather than the inotropic agent.<sup>72</sup>

**Preload.** In patients with septic shock there is an increased pulmonary capillary permeability and an increased risk of non cardiogenic pulmonary oedema if the PAoP is increased above 10 mmHg.<sup>73,74</sup> Thus, intravenous fluids (e.g. blood, or 0.9% saline solutions with or without colloid) are usually administered to achieve PAoP values up to 10 mmHg, and values greater than this are attempted with care.

**Contractility.** In clinical practice, following the replacement of an intravascular volume deficit, if the

**Table 2. Haemodynamic and immunotherapy used in the management of septic shock****Haemodynamic therapy***Preload*

Blood, colloids, crystalloids

*Contractility*

Catecholamines (adrenaline, noradrenaline, dobutamine, dopamine)

Digoxin

*Afterload*

Pressor sympathomimetics

(adrenaline, noradrenaline, dopamine, metaraminol, aramine)

Dilator sympathomimetics (isoprenaline)

NO synthase inhibitors (L-NMMA, L-NAME, L-NMA)

Other agents:

vasopressin

endothelin-1 inhibitors

bradykinin antagonists

ATP-MgCl<sub>2</sub>**Immunotherapy**

Anti-lipid A, endotoxin neutralising protein

Lipid A analogues, CD14 antibody

Cytokine inhibition or stimulation

(e.g. TNF- $\alpha$ , IL-1, IL-4, IL-6, IL-8, IL-10)

Platelet activating factor inhibition

Anti-adhesion molecules

G-CSF, interferon- $\gamma$ , immunoglobulin

Arachidonic acid metabolite inhibitors

Coagulation factors and coagulation factor inhibitors

Hormones

(e.g. glucocorticoids, glucagon, insulin, growth hormone, thyroxine, TRH)

Other therapy

Naloxone, oxpentifylline, N-acetylcysteine, fibronectin, plasmafiltration, plasmapheresis, adenosine, chloroquine, chlorpromazine, surfactant, dehydroepiandrosterone, hydrazine, oestrogen, pentamidine, thalidomide

patient is still hypotensive and the cardiac output and peripheral perfusion are judged insufficient, inotropic agents are often used. As coronary perfusion is not primarily reduced in septic shock<sup>50</sup> and down-regulation of the adrenergic receptors may be present,<sup>58</sup> any of the catecholamines (e.g. intravenous adrenaline, isoprenaline or noradrenaline from 2 - 20  $\mu$ g/min or dobutamine or dopamine from 2 - 20  $\mu$ g/kg/min) may be used to advantage. Digoxin (0.75 - 1.0 mg/70kg i.v.) may also be used,<sup>75</sup> particularly in the presence of cardiac dilation and atrial fibrillation.

**Afterload.** When inotropic agents are used, if the haemodynamic variables reveal a low systemic vascular resistance (due to increased synthesis of nitric oxide, activation of the vascular ATP-sensitive K<sup>+</sup> channel or vasopressin deficiency<sup>76</sup>), then inotropic agents with a peripheral vasoconstricting effect (e.g. adrenaline,<sup>77</sup> noradrenaline<sup>78</sup>) are often chosen. Likewise, if the peripheral vascular resistance is high, inotropic agents with vasodilating effects (e.g. isoprenaline) may be used.<sup>79</sup>

While therapy aims to improve peripheral perfusion (to improve cerebral, cardiac, renal, hepatic, and gastrointestinal function), as the predominant defect in septic shock is a vasomotor abnormality, treatment to alter this defect (e.g. nitric oxide synthase inhibitors, vasopressin, bradykinin antagonists, endothelin-1 antagonists, ATP-MgCl<sub>2</sub>) has been proposed.

**Nitric oxide synthase inhibitors:** As sepsis increases the activity of inducible nitric oxide synthase, the formation of the vasodilator nitric oxide from L-arginine is increased. The synthesis of nitric oxide can be inhibited by nitric oxide synthase inhibitors, for example N<sup>G</sup>-monomethyl-L-arginine (L-NMMA) or N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME), and both have been reported to reverse the peripheral vasodilation in patients with septic shock.<sup>80,81</sup> The use of these agents in septic shock, however, is still experimental as an increase in hepatic damage in endotoxin treated mice during L-NMMA administration has been reported,<sup>82,83</sup> and administration of nitric oxide synthase inhibitors in the experimental model reduces blood flow to most organs including brain, heart and kidney.<sup>37</sup> In one clinical report of two patients with unresponsive septic shock, prolonged infusions of L-NMMA (e.g. 27 - 72 hours) were associated with sudden death due to acute left ventricular failure.<sup>84</sup> A recent large randomised, placebo controlled, multicentred trial of the non-selective nitric oxide synthase inhibitor L- N<sup>G</sup>-methylarginine (NMA) hydrochloride for the treatment of patients with septic shock was terminated as it was associated with a significant increase in mortality.<sup>85,86</sup> Methylene blue (a potent guanylate cyclase inhibitor) has also been used to inhibit nitric oxide activity during sepsis,<sup>87</sup> causing a transient increase in arterial pressure and reduction in reduction in plasma lactate, although there was no measurable increase in cellular oxygen availability.<sup>88</sup>

Currently, nitric oxide synthase inhibitors cannot be recommended for the management of septic shock. However, nitric oxide scavengers (e.g. vitamin B<sub>12</sub>) to reduce the effect of nitric oxide production may be more useful. In the experimental model hydroxo-cobalamin

has been shown to reduce mortality associated with hypotensive endotoxemia.<sup>89</sup>

**Vasopressin:** Vasopressin causes vasoconstriction by stimulating the vascular V<sub>1</sub> receptors and deficiency of vasopressin has been described in patients in septic shock.<sup>90</sup> In these patients, an infusion of vasopressin at 0.04 u per minute increased the systolic blood pressure from 92 to 146 mmHg and at 0.01 u per minute increased the systolic blood pressure from 83 to 115 mmHg.<sup>90</sup> In another study of patients with septic shock, vasopressin at 0.04 u per minute increased the systolic blood pressure from 98 ± 5 mmHg to 125 ± 8 mmHg.<sup>91</sup> However, there are no prospective randomised trials to show a beneficial effect on mortality with vasopressin therapy in patients with septic shock.

**Bradykinin antagonists:** Bradykinin is a vasoactive peptide which acts on specific receptors (e.g. BK<sub>1</sub> and BK<sub>2</sub> receptors) to cause an increase in vascular permeability, vasodilation, pain and neurotransmitter release. The BK<sub>2</sub> receptor is present on most tissues throughout the body and modulates most of the actions of the kallikrein-kinin system. The BK<sub>2</sub> bradykinin antagonist, CP-0127, significantly increases survival in animal models of endotoxic shock.<sup>92</sup> However, one randomised double-blind placebo controlled trial of CP-0127 in patients with the systemic inflammatory response syndrome with either hypotension or dysfunction of two organ systems, revealed no significant effect on survival at 28 days, although, there was an improvement in survival in a subset of patients with Gram-negative infections.<sup>93</sup>

**Endothelin-1 antagonists:** Selective and nonselective endothelin receptor inhibitors, monoclonal antibodies to endothelin and endothelin converting enzyme inhibitors, have been developed as possible therapeutic agents for vasospastic diseases. However, there have been no studies that have shown benefit in using these agents in septic shock.<sup>94</sup>

**ATP-MgCl<sub>2</sub>:** Adenosine triphosphate complexed with magnesium chloride (ATP-MgCl<sub>2</sub>) has been used as a vasodilator and an energy source to improve survival in experimental shock,<sup>95</sup> although currently there are no studies which have demonstrated a clear benefit with the use this agent in patients with shock.

**Therapy to increase oxygen delivery.** Haemodynamic management of shock is usually directed to achieve a MAP between 60 - 80 mmHg and cardiac index > 2.5 L/min/m<sup>2</sup>. However, some authors believe that supernormal haemodynamic values are required to

reduce mortality in the critically ill patient (e.g.  $\dot{D}O_2 > 600$  mL/min/m<sup>2</sup>, in association with a cardiac index > 4.5 L/min/m<sup>2</sup> and a  $\dot{V}O_2 > 170$  mL/min/m<sup>2</sup>),<sup>96,97</sup> although, recent large prospective randomised, controlled clinical studies have demonstrated improved,<sup>98</sup> unchanged,<sup>99</sup> and decreased<sup>100</sup> survivals when volume expansion and inotropic agents were used in an attempt to achieve these therapeutic goals.

In the largest controlled study of critically ill patients, intravascular volume expansion, inotropic agents, and vasodilator agents were used to increase the cardiac index (in one group) to greater than 4.5 L/min/m<sup>2</sup>, or the mixed venous oxygen saturation to 70% or greater (in another group). Both therapeutic interventions were not associated with a reduction in mortality.<sup>99</sup>

Currently, supranormal haemodynamic goals are not recommended for the management of a patient with septic shock.

### Immunotherapy

**Anti-lipid A.** Anti-lipid A is an antitoxin and not an opsonin and will not aid in the resolution of the Gram-negative infection. Infusions of either human antiserum (i.e. polyclonal antibody) or E5 murine monoclonal antiendotoxin IgM antibody (2 mg/kg once daily for two days), both of which cross react with lipid A and lipopolysaccharide structures from a broad range of pathogenic Gram-negative organisms, have been reported to reduce mortality ranging from 23% - 40% to 12% - 30% and increase the rate of reversal of multiple organ failure (e.g. DIC, acute renal failure and ARDS) in patients with Gram-negative endotoxaemia without shock.<sup>101-104</sup> However, these initial results from subset analysis have not been confirmed, as a large prospective randomised controlled trial, showed that E5 had no effect on mortality in non-shocked patients with Gram-negative sepsis.<sup>105</sup>

In another study, the mortality in patients with Gram-negative bacteraemia and shock decreased from 57 to 33% by the use of a single 100 mg dose of HA-1A human monoclonal antiendotoxin IgM antibody.<sup>106</sup> However, no benefit was demonstrated in patients with sepsis who did not prove to have Gram-negative bacteraemia,<sup>106</sup> and an interim analysis of a double blind, placebo controlled trial of HA-1A has revealed that it may even increase the mortality in this group of patients.<sup>107</sup> In a large multicentered randomised, double-blind, placebo-controlled trial of HA-1A in patients with septic shock, HA-1A was not effective in reducing the 14 day mortality in patients with Gram-negative bacteraemia and septic shock,<sup>108</sup> and in a controlled trial of HA-1A in a canine model of Gram-negative septic shock, mortality was increased.<sup>109</sup>

The place of anti-lipid A therapy in patients who have Gram-negative sepsis, is at best not yet clear; therefore these agents should only be used in patients who are involved in clinical trials.<sup>110-112</sup>

**Endotoxin neutralizing protein.** A number of endogenous neutrophil proteins (e.g. bactericidal permeability-increasing protein) have a higher affinity for endotoxin than LBP and therefore compete with LBP for binding to endotoxin, neutralizing many of its adverse biological effects.<sup>113</sup> In a preliminary clinical study in children with severe meningococcaemia, the use of a recombinant amino-terminal fragment of human bactericidal permeability-increasing protein appeared to reduce mortality.<sup>114</sup>

Polymyxin B binds to lipopolysaccharide and has endotoxin neutralizing capacity<sup>113,115</sup> and extracorporeal removal of endotoxin from plasma by absorption to polymyxin B has been tried with some success in animal models,<sup>116</sup> and in clinical practice.<sup>117</sup>

**Lipid A analogues.** In animal models, monophosphoryl lipid A (MPL) if administered before Gram-negative sepsis, blocks the effects of endotoxin on macrophages, neutrophils and endothelial cells.<sup>113</sup> Clinical efficacy of MPL in patients with septic shock has not yet been demonstrated.

**CD14 antibody.** Inhibition of the endotoxin/LBP complex binding to cells using monoclonal antibodies to CD14 has been used experimentally to reduce macrophage and neutrophil responses to endotoxin. Soluble CD14 and CD14 antibodies have not yet undergone clinical trials.

**Proinflammatory cytokine inhibition.** While cytokine inhibition may be achieved by antibodies or inhibitors to the cytokine or cytokine receptor,<sup>14</sup> cytokines (e.g. TNF- $\alpha$  and IL-1) possess both pathogenic and protective roles and their inhibition may not benefit patients with septic shock.<sup>118</sup> Specific blockade of the proinflammatory cytokines IL-1 or TNF- $\alpha$ , by using antibodies to TNF- $\alpha$  or IL-1 receptors, have reduced the morbidity and mortality associated with experimental septic shock,<sup>13,14,119-121</sup> although, depending on the dose of the IL-1 receptor antagonist used, mortality associated with experimental infection may be either reduced or increased.<sup>122</sup>

In two recent randomized double-blind, placebo-controlled, multicenter trials of patients with severe sepsis (defined in both studies as 'sepsis syndrome'), statistically significant increases in survival in patients with or without shock, were not demonstrated in patients treated with either TNF- $\alpha$  antibody,<sup>123</sup> or with

recombinant IL-1 receptor antagonist.<sup>124</sup> In a randomised, double-blind, placebo-controlled, multicenter study of 141 patients with septic shock, an infusion of TNF-R2 receptor linked with the Fc portion of human IgG1 (neutralizing circulating TNF- $\alpha$ ) did not reduce mortality, and in high doses may have increased mortality.<sup>125</sup> In a similar trial infusing TNF-R1 receptor linked with Fc portion of human IgG1 in patients with severe sepsis or septic shock, there was no significant reduction in mortality (although there was a trend towards a reduction in mortality).<sup>126</sup> In another large randomised, multicentred, double blind, placebo-controlled trial using a single infusion of TNF- $\alpha$  murine monoclonal antibody in patients with septic shock found no reduction in shock or 28 day mortality.<sup>127</sup>

As IL-6 inhibits TNF- $\alpha$  and IL-1 production, recombinant IL-6 (or agents that stimulate IL-6 secretion, for example  $\beta_2$  adrenergic agonists and  $\alpha_2$  adrenergic antagonists) may be useful in the management of patients with septic shock.<sup>128</sup> There have been no clinical studies using IL-6 that have shown a reduction in mortality in patients with sepsis or septic shock; also there have been no clinical studies using IL-8 or anti-IL-8 agents in patients with sepsis.<sup>129</sup> If adrenaline (due to both  $\beta_1$  and  $\beta_2$  adrenergic receptor effects) or aminophylline is administered three hours before an injection of endotoxin, TNF- $\alpha$  production is reduced, an effect which may be mediated by an increase in IL-10 production.<sup>130</sup>

The heat shock response (initiating a group of intracellular chaperone proteins) inhibits the pro-inflammatory gene expression involved in the pathophysiology of sepsis<sup>131</sup> and protects cells against the cytotoxicity of TNF $\alpha$ .<sup>132</sup> However, there have been no studies utilising this effect in septic patients.

**Anti-inflammatory cytokine stimulation.** IL-4, IL-10 and IL-13 inhibit the production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF- $\alpha$ , following activation of monocytes by endotoxin.<sup>92</sup> IL-10 also enhances production of IL-1ra. While preliminary data showed that administration of IL-10 prevented death in mice following endotoxin-induced toxic shock,<sup>133</sup> there have been no clinical studies showing the benefits of these agents in septic shock. In one study of hospitalised febrile patients, a high ratio of plasma IL-10/TNF- $\alpha$  was associated with a high mortality, leading to the cautioning against a wide-spread use of proinflammatory cytokine inhibition (or perhaps anti-inflammatory stimulation) in patients with sepsis.<sup>134</sup>

**Platelet-activating factor inhibition.** In one study of 262 patients with severe sepsis, platelet-activating factor receptor antagonist decreased the mortality by 42% in a

subset of patients with documented Gram-negative sepsis,<sup>135</sup> with an adjusted reduction in mortality of 39%.<sup>136</sup> However, a beneficial effect was not observed in patients with Gram-positive sepsis.<sup>136</sup>

**Anti-adhesion molecules.** In animal studies, administration of monoclonal antibodies to ICAM-1 has reduced tissue injury caused by endotoxaemia.<sup>92</sup> In a study of nine patients with septic shock, an intravenous bolus of murine monoclonal antibody to E-selectin was associated with resolution of shock in all patients and reversal of organ failure in eight patients.<sup>137</sup> However, prospective, randomised and controlled clinical studies with these agents have not yet been performed.

**Granulocyte colony-stimulating factor (G-CSF).** G-CSF is a glycoprotein that stimulates activation, proliferation and differentiation of neutrophil progenitor cells.<sup>138</sup> In experimental studies, pretreatment with G-CSF has been associated with a reduction in TNF- $\alpha$  and a reduction in mortality caused by endotoxin administration.<sup>139</sup> In normal human subjects, G-CSF (300  $\mu$ g, subcutaneously) increased granulocyte and monocyte counts, plasma TNF- $\alpha$ , soluble TNF receptors and IL-1 receptor antagonist levels.<sup>140</sup> When 300  $\mu$ g of G-CSF was given 12 hours before endotoxin, then TNF- $\alpha$ , soluble TNF receptors and IL-1 receptor antagonist levels were increased compared with controls.<sup>140</sup> Prospective, randomised and controlled clinical studies with G-CSF in septic or shocked patients have not yet been performed.

**Interferon- $\gamma$ .** Interferon- $\gamma$  has immuno-stimulatory properties and has been used in critically ill trauma and burns patients in an attempt to reduce the mortality associated with infection and sepsis. Trials to date have revealed no reduction in infection rate or decrease in mortality when interferon- $\gamma$  has been used in either of these groups.<sup>141,142</sup>

**Immunoglobulin.** In sepsis and septic shock, immunoglobulin has been administered in an attempt to improve serum bactericidal activity due to neutralizing and opsonizing immunoglobulin (IgG- and IgM-antibodies), to stimulate phagocytosis and neutralisation of bacterial endo- and exotoxins, and to modify and suppress proinflammatory cytokine release from endotoxin- and superantigen-activated blood cells. While one study documented a reduction in septic complications (e.g pneumonia and non-catheter-related infections) in trauma patients given intravenous immunoglobulin,<sup>143</sup> another study did not.<sup>144</sup> Although there have been no multicentre prospective randomised controlled studies that have shown a reduction in

mortality by the use of intravenous immune globulin in septic patients,<sup>145</sup> a recent meta-analysis, which included 23 trials concluded that polyclonal human immunoglobulin significantly reduces mortality when used as an adjuvant treatment for sepsis and septic shock.<sup>146</sup>

**Arachidonic acid metabolite inhibitors.** Despite the impressive experimental evidence supporting the use of cyclooxygenase inhibitors in septic shock,<sup>147</sup> clinical evidence of efficacy is lacking, and adverse effects (e.g. renal failure, bronchospasm) are well documented.<sup>58</sup> In one randomised, double-blind, placebo-controlled trial of patients with sepsis, ibuprofen did not prevent the development of shock or ARDS and did not improve survival.<sup>148</sup>

**Coagulation factors and coagulation factor inhibitors.** While coagulation factors and platelets are often administered in patients with sepsis and DIC who have low levels of these factors and are bleeding, they have not been found to reduce mortality when administered specifically to manage septic shock. Also inhibition of thrombin generation with heparin, has not been associated with improved survival.<sup>149</sup>

Antithrombin III infusions have been reported to be of use in patients with severe DIC,<sup>150,151</sup> although no significant reduction in mortality has been observed.<sup>152</sup> While one study of ATIII infusions in critically ill patients without severe DIC but who had acquired low levels of ATIII, appeared to be without benefit,<sup>153</sup> another double blind placebo controlled study of patients requiring respiratory and/or hemodynamic support because of severe sepsis and/or post-surgery complications found that antithrombin III infusions to normalize plasma antithrombin activity had a net beneficial effect on the 30-day survival.<sup>154</sup>

Protein C infusions (100 IU/kg 8-hourly for 24 hr and thereafter according to plasma protein C levels) have also been used to treat patients with sepsis-induced DIC<sup>155</sup> (particularly when associated with meningococcal disease<sup>156</sup>).

Thrombomodulin infusions have been shown to have beneficial effects in the experimental model of DIC, although currently no studies on thrombomodulin treatment in humans with DIC have been reported.<sup>152</sup>

Infusions of recombinant tissue factor pathway inhibitor (TFPI) have also been shown to have beneficial effects in the experimental model of DIC, although no studies on TFPI treatment in humans with DIC have been reported.<sup>152</sup> Secondary fibrinolysis associated with DIC should not be inhibited.

Despite experimental evidence supporting the efficacy of plasma coagulation factor inhibitors (e.g. ATIII, aprotinin) in septic shock, clinical data

supporting the efficacy of these agents are still lacking.<sup>157</sup> Currently, several large clinical trials reviewing the effects of coagulation inhibitors (e.g. protein C, ATIII, TFPI and thrombomodulin) in patients with sepsis and septic shock are underway.

**Corticosteroids.** The adrenal glands normally respond to stress by increasing cortisol excretion by up to 300 mg/day. Thus, hydrocortisone 300 mg/day is all that is required to correct adrenal insufficiency associated with shock (e.g. Addisonian crisis). The use of a massive 24 hr dose of a glucocorticoid (e.g. 1 - 2 g/70 kg of methylprednisolone, or 100-200 mg/70 kg of dexamethasone), for patients in early septic shock, to stabilise lysosomal membranes, inhibit complement-induced polymorphonuclear leucocyte aggregation, and inhibit endothelial cell cytotoxic effects of arachidonic acid derivatives, molecular oxygen and lysosomal enzymes, remains controversial.<sup>158</sup> These inflammatory effects are also required by the host to rid itself of tissue infection, and their suppression by glucocorticoids reduces the ability of the neutrophil to kill bacteria.<sup>159</sup>

In septic patients, who are vasodilated and hypotensive, pharmacological doses of glucocorticoids have been shown to enhance the vasoconstrictor actions of noradrenaline<sup>160</sup> and angiotensin II, increase transcription of the  $\beta_2$ -adrenoreceptor gene, reduce desensitisation and downregulation of the  $\beta_2$ -adrenoreceptor<sup>161</sup> and appear to have beneficial haemodynamic effects.<sup>162</sup> In two prospective, randomised, and controlled clinical studies in patients with septic shock, hydrocortisone (100 mg 8-hourly for 5 days<sup>163</sup> or 100 mg bolus followed by 0.18 mg/kg/hr until shock reversed then 0.08 mg/kg/hr for 6 days<sup>164</sup>) improved the haemodynamic status compared with the control group. However they did so without significantly altering the mortality rate.

The reduction in mortality associated with corticosteroid administration has only been consistently demonstrated in animals if given before, with, or immediately after the injection of endotoxin.<sup>165</sup> If corticosteroids are given a few hours later, the effect is lost. Furthermore, in the experimental animal, corticosteroids administered without antibiotics are associated with 100% mortality, which may in clinical practice be analogous to giving corticosteroids to a patient who has a resistant infection.<sup>159</sup>

In an early double-blind prospective trial, Schumer found that patients receiving methylprednisolone in addition to standard treatment had a mortality rate of 11.6% which compared favourably with the rate of 38.4% in the group not given steroids.<sup>166</sup> However, in two subsequent prospective randomised studies, corticosteroids were not shown to improve the overall

survival of patients with septic shock.<sup>167,168</sup> A recently completed trial in patients with sepsis syndrome or septic shock treated with methylprednisolone, 30 mg/kg 6-hourly for four doses, showed an increase in mortality in a subgroup of patients who entered the study with a high creatinine level or who developed a secondary infection after therapy began.<sup>169</sup> Two recent meta-analysis concluded that corticosteroids do not reduce mortality in patients with sepsis, septic shock, or severe infections.<sup>170,171</sup>

Currently massive dosage of corticosteroids are not recommended in septic shock.<sup>172</sup>

#### **Thyrotropin-releasing hormone (TRH, Protirelin).**

Normally, TRH functions to release thyrotropin. It is a peptide that also acts physiologically as a partial opiate antagonist but, unlike naloxone, does not reverse the analgesic action of opiates. In animals, this peptide has been found to be effective in spinal cord trauma,<sup>32,173</sup> anaphylactic shock,<sup>174</sup> haemorrhagic shock and septic shock.<sup>173</sup> The effect of TRH is additive to naloxone and also appears to work through the central nervous system autonomic pathways.<sup>175</sup> However, there have been no prospective randomised, controlled clinical studies of TSH that have confirmed these beneficial effects in humans.

**Naloxone.** Naloxone at high doses will antagonise opiate receptors and have a nonopiate receptor effect on calcium flux, lipid peroxidation and gamma-aminobutyric acid systems. Any of these actions may be the reason for the haemodynamic changes observed in naloxone treatment of shock.<sup>175</sup> Naloxone may block and reverse hypotension caused by endotoxin, hypovolaemia, and spinal injury, and improve survival in experimental animals with these conditions.<sup>176</sup>

Bolus doses of up to 0.3 mg/kg (20 mg/70 kg) have been used in patients with septic shock<sup>177</sup> and have been followed by an infusion at 0.4-10 mg/hr. While the optimal doses of 1-2 mg/kg (70-140 mg/70 kg), which have been shown in animal studies to be effective in improving survival, have not been used in humans, one study using a bolus of 0.03 mg/kg (2 mg/70 kg) followed by an infusion of 0.03 mg/kg/hr (2 mg per 70 kg/hr) for 8-16 hr, reported the need for less inotropic agents for patients in septic shock when compared with a control group.<sup>178</sup> However, naloxone may precipitate shock in opiate addicts and, in large doses, may precipitate seizures and arrhythmias.<sup>179,180</sup> Hypertensive crisis,<sup>181</sup> pulmonary oedema<sup>182</sup> and intractable ventricular fibrillation<sup>183</sup> have also been reported when it has been used to reverse opioid anaesthesia.

While clinical studies have demonstrated improvement in blood pressure with naloxone, it has not been

shown to significantly improve survival in patients with septic shock.<sup>184</sup> Currently naloxone is not recommended for the standard management of patients in septic shock.<sup>175,180</sup>

**N-acetylcystine.** As a sulphhydryl donor, antioxidant and free oxygen radical inhibitor, N-acetylcystine has been found to have some useful effects in experimental sepsis. In one study of 22 patients with septic shock, an N-acetylcystine infusion (150 mg/kg bolus, followed by a continuous infusion of 50 mg/kg over 4 h) had no effect on plasma levels of TNF- $\alpha$ , IL-1, IL-6 or IL-10 levels but acutely decreased IL-8 levels (which may have been responsible for the observed improved oxygenation).<sup>185</sup> However, there was no change in mortality.<sup>185</sup>

**Oxpentifylline (pentoxifylline).** Compounds that increase intracellular levels of cyclic AMP decrease the expression of TNF- $\alpha$  mRNA. The phosphodiesterase inhibitor, oxpentifylline, in addition to inhibiting TNF- $\alpha$  release, reduces neutrophil activation, adhesiveness and degranulation, inhibits platelet adhesion, stimulates fibrinolysis, and stimulates prostacyclin and tPA release, all of which may reduce tissue damage during Gram-negative septicaemia. However, it does not reduce the circulating levels of IL-1, IL-6 or IL-8,<sup>186</sup> and data supporting the clinical efficacy of oxpentifylline are still lacking.<sup>187</sup>

**Fibronectin.** While it would seem to be reasonable to elevate the opsonic protein fibronectin in acutely ill patients, cryoprecipitate infusions to elevate fibronectin levels in patients with septic shock in one randomised controlled study, and an infusion of virus inactivated purified fibronectin in another double-blind randomised placebo-controlled study, failed to show any significant improvement in cardiovascular, renal or pulmonary function, or any reduction in sepsis or mortality.<sup>188,189</sup>

**Plasmafiltration or plasmapheresis.** One prospective randomised controlled study in 30 patients with sepsis syndrome found 34 hours of plasmafiltration (with replacement of plasma with fresh frozen plasma and a protein and electrolyte solution) did not reduce mortality.<sup>190</sup> While plasmapheresis may remove a greater number of inflammatory cytokines when compared with plasmafiltration, currently there are no trials that have shown a reduction in mortality with its use.<sup>191</sup>

**Miscellaneous agents.** Adenosine,<sup>192</sup> chloroquine,<sup>193</sup> chlorpromazine,<sup>194</sup> dehydroepiandrosterone,<sup>195</sup> hydrazine,<sup>196</sup> oestrogen,<sup>197</sup> pentamidine,<sup>198</sup> surfactant,<sup>199</sup>

thalidomide<sup>200</sup> (to name a few) have also been used experimentally to reduce the inflammatory response associated with septic shock. However, none of these agents have undergone large clinical trials to reveal the effects of these agents.

In summary, management of septic shock usually includes treatment of the septic focus (e.g. drainage of the infective lesion, antibiotics) and physiological support for the haemodynamic disorder and organ failures (e.g. renal failure, respiratory failure, hepatic failure, etc.). To date, there are no studies of therapies that alter inflammation that have reduced mortality significantly in patients with sepsis or septic shock.<sup>85,201</sup>

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