Sepsis, severe sepsis and septic shock in adults and anaesthesia

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Anaesthesiologists commonly encounter sepsis in varying degrees. It may be during the initial surgery or in the course of the patient's treatment in the intensive care unit(ICU). In this article the pathophysiology, the systemic effects and the perioperative management of patients with sepsis, severe sepsis and septic shock will be discussed.

In 1991 the American College of Chest Physicians/ Society of Critical Care Medicine consensus conference[1,2] defined the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock.

SIRS: Systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following: temperature > 38 °C or < 36 °C; heart rate >90 beats/min; respiratory rate > 20 breaths/min; and white blood cell count > 12000 mm^{-3}, < 4000 mm^{-3} or > 10% immature (band) forms

Infection: Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Sepsis: Systemic response to infection, manifested by two or more of the following as a result of infection: temperature > 38 °C or < 36 °C; heart rate > 90 beats/min; respiratory rate >20 breaths min; and white blood cell count > 12000 mm^{-3}, < 4000mm^{-3} or > 10% immature (band) forms.

Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status.

Septic shock: Sepsis, induced with hypotension (systolic blood pressure, 90mmHg or a reduction of > 40 mmHg from baseline in the absence of other cause s for hypotension), despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. These may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

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However, these definitions are still the source of much controversy, as no single physical sign or laboratory value is able to characterize each phase. Many of the phases of sepsis have sterile counterparts that cannot be easily separated from their infected counterparts. Given the short comings of these definitions at the recent Society of Critical Care Medicine conference 2002, Marshall J introduced the PIRO diagnostic system which re-defines sepsis. This system consists of four parts:

- Pre-existing conditions – genetic predisposition and chronic illness
- Insult – infection, endotoxin, microbes, injury and ischaemia
- Response – physiological shock, mediators and markers of severity of sepsis
- Organ dysfunction

Although at this stage details of this system are not available they will emerge soon and replace or modify current definitions.[3-7]

Not all patients with sepsis are equally ill. Sepsis, severe sepsis and septic shock constitute a different gradation of an ongoing disease process, resulting in an increasing degree of organ dysfunction, morbidity and mortality. Patients with Sepsis have a mortality of less than 10% and can be treated in the ward. Severe sepsis has a mortality of 20% and septic shock greater than 50%. Both these sets of patients require ICU management. Sepsis is the leading cause of death in non-coronary intensive care units

The incidence of sepsis has increased over the past three decades. It is likely to continue to increase as the population ages, the number of immune compromised patients' increases, the use of invasive procedures rises and the development of resistant organisms evolves.[3-7]

PATHOPHYSIOLOGY OF SEPSIS, SEVERE SEPSIS AND SEPTIC SHOCK

In 1994 Richards stated[8] "The mechanism whereby SIRS and sepsis develops are not completely understood, but are being elucidated at present." In 2002 the puzzle is still being unraveled, but there is now some profound understanding of the pathophysiology. Recent advances in biotechnology and the sequencing of the human genome has lead to an increase in the

understanding of critical illness. Critical illness is unlikely to be determined by a single gene action, but rather by the simultaneous activity of a multitude of genes. Many sets of genes are involved in determining a particular response. Functional genomics will provide the scientific basis for the improvement in accuracy of diagnosis and prognosis; the identification of new therapeutic interventions; understanding the global view of cellular biology and its interrelationships; and the predisposition to develop sepsis, severe sepsis and septic shock.

This complex condition is becoming more clearly defined.[9] The process consists of the interaction of chemical mediators and cells. It is now clear that after the first pro-inflammatory mediators are released, the body mounts a compensatory anti-inflammatory reaction to regulate the inflammatory process. When the balance between these two groups is lost, many of these substances become harmful[10] and the cellular components are further activated. This syndrome initially involves the innate immune system.

The adaptive system serves to enhance the innate immune system.[11] The innate immune system is not enhanced by exposure and does not discriminate between foreign substances. This system is mediated by macrophages, monocytes, natural killer cells and polymorphonuclear cells (neutrophil). The macrophage plays a pivotal role, as it is the principle source of the key mediators of sepsis, severe sepsis and septic shock.[12] These cells have toll - like - receptors (TLR) on their membrane as do most other cells; for example the endothelium. They are Type 1 transmembrane polypeptide receptors. The N terminal is found extracellularly; there is a single transmembrane domain and C terminal intracellularly. It is remarkably similar to the interleukin – 1 receptor (IL – 1R) and the toll receptor found in *Drosophila* (the fruit fly). Ten human TLRs have been identified and each responds to a different biological component. Several microbial molecules bind or activate them:- Lipoprotein, lipopolyssacharide (LPS), lipoteichoic acid, peptidoglycans, manams of yeast and live or killed organisms.[13] An extracellular adapter protein e.g. MD-2 binds to the toll - like - receptor and confers responsiveness to these components. [14, 15] In the unstimulated cell, nuclear transcription factor (NF – κB) is found in the cytoplasm bound to IκBα and IκBβ, which prevents it entering the nuclease.[16] When the toll - like - receptor is stimulated it activates a cascade of kinases similar to IL –1 (see below) which causes phosphorylation of the complex and frees NF– κB. This is free to enter the nuclease. Oxidants, viruses, interleukin – 1 (IL-1) and tumour necrosis factor (TNF), can also release NF– κB from the complex directly. In acute lung injury and in acute respiratory distress syndrome, IL-1, TNF and LPS, activate NF– κB in the alveolar macrophage.[16]

In the nuclease NF– κB binds to the promoter site of the genes which produces pro-inflammatory cytokines (IL-1, TNFα), chemotactic cytokines - IL-8, adhesion molecules and immune receptors. It also induces inducible nitric oxide synthetase (iNOS), cyclo-oxygenase, granulocyte macrophage colony stimulating factor and platelet activating factor (PAF).[16] The process is terminated by the transcription of the gene that results in the synthesis of IκBα, which then binds up NF– κB. [16]

NF– κB effects are inhibited by glucocorticoids, which increase the transcription of both IκBα and aspirin in high concentration. IL-10 inhibits by increasing IκBβ. Ghotoxin found in aspergillus is a potent inhibitor. Vitamin C and E and also n-acetyl cystein are weak inhibitors.[16]

Cytokines are small (less than 80kDaltons) glycosylated, proteins, produced by all nucleated cells.[11] Ultra violet (UV) light hyperosmolarity and the presence and adherence of foreign materials, stimulates the release of these cytokines.

Proinflammatory cytokines, TNFα, IL-1 and IL-8 are the most important mediators promoting sepsis.

Tissue necrosis factor is produced as a prohormone of 233 amino acids, which is processed to a 157 amino acid mature proteins. [17, 18, 19] There are two distinct forms alpha and beta which bind to the same receptor and produce similar but not identical effects.

LPS enhances TNF α gene transcription. Interferon – γ enhances the production. TNFα synthesis is inhibited by glucocorticoids, IL-4 and IL-6.

TNFα is central to the development of sepsis, severe sepsis and septic shock.[18, 19] Besides activating NF– κB, it can also activate phospholipase A_2 (PLA_2), cyclo-oxygenase (COX), inducible nitric oxide synthetase (iNOS), adhesion molecules and chemokines directly. This results in the formation of arachidonic acid, PgE_2, prostacycline and leukotrienes, nitric oxide (NO) and the increase in platelet activating factor (PAF); and neutrophil migration. Centrally TNFα induces sleep, fever and anorexia. [20] TNFα inhibits lipid uptake in adipose tissue and enhances lipogenesis in the liver. TNFα causes efflux of amino acids from skeletal muscle and decrease proteolysis in the liver. TNFα stimulates the anterior pituitary adrenal cortex and pancreas and causes activation of the sympathetic nervous system.[18] TNFα has also been shown to cause myocardial dysfunction[21,22] and direct damage to the endothelium.[23]

Interleukin 1 (IL – 1) exist in two forms alpha and beta. The synthesis and the release of IL -1 is initiated by microorganisms, toxins, NF– κB, TNFα and itself.[11,18] IL - 1 binds to a specific receptor Interleukin 1 Receptor (IL – 1R) that couples with an accessory protein. The intracellular portion forms an active complex with an adapter protein (MyD88) and 2 putative serine threonine kinase (IRAK & IRAK2). A protein (TRAF6) bridges it to another protein kinase which ultimately activates NF– κB.[14]

IL – 8 is a potent chemokine that facilitates movement of leukocytes from the vascular to the interstitial compartment. It also induces degranulation of the leukocytes. It has also been shown to have antigenic activity. TNFα and IL-1 stimulate its secretion.[11,18]

Nitric oxide synthetase (NOS) is found in many cells and two types are distinguished namely constitutive and inducible forms.[18,23]

There are two isoforms of constitutive NOS being, eNOS and nNOS found in the endothelium and the neurons respectively. This form of NOS is calcium dependent. The synthesis of NO by this enzyme has an important role in vasodilatation, inhibition of platelet function and neurotransmission.

The inducible form is not normally active. Small amounts are found in the lung, small intestine and platelets. It does not require calcium for its action. In sepsis NF– κB, TNFα, IL –1 and bacterial toxins cause its induction. IL-4, IL-10 and glucocorticoids suppress the induction of iNOS activity.

NOS catalyses the conversion of l- arginine and O_2 to l – citrulline and NO. Nitric oxide is the smallest known biologically active molecule. It is an uncharged molecule, thus it can diffuse easily across the cell membrane. NO has an unpaired electron in its outer shell and thus it is a free radical. It is highly reactive, having a half- life of 2 – 30 seconds. In the target cells

it complexes with iron containing proteins such as haem and nucleic acids. [24] NO causes smooth muscle relaxation by activating cGMP, myocardial depression and platelet inactivation. It also damages nuclear protein, oxidizes phospholipids, interacts with superoxides and inhibits mitochondrial respiration. [18,23, 24]

Neutrophils are the prime cause of organ damage in sepsis. The process whereby the neutrophils mediate organ damage requires a number of steps, involving the adhesion of the neutrophil to the vascular endothelium. Adhesion requires, initially, a mechanical slowing of the flowing cells and primary bonding of the cell to the endothelium, with secondary stabilization of the bonds and in some cases, changes in shape of the cell. Leukocytes travel slowly through the microcirculation. If the perfusion pressure drops or the neutrophils become activated they will adhere to the vessel wall.

Primary adhesion is mediated by selectins – L, E and P. L Selectin is found on the leukocytes and mediates a low affinity-rolling interaction with the E selectin found on the endothelium. The latter is synthesized and expressed under the influence of cytokines. P selectin is found in platelets and the endothelium.[21, 25, 26, 27]

Secondary adhesion is mediated by interaction of β-intergrins found on the neutrophil and immunoglobulin superfamily found in the endothelium. This needs conformational changes before optimal binding occurs. This process results in firm adherence of the neutrophil to the endothelium. There are 2 forms of intergrins - β1 and β2. β1- intergrin VLA- 4 is found in lymphocytes and monocytes and binds to the endothelial immunoglobulin superfamily VCAM-1 which is expressed in response to cytokines. β2-intergrins are found in the neutrophil and monocytes. Mac – 1 and LFA - 1 are the β2 intergrins found on polymorpho nuclear leucocyte (PMNLs). Chemokines promote the movement of Mac-1 from the intracellular milieu to the surface These intergrins bind to the ICAM immunoglobulin super family found on the endothelium. ICAM-2 is found constitutively on the endothelium.[26] Inflammatory cytokines increase the production of ICAM-1.[8, 26,27] ICAM-1 recognizes LFA-1. ELAM-1 and GMP-140 are immunoglobulin super family upregulated by IL –1 and TNF,[8] and bind to the neutrophil intergrins in sepsis. Intergrins and the immunoglobulin super family also aid in the diapedesis through the endothelium. [26] Endotoxin, PAF, IL - 8, TNFα, granulocyte colony stimulating factor, shear stress and exposure to collagen found in the basement membrane results in priming of the neutrophil. [28] A second stimulus is needed to cause degranulation and the release of elastases, peroxidases, arachnodonic acid, gelatinase and collagenase

Some of the foreign material engulfed by the macrophages monocytes and NK cells may be extruded onto the cell surface so becoming antigen presenting cells (APC). Peptide fragments derived from extracellular protein following phagocytosis are expressed on the surface bound to class II major histocompatibility complex (MHC) and are recognized by T helper cells (Th). In contrast peptides derived from protein synthesis in the cells from foreign genetic material are presented with class I MHC molecules and are recognized by cytolytic T cells. This process is enhanced by TNFα. [26] The T helper cells when activated produce cytokines, which enhance the development and differentiation of the T helper cells. T helper 1 cells are produced by, the action of Interferon, IL – 2 and IL – 12, and activate cell mediated immunity. Interferon-γ is produced by the lymphocytes in response to IL - 1. T helper 2 cells are produced by the effects of IL-4, IL – 6, IL- 10, IL-13 and control B cell development and thus mediate humoral responses. [26] B cells have membrane bound antibodies. Antigens bind to the antibodies activating the cell to produce and secrete antibodies[11, 23]

Activation of the classic and alternate complement cascade occurs during sepsis. This may be directly as a result of direct interaction with the organism or foreign toxins, or as a consequence of cytokine activity. IL - 2 and IL - 6 induce the synthesis of C-reactive proteins (CRP) in the liver. CRP binds to phosphocholine on the cell membrane and induces the compliment cascade. Products of the complement cascade C_3a and C_5a can also enhance the release of TNF, IL-1 and IL-6. Together these factors may have a synergistic effect on the on the activation of granulocytes.[20,28]

At the same time as the inflammatory mediators are released, anti-inflammatory mediators are elucidated. These are cytokines (IL – 4, IL-10, IL-11, IL-13), cytokines inhibitors (tissue growth factor B blocks the effects of IL-1, TNF and LPS) or soluble cytokine receptors (IL –1rc inhibits binding to receptor of IL-1, soluble TNF receptors).

These factors work to diminish macrophage and monocytes expressing antigen linked to MHC and reduce the effects of inflammatory mediators. It is possible that the compensatory process can be inappropriate, resulting in immunosupression and giving rise to a compensatory anti-inflammatory response syndrome (CARS).[12]

THE SYSTEMIC EFFECTS OF SEPSIS

The prognosis of patients with sepsis, severe sepsis and septic shock deteriorates as the number of organ system failures increases. Therefore the anaethesiologist should be aware of the subtle and obvious signs of organ failure that can occur in these syndromes.

Central Nervous System

Patients with sepsis commonly have altered levels of consciousness ranging from mild confusion to delirium and coma. Altered level of mental status is probably one of the earliest signs of worsening sepsis and is a poor prognostic sign.[3,30] Also common in sepsis is an altered thermoregulation. Fever is stimulated by inflammatory mediators.[31,32] The cause of hypothermia is not understood but its presence is a poor prognostic feature. It is more common with extremes of age and in immune suppressed conditions. Although not common in the acute phase, polyneuropathies and myopathies occur with prolonged sepsis.[30]

Cardiovascular system

Hypotension and the resultant compensatory tachycardia commonly occur in sepsis, severe sepsis and septic shock. This may be due to hypovolaemia, myocardial dysfunction and alteration in vascular tone.

Hypovolaemia may be due to absolute or relative loss of fluid. Absolute loss of fluid occurs through the endothelium, due to increased permeability of the membrane, poor oral intake, urinary losses, vomiting, diarrhoea and insensible loss due to fever. Relative deficiency occurs due to increased size of the vascular compartment. This is due to NO, IL – 1 and prostaglandins and decreased adrenergic reactivity and peripheral pooling in capacitance vessels.[3,32,33,34] Oedema formation may be due to

increased vascular permeability and decreased albumin.[30] Although an imperfect estimate, the pulmonary capillary wedge pressure provides a better estimate of volume status than central venous pressure.[34,35]

Myocardial depression is less obvious than a decrease in vascular tone. Myocardial performance may be depressed in the face of a normal or high cardiac output.[30] Sepsis induces changes in the elastic properties of the left ventricle, that may reduce diastolic compliance and limit exploitation of the Frank – Starling relationship for improving cardiac output with increased preload. Abnormalities in right ventricular function exist in parallel with those observed in the left ventricle. Owing to ventricular interdependence, right ventricular dysfunction may limit left ventricular pre-load.[35]

Ventricular dilatation occurs early in sepsis and is more pronounced in survivors than non - survivors, as it allows them to exploit cardiac reserve and increase cardiac output. Failure to dilate may be due to the result of myocardial oedema secondary to diffuse capillary leak.[30,33,35] Besides oedema, myocardial dysfunction is due to myocardial depression due to TNFα, IL-1, PAF and NO.[22,34] Ischaemia has been shown to have a minimal role in myocardial dysfunction.[22,30,32,33,34,35]

Due to the presence of inflammatory mediators (TNF, IL-1, NO amongst many) and impaired adrenergic function, the systemic vascular resistance decreases.[22,30]

Clinical studies have shown that non-survivors have more severe alteration in ventricular function than survivors. Right ventricular dysfunction may be a particularly sensitive marker, as it may also reflect the presence of pulmonary hypertension. However, myocardial function in isolation has been shown not to be a good predictor of outcome. The most striking change in survivors is an increase in mean arterial pressure due to both an increase in vascular tone and improved ventricular function.[22]

Pulmonary system

The presence of inflammatory mediators, in particular, and anti-inflammatory mediators, in sepsis, severe sepsis and septic shock results in damage to the respiratory system. The effects may vary from minimal respiratory dysfunction to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). When the first clinical signs of sepsis appear between 28 % and 33 % of patients meet the criteria for ALI/ARDS.[36] In approximately 40 % of cases with sepsis, severe sepsis and septic shock, acute lung injury and acute respiratory distress syndrome will develop.[37,38] The production of inflammatory mediators causes: - damage and destruction of type I alveolar cells and attendant loss of surfactant; the increased permeability and damage of the vascular endothelium; and accumulation of cell debris, protein and fluid in the alveoli and interstium. These changes result in significant alteration in respiratory rate, lung volumes, pulmonary mechanics and gas exchange and have implications for clinical management.

An increase in respiratory rate (tachypnoea) is an early clinical sign of sepsis, probably stimulated in part by endotoxin and other inflammatory mediators.[30]

Alveolar epithelial inflammation, flooding of the alveolus with plasma protein and cell debris, inactivation and depletion of surfactant and loss of normal endothelium function results in atelectasis and decreased lung volumes in the early stages of ALI/ARDS. This has given rise to the concept of the small lung. The ratio of dead space to tidal volume increases as lung damage progresses.[37]

The loss of surfactant, interstitial oedema, the accumulation of debris in the alveolus and atelectasis, result in a decrease in compliance in the early (exudative) phase exclusive of changes in the intrinsic elastic properties of the lung. In the later phases of ALI/ARDS fibrosis occurs, resulting in a stiff lung and a decrease in compliance. Decreased compliance will be indicated by an elevation in the pause or plateau pressure, in ventilated patients. In some patients, the peak airway pressure may be markedly elevated indicating an increase in airway resistance. This may be due to secretions, oedema and /or bronchoconstriction due to inflammatory mediators. The cause of increased work of breathing is multifactorial. It includes hypoxia, increase in dead space ventilation, increased airway resistance, elevated respiratory rate and decreased compliance. In ARDS the oxygen (O_2) requirements for the work of breathing increases dramatically.[37]

The principle cause of hypoxaemia is an increase in right to left shunt. In ARDS there is persistent perfusion of atelectatic and debris filled alveoli. Hypoxic vasoconstriction may be ineffective or absent, thereby aggravating the right to left shunt.[37]

During sepsis, severe, sepsis and septic shock, oxygen metabolism is altered by three major changes. i) Increased oxygen demand due to increased metabolism; ii) Decreased oxygen extraction; and iii) Reduced oxygen delivery (DO_2). This creates an imbalance in oxygen supply and demand. Under normal physiological conditions as DO_2 falls due to a fall in cardiac output, oxygen extraction increases maintaining oxygen consumption. As the DO_2 falls further a critical point is reached when oxygen extraction can no longer compensate for a fall in DO_2. At this point and below, oxygen consumption becomes dependent on DO_2 and lactate rises. Nelson et al and Whang et al[37] showed in dogs that received endotoxin, that the DO_2 (at which the oxygen consumption became dependent on the DO_2) was higher and the O_2 extraction was lower at this level than in dogs that did not have endotoxin. The release of inflammatory mediators is largely responsible for this change.[30,37]

Renal System

The cause of acute renal failure in sepsis, severe sepsis and septic shock is due to many factors. Hypotension and ischaemia causes renal tubular cell damage and cast formation, resulting in obstruction and a decrease in glomerular filtration. Endotoxins have been shown to cause renal vascular vasoconstriction interfering with renovascular autoregulation.[32] Oxidants are released from activated neutrophils, which have migrated into the interstium under the effects of cytokines. There are numerous drugs that have direct toxic effects on the kidney, for example antibiotics and non-steroidals.

Gastrointestinal System

The gastrointestinal system plays a pivotal role in sepsis, severe sepsis and septic shock. It is both a target and a cause. During hypotension much of the blood supply is diverted from the splanchnic bed, resulting in hypoperfusion and ischaemia. The gut may have a higher critical DO_2 than other organs. In sepsis there is redistribution of flow away from the mucosa towards the muscularis and the serosa. The villus arterioles are constricted and the capillary density at the tip of the villus is decreased.[34] Ischaemia of the gastric beds is thought to be an early marker in the development of multiple organ failure.[39] In

some centres gastric tonometry is used to assess splanchnic perfusion and end points of resuscitation.[34,39,40] The altered blood supply results in decreased gastrointestinal motility, ulceration and altered mucosal barrier function. The decrease in motility may give rise to an ileus and necessitates the placement of an orogastric tube. The increased permeability may result in the translocation of bacteria and foreign materials that may aggravate and perpetuate the inflammatory process.

Hepatic dysfunction is a common and early finding in sepsis with moderate elevation of alkaline phophatase and transaminases preceding the diagnosis.[30] Hypoalbuminaemia is common in sepsis, severe sepsis and septic shock. The rate of albumin synthesis is altered significantly. TNFα and IL-6 reduce gene transcription and synthesis of albumin.[41] Ischaemic hepatitis has been reported in septic shock.[30,42] NO has been implicated as one of the likely causes.[43]

Acalculus cholecystitis occurs in sepsis, severe sepsis and septic shock, either on presentation, or in the course of the illness. It is an infrequent but probably underdiagnosed complication. The majority of cases follow trauma or billiary surgery. It should be suspected in patients who have right upper quadrant pain or have evidence of obstructive jaundice.[42]

Haematology

Haematological changes in sepsis, severe sepsis and septic shock are primarily, alteration in neutrophils, platelets, coagulation[44] and erythrocytes.

In sepsis, severe sepsis and septic shock it is observed that hemoglobin concentration and erythrocyte count decline over the course of the illness. It is normally normocytic, normochromic in character. However, many patients have a microcytic, hypochromic anaemia. The etiology of this anaemia is multifactorial. It may be due to decreased synthesis and/or increased destruction of erythrocytes. This may be due to:- inflammatory mediators (TNFα, IL - 1, and interferon γ); nutritional deficiencies (Iron, Folate); hormonal changes (hypothyroidism, decreased erythropoeitin due to renal failure); the effects of toxins and oxidants; increased macrophage activity on damaged cell membranes and iatrogenic (phlebotomy).[45]

Neutrophils may increase in number. This may initially be due to mobilization of marginalized neutrophils. There may be a left shift and the presence of toxic granulations.[30] A neutropenia may develop and this may indicate increasing severity of sepsis, severe sepsis and septic shock.

Cytokines activate the coagulation system, depress the inhibition of coagulation and inhibit the fibrinolytic system. Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic intravascular activation of coagulation, with decreased fibrinolysis leading to widespread deposition of fibrin in the microcirculation. Tissue factor/factor VIIa pathway is responsible for the development of DIC. Endotoxin IL-1 and TNF cause tissue factor to be introduced into the blood from mononuclear cells and vascular endothelium. IL-6 has been implicated as the mediator of endotoxin induced coagulation. The contact system dependent pathway (intrinsic) amplifies the thrombotic events and results in hypotension by generating kinins. It does not seem to have a primary role in the development of DIC.[46,47]

Cytokines inhibit the protein C system (down regulation). Therefore coagulation can occur unopposed. Antithrombin (which bind and inactivates thrombin and factor Xa) levels are decreased during sepsis due to increased consumption, decreased hepatic synthesis and degradation. Low antithrombin levels are associated with increased mortality. Tissue factor pathway inhibitor (TFPI) (inhibits factor Xa and tissue factor/ factor VIIa complex) is enhanced by endotoxin.

Fibrin is deposited in the microvasculature due to increased coagulation and decreased breakdown of fibrin. Even though septic patients do have increased fibrin degradation products and elevated plasmin, the fibrinolytic pathway is insufficient to combat the increased formation. The inhibition of the fibrinolytic pathway is due to TNFα.

Activated coagulants and natural coagulant inhibitors also modulate the inflammatory response. It has been shown that activated coagulation factors such as VIIa and Xa can activate cells to release cytokines. Activated protein C tissue factor/ VIIa complex has been shown to inhibit the inflammatory response. It is becoming increasingly clear that agents that inhibit coagulation in DIC can also have beneficial effects on inflammation.[44,46,47]

Low platelets (thrombocytopenia) may be one of the earliest signs of sepsis, severe sepsis and septic shock. The decline in platelet count may be due to a DIC, platelet interaction with foreign particles, immunolgical effects and drug interactions.[44] In some cases it may be a laboratory error due to clumping. If in doubt microscopic evaluation should be requested.

Endocrine System

The hypothalamic pituitary adrenal (HPA) axis and the sympathoadrenal axis have an important role in the response to sepsis, severe sepsis and septic shock.[18,32] The adequacy of its response or lack there of, is probably more important. In critical illness there may be an absolute or relative adrenal insufficiency.[32]

In the acute phase of sepsis, serum cortisol levels are raised and the circadian rhythm is lost.[18,32] This may be the result of corticotrophin-releasing hormone release from the hypothalamus due to the direct effects of toxins, increased pituitary release of adreno cortico tropic hormone (ACTH), decreased extraction of cortisol, decreased levels of cortisol binding globulin (CBG) and/or decreased binding capacity of CBG. TNFα, IL - 1, IL - 6 also stimulate the HPA axis directly. In the later phases, the cortisol level remains elevated with low ACTH levels. The reason for this is unclear.[18]

Epinephrine and nor-epinephrine are well-recognized stress hormones. Epinephrine is secreted from the adrenal medulla, where as nor-epinephrine is mostly derived from adrenergic nerve endings. The sympathoadrenal response plays an important role in supporting cardiovascular function and metabolic alterations in the early stages of sepsis.

Patients with sepsis may develop euthyroid sic syndrome. This is characterized by low 3,5,3 - triiodothyromine (T3), a high reverse T3, normal or low thyroxine (T4) and a high thyroid stimulating hormone (TSH). These patients rarely develop clinically significant hypothyroidism,[32] although they appear to have a higher mortality rate.[18] Dopamine infusion induces or aggravates this condition as it suppresses TSH secretion.[18]

Growth hormone (GH) is secreted in a pulsatile basal rate and has diurnal variation. In sepsis, the basal level is elevated and the diurnal variation is lost. A low GH level is associated with an increase in mortality.

In sepsis, elevated glucose results from increased catechola-

mines, glucocorticoids, glucagon and cytokines. Cytokines may also induce insulin resistance.

Endogenous opioid peptides have been shown to cause a down regulation of the HPA axis. The sympathetic adrenal axis infusion of opioid antagonists has been shown to improve haemodynamics in a small group of patients.[48]

Calcitonin is elevated in sepsis. It is a potent vasodilator and has positive inotropic and chronotropic effects. Procalcitonin is a 116 amino acid peptide. It is not a precursor of calcitonin. In healthy patients its level is low. Endotoxin induces an increase level of procalcitonin. Serum concentrations seem to parallel the severity of sepsis. It is hoped that this could be used as a marker of severity, but the results have so far not realized the hoped for potential. As it is not released by viruses, allergy or non-bacterial inflammation, it may have a role in differentiating sepsis from SIRS.[18]

THE PERIOPERATIVE MANAGEMENT OF THE PATIENT WITH SEPSIS, SEVERE SEPSIS AND SEPTIC SHOCK

As outlined above the patient with sepsis, severe sepsis and septic shock, potentially has multiple abnormalities, which need to be addressed. The anaesthesiologist may encounter the patient in both the acute phase or when the patient has been ill for a prolonged period of time. Patients given therapy appropriate to the underlying condition are more likely to survive than those given inadequate or inappropriate treatment.[40,49,50] Preoperative evaluation of the patient should include standard systematic assessment of the history, examination, laboratory results and radiological data. In many cases patient transport to theater may be extremely hazardous and requires careful coordination. The patient may require ventilatory support and specialized equipment and monitors

In most cases, given the haemodynamic instability and multiple organ dysfunction, general anaesthesia is the technique of choice. Monitoring required needs to be individualized according to the patients needs. (See below)

Source Control

Despite the increased understanding of the pathophysiology of sepsis, severe sepsis and septic shock, no specific therapeutic intervention has been shown to confer a mortality benefit in controlled trials.[38,51] Management is directed at treating the underlying infection, ensuring adequate oxygen delivery to the various organs and maintaining their functional integrity.[38] At present the best way to reduce the release of mediators is to control the source.[51] Source control measures should only be carried out once the patient has been appropriately stabilized. Rarely, in some cases, source control is part of the resuscitation. Aggressive rapid resuscitation can reduce the risk in anaesthesia. Source control is an urgency not an emergency.[52] Source control measures may include drainage of pus collections, debridement of dead tissue, removal of devices and / or antimicrobial therapy. Anaesthesiologists may be involved in all of these processes, either administering anaesthesia and/or initiating the administration of antimicrobial drugs. In the latter the agents used should be appropriate for the setting. Inadequate dosaging and drug choice results in a higher mortality.[53,54] Community acquired infections should not be treated with potent newer generation antimicrobials as many of the organisms are still susceptible to the older drugs. The newer agents should be used only in nosocomial infection and in the immune compromised patient when the organism and the drug sensitivity have been identified. In some cases of nosocomial infections in the infected, immune compromised patient, empirical therapy should be guided by the knowledge of the microbial flora and fauna to which the patient has been exposed. Most authors advocate the use of beta-lactam antibiotics. The superiority of combining them with an aminoglycoside is a matter of disagrement.[53,54] In abdominal sepsis, anaerobic cover should be in added.

Airway management and Ventilation

Patients with sepsis, severe sepsis and septic shock often require early intubation and ventilation prior to arriving in theatre.[30] Orotracheal intubation is the preferred route. The intubation of these patients may be quite challenging. Most of the hypnotic agents commonly available depress the myocardium to varying degrees. The administration of these drugs in this situation may unmask marginal cardiac reserve. Etomidate has relatively minor cardiac depressant effects and has been used extensively in haemodynamically unstable patients. Prolonged or repeated use of the agent has been shown to cause adrenocortical suppression. It has also been shown to temporarily cause a decline in adrenal steroid synthesis after a single dose. The clinical impact of this is not substantial. It is probably advisable not to use this drug in patients with known decreased adrenal function.[28] The relative maintenance of sympathetic tone by ketamine makes it an attractive drug in haemodynamically unstable patients. Ketamine also suppresses pro-inflammatory cytokine production. The clinical relevance of this is unknown.[55] Propofol inhibits NOS, but as it profoundly depresses myocardial function and increases TNF, it should be avoided.[32]

Probably more important than the choice of the agent is the careful dosing. Given the hyperdynamic circulation, altered volume of distribution and altered albumin concentration, far lower doses are required. The patient should also be closely monitored and adequate precautions should be in place for anticipated haemodynamic instability as a result of intubation and the initiation of positive pressure ventilation.[30, 32 37] The use of succinylcholine to facilitate intubation in sepsis, severe sepsis and septic shock has been questioned. Sepsis mediators may induce extrajunctional receptors and hyperkalaemia may result with the administration of succinylcholine. Careful risk benefit assessment must precede its use in these high-risk patients.[56,57]

Non-invasive positive pressure ventilation has been shown not to be effective in sepsis, severe sepsis and septic shock.[40] The institution of mechanical ventilation should not be delayed in a hypoxic deteriorating patient. Mechanical ventilation reduces the work of breathing. As many of these patients will develop ALI/ARDS it is advisable to adopt ventilation strategies appropriate for ALI/ARDS. No mode of ventilation has been shown to be superior to others in terms of outcome. Volume controlled ventilation is therefore an appropriate starting point. Pressure limit ventilation has been shown to cause less respiratory morbidity. Peak pressure should be limited to $38cmH_2O$ and the plateau pressure to $35cmH_2O$. Conventional tidal volumes of 10 – 15ml/kg will result in barotrauma and volutrauma. Tidal volume should be between 6-8 ml/kg. Permissive hypercapnia, allowing the PCO_2 to rise using smaller tidal volumes limits respiratory trauma. However, in septic shock,

this should be done with extreme caution, ventilating so as to maintain normocapnia and even slight hypocapnia. Positive end expiratory pressure (PEEP) of 8-10cm H_2O will improve oxygenation, ventilation and compliance by recruiting collapsed alveoli. Placing the patient prone and the use of active recruitment manuvoures should be considered in patients requiring high levels of O_2 ($FiO_2 > 0.6$). A sustained PEEP of 40 cm H_2O for two minutes in a non- breathing patient has been shown to improve compliance and oxygenation. It is important to note that these guidelines are as applicable intraoperatively as in the intensive care unit (ICU). Operating theatres dealing with these patients must be equipped with ventilators that can provide these ventilation parameters and be able to provide the same settings that the patient was on in the ICU.

Haemodynamic Management

As discussed previously sepsis, severe sepsis and septic shock results in haemodynamic instability due to hypovolaemia, myocardial dysfunction and vasodilatation. The anaesthesiologist will have to deal with these perturbations pre- intra- and postoperatively. The ultimate goal of haemodynamic therapy is to improve effective tissue perfusion and the delivery of O_2 and to normalize cellular metabolism.[30, 34, 39] The majority of these patients require central venous pressure (CVP) monitoring. In many cases these patients require invasive arterial blood pressure monitoring (non-invasive blood pressure cuffs are often inaccurate in this setting). In some cases these patients require more sophisticated haemodynamic monitoring (pulmonary artery floatation catheters {PAFC}, ultrasonic measuring devices, bioimpedence monitors). When these devices should be used and whether they impact on outcome, is the subject of lively debate.

Fluid replacement should be the initial step in these patients. Fluids alone may significantly improve and restore haemodynamic instability.[30,34,39,40,53] The crystalloid/ colloid debate as to what fluids to use continues. There are no definitive studies that show superiority of one over the other. In Europe colloids are used more whereas in the USA, crystalloids hold sway. There is some concern that the use of colloids or crystalloids may be associated with a higher mortality. Colloids may dehydrate the cell and induce cell dysfunction. However, these studies used heterogeneous groups of patients (burns, trauma, SIRS, cardiac surgery), different fluid protocols, drugs and monitoring strategies. Intuitively it is probably best to use a mixture of crystalloids and colloids.

Crystalloids are the initial choice as they are readily available, inexpensive and distribute through the extracellular compartment predominantly. A balanced salt solution e.g. Ringers lactate is preferable to normal saline. The latter may aggravate acidosis.[58] It has recently been suggested that small volumes of hypertonic saline may be of benefit. Animal and in vitrio studies show that hypertonic saline may have direct inotropic effects, improve rheology, enhance microcirculation and reduce leukocyte adherence. However, there is no clinical data to supports its use in sepsis, severe sepsis and septic shock.[39]

There are no perfect colloids available at present. All have potential adverse effect on sepsis, severe sepsis and septic shock.[59] There are two categories of colloids- natural colloids (albumin, blood and fresh frozen plasma) and synthetic colloids (starches, gelatins, dextrans).

Intra vascularly, albumin accounts for approximately 80% of the oncotic pressure. Infusion of 20 –25% albumin solution will effectively mobilize oedema.[40] It is, however, expensive and despite improving albumin levels there is no benefit in outcome.[41] There is no benefit compared with other colloids in outcome[60] and the use of albumin is associated with an increase in mortality.[65] Given the above, the use of albumin in sepsis, severe sepsis and septic shock cannot be justified.

Blood, if used injudisciously, is a dangerous colloid and should not be used to expand the intravascular compartment. Besides its well-known complications, it has been shown that stored old blood impairs regional circulation[62] and causes immunosupression.[32,34,39] Patients with cardiac disease tolerate a haemoglobin level of 9 –10g/dl. This is because of a decrease in viscosity, resulting in a decreased afterload, elevated venous return and improved cardiac output.[34,39] It is not known what the trigger value (of haemoglobin) for transfusion is in patients with sepsis, severe sepsis or septic shock.[53] Herbert et al.[63] showed that patients with haemoglobins of 7-8g/dl had a non-significant trend to decreased mortality and a significantly lower incidence of multiple organ failure compared to a group with haemoglobin >12g/dl. There is very little evidence that blood transfusion relieves hypoxia in critically ill patients.[64] Blood should be transfused if there is a low haemoglobin associated with a very low CVP, persistent lactic acidosis, a low mixed venous O_2 or an elevated PCO_2 in the gastric mucosa.[39]

Fresh frozen plasma only has a role in the replacement of clotting factors in patients that are actively bleeding.

6% hydroxyethyl starch is the commonly used starch. It has been shown to reduce endothelial damage, reduce capillary leakage by forming plugs at the leaking site, improve microcirculation and suppress macrophage function. It has been noted that it can cause a decrease in factor VIII and prolong prothrombin time. For this reason, it has been suggested that the amount given should be restricted to 20ml/kg. However, published data does not support this level.[65, 66] A recent study published in the Lancet[67] has questioned the safety of the starches in sepsis and renal failure.

The gelatins are small molecules which migrate rapidly into the interstitial space. They thus have a short half-life. They cause a dilutional coagulopathy and have a high incidence of anaphylaxis and histamine release.[65]

Dextrans are linear polysaccharides which decrease blood viscosity, minimize erythrocyte, endothelial and leukocyte adherence and enhance the microcirculation. The high incidence of anaphylaxis has limited its use. The introduction of a hapten bound product has seen a resurgence of interest in its use.

At this point the starches appear to be the most widely recommended colloid of choice.[34,35,39,53,59 65]

Probably more important than the type of fluid, is the amount of fluid that needs to be administered judiciously. These patients need large volumes of fluid – approximately 6 litres or more of crystalloid or 2 –4l of colloid.[33,35,39] Fluids should be administered as boluses until end points are reached. These end points may be: a decreasing heart rate with a normal blood pressure; increased urine output; improved sensorium; [40] a loss of baseline variability with respiration on the arterial trace; declining lactate level and an elevated CVP of 10 –12 cmH_2O. In some centres a decline in gastric $PaCO_2$ is used as an indicator of enhanced regional perfusion.[39] If, despite these measures, the haemodynamics have not responded, then the measurement of cardiac output, pulmonary capillary wedge pressure

and the derivation of vascular resistance by the use of PAFC, the bio-impedence monitor or the ultrasonic measuring device is indicated.[30,40]

The use of vasoactive agents is indicated, when despite adequate fluid resuscitation, the patient blood pressure fails to respond. Vasoactive agents may be transiently required in the face of life threatening hypotension even when cardiac pressures are not elevated. The precise level at which to aim for is unclear. Animal studies have shown that loss of auto regulation occurs at a mean arterial pressure of less than 60mmHg.It is currently suggested that a mean arterial pressure of greater than 75 mmHg is appropriate.[39] Elderly patients may require higher blood pressures. These agents should not be used until adequate fluid resuscitation has been instituted. The choice of agent needs to be individualized and invasive sophisticated monitors may be invaluable in aiding in the choice of agent (s.).[30,32,34]

Nor-epinephrine has predominantly α_1 adrenergic effects and moderate β_1 and β_2 adrenergic effects.[32, 39, 42] It is a potent adrenergic agonist and raises the mean arterial pressure by increasing the systemic vascular resistance. The normal starting range is 0.2 - 1.3ug/kg/min. It is the most effective agent in raising the blood pressure. In sepsis, provided that the intravascular volume has been adequately restored, the increase alpha effect does not impact on the splanchnic or renal circulation. On the contrary, the use of Norepinephrine in sepsis may even improve and enhance renal blood flow and renal vascular resistance and urine output.[42] Norepinephrine is not available in South Africa.

Dopamine is a precursor of norepinephrine and epinephrine. Its effects are mediated via dopaminergic (DA) and α and β adrenergic receptors in a dose dependent manner:- < 5ug/kg/min DA1 β_1 adrenergic receptors, 5-10ug/kg/min β_1 and a_1 adrenergic receptors and > 10ug/kg/min α_1 adrenergic receptors.[27, 31] Dopamine increases blood pressure by increasing the cardiac output (increased heart rate and stroke volume), by decreasing the secretion of a hormone. Dopamine may be able to modulate the immune response.[32] At doses of > 20 ug/kg/min it causes an increased pulmonary capillary wedge pressure, pulmonary shunting and right sided cardiac pressures.[32, 39] It has also been shown to impair regional blood flow.[39,63] Low dose dopamine does not impart renal protection.[30, 40,53] In many centers dopamine is still used as the vasopressor of choice.

Dobutamine acts via β_1 and β_2 adrenergic receptors.[34] It is associated with an increase in heart rate and decreased systemic vascular resistance.[30, 32,36] Some authors believe that it is the drug of choice to increase myocardial contractility and achieve supranormal cardiac output and DO_2. In some patients this effect may be detrimental.[39] Dobutamine has been shown to increase splanchnic perfusion and oxygenation. However, these effects parallel an increase in cardiac output. Therefore selective splanchnic effects are unlikely.[39] The effects on renal perfusion are debatable.

Epinephrine increases the arterial pressure by increasing cardiac index, stroke volume and systemic vascular resistance.[30,32,39,42] β adrenergic receptors mediate an increased cardiac output whilst, the α adrenergic receptors mediate the effects on the systemic vascular resistance. It may also cause an increase in heart rate, decreased splanchnic circulation and an increase in lactate [34, 39, 42]. Many authors do not recommend its use as a first line agent for these reasons.[30, 32,34,39,42,53] However, due to the unavailability of some other agents and the expense of others, it has become the first line agent in many centres, including Johannesburg.[68] At the Johannesburg Hospital, at high doses of epinephrine, the splanchnic vasoconstriction is counteracted by low dose dobutamine (5.5ug/kg/min)

Other agents

Isoproterenol is a β_1 and β_2 adrenergic agonist. It causes a tachycardia and hypotension. This drug is no longer readily available. Phosphodiesterase III inhibitors are ionodilators.[32 39 42] They can case profound hypotension, induce thrombocytopenia and show no clear evidence of regional effects.[32 39 42] They also have long half lives [39] Dopexamine has β_2 adrenergic dopaminergic effects, and enhances splanchnic flow. However, further studies on its efficacy are still required.[39] Prostacycline recruits capillaries and enhances microcirculation, but it causes marked vasodilatation and profound hypotension. Phenylephrine is a potent α_1 adrenergic agent. It may cause a decrease in heart rate, cardiac output and severe regional ischaemia. It has no role in the management of sepsis, severe sepsis or septic shock

Shoemaker, et al observed that patients who survived general surgery and trauma had a higher DO_2 than non-survivors. This lead to a proposal that therapy should be aimed at achieving supranormal values (Cardiac index> 4.5l/min.m^2; DO_2> 600ml/min.m^2 O_2 uptake >170ml/min.m^2). This idea showed promise in these homogeneous groups. But this promise has not been sustained in the more heterogeneous groups of the critically ill.[34, 49] In this group, there is still a need to identify patients who will benefit from this approach. In some studies it has been shown that supra-normalization may be of no benefit.[39] Given these findings it would be prudent to individualize haemodynamic therapy in sepsis, severe sepsis and septic shock.

Patients with sepsis, severe sepsis or septic shock are at a higher risk of bleeding in the perioperative period. As previously mentioned these patients may have an isolated thrombocytopenia, platelet dysfunction (due to drugs,renal failure or toxins) are prone to develop DIC, and have hepatic dysfunction.

Platelets should be replaced if the count is<50000 and is rarely required if the level is > 100000. Between 50 –100 000 the risk of bleeding must be considered. [32]

Traditionally the management of DIC has involved three steps; removal of the underlying cause, arrest of the intravascular clotting and the replacement of consumed and depleted coagulation factors.[46] The inflammatory reaction activates the clotting system, inhibits the endogenous anticoagulants and attenuates the fibrinolytic pathway. The use of activated protein C, antithrombin and TFPI have been postulated in the treatment of DIC and with the added spin off of inhibiting the inflammatory pathways. Of the three agents activated protein C shows much promise .[47]

If hepatic dysfunction is considered to be the cause vitamin K and fresh frozen plasma are appropriate therapies.

Anti-sepsis therapies have been aimed at limiting the inflammatory response. There are many possible reasons for the failure of these approaches. The details of these agents and lack of success is beyond the scope of this paper. Corticosteroids in high doses have been shown to have no role in the treatment of sepsis [62, 69] Low dose therapy 50-100mg three times

per day for five days or more can be used in refractory shock. As has been mentioned many of the patients develop an ileus and will require a gastric tube. Given the risk of developing sinusitis it is recommended that this tube also be placed orally.

The maintenance phase of anaesthesia is subject to the standard considerations based on the patient's medical profile. Most volatiles except ethrane can be used. However, the minimum alveolar concentration (MAC) has been shown to be reduced in sepsis.

Most muscle relaxants can be used. Pancuronium has the added advantage of maintaining sympathetic activity. Atracurium and cisatracurium have the added benefit of not requiring hepatic or renal function for metabolism. Vecuronium and rocuronium are the most cardiac stable of the neuromuscular blockers. Extreme caution should be taken in using muscle relaxants in these patients as a combination of sepsis, severe sepsis and septic shock, the concomitant administration of adjuvant drug therapy and organ dysfunction may result in unwanted prolonged action of the muscle relaxant or the development of critical illness polyneuropathy. Monitoring of the degree of neuromuscular blockade with a nerve stimulator should therefore be mandatory in this group of patients.

Morphine requires adequate renal and hepatic function for it's metabolism and excretion. This drug also relies on these organs for the excretion of their metabolites, many of which are more potent than the parent drug. It also causes haemodynamic instability. It should therefore not be used intraoperatively. Fentanyl and sufentanil are more cardiovascularly stable and are commonly used. Remifentanil is a new analgesic agent, which has a short half- life and acts via mu receptors. It is metabolized by esterases (thus independent of hepatic and renal function). Remifentanil's metabolites are said to be extremely impotent. Remifentanil is probably the analgesic agent of choice. Care should be exercised in administering the drug as it can cause marked vasodilatation. However, it is expensive and this precludes its widespread use in this country. It has recently been noted that careful tight control of glucose (glucose maintained between 3 and 6 mmol/l) reduces mortality by approximately 50% in septic patients who were treated in ICU for more than 5 days. [70] It would be prudent to suggest that this approach should be maintained intraoperatively. However, further studies validating this need to be carried out.

Postoperatively, many of the patients will require admission to an ICU or a high care facility for continued therapy. This may include ventilation, haemodynamic management and adjuvant drug therapy. Discussion on these topics is beyond the scope of this paper. Nutritional support is important in these patients. There is, however, no urgency for nutritional support in the first twenty-four hours. Following adequate resuscitation most septic patients will tolerate early enteral feeding which intuitively, practically and economically is better than parenteral feeding.[62] The incidence of deep vein thrombosis (DVT) in non-surgical ICU patients is about 30%.There is no data in the literature with regard to the prevention of DVT in septic patients. Many of these patients are at high risk to develop DVTs and therefore prophylaxis is warranted. Currently low molecular weight heparins are used widely. However, therapy may, in some cases, need to be modified or stopped temporarily, depending on the patients underlying coagulation state. The role of mechanical intermittent pneumatic compression and elastic stockings still needs to be elucidated.

CONCLUSION

Sepsis, severe sepsis and septic shock constitute an ongoing disease process of increasing severity. The patient with sepsis, severe sepsis and septic shock is a high risk patient who's underlying pathology should not be taken lightly. Careful planning and management of the patient is required. In this paper, the current understanding of the pathophysiology of sepsis, severe sepsis and septic shock has been outlined. At this stage there are no successful therapeutic strategies that will intervene in the cascade. An understanding and awareness of the pathophysiolgy and the systemic derangement that sepsis, severe sepsis and septic shock can cause and the implication of this state for the conduct of anaesthesia, will assist the anaesthesiologist in providing optimum and appropriate management. The management must aim to ensure tissue function, haemodynamic stability and adequate oxygen delivery. Treatment should be individualised based on repeated clinical and laboratory evaluation and assessment.

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