Review Article

Septic Shock

Fred Baxter MD, CCFP, FRCPC

Purpose: Many patients with sepsis require surgery for their management, often on an urgent or emergency basis. Anaesthetists are commonly required to manage patients with sepsis and septic shock in the operating room, post anaesthesia recovery area, and the intensive care unit. Since little has been written in the Anaesthesia literature on sepsis and septic shock, a review of this topic was considered appropriate.

Source: References were obtained from computerized searches of the National Library of Medicine (English language), recent review articles and personal files.

Principle Findings: Septic shock is a common cause of morbidity and mortality. Its presentation may be subtle or catastrophic. Successful management depends on an understanding of the pathophysiology of the syndrome, allowing rapid, appropriate resuscitation. This often requires aggressive correction of volume deficit, maintenance of adequate perfusion pressure with inotropic and vasopressor therapy, mechanical ventilation and correction of coagulopathy. Appropriate cultures must be taken and antibiotic therapy started, often empirically. Anaesthetic management should include careful haemodynamic monitoring. Anaesthesia induction and maintenance must be tailored to the haemodynamically unstable patient.

Conclusions: The management of the septic patient in the perioperative period presents a challenge for the anaesthetist. Haemodynamic and respiratory instability should be anticipated. Management requires multisystem intervention and careful anaesthetic management.

Objectif : L'état septique entraîne souvent des interventions chirurgicales dont quelques-unes sont urgentes. On fait fréquemment appel aux anesthésistes pour la prise en charge de l'état ou du choc septique à la salle d'opération, à l'unité des soins postanesthésiques et aux soins intensifs. Comme la littérature anesthésique mentionne rarement l'état ou le choc septique, il semble pertinent de revoir ce sujet.

Sources : Les références ont été obtenues par recherches informatisée de la *National Library of Medicine*(en langue anglaise), des articles de revue récents et à partir de dossiers personnels.

Principales constatations : Le choc septique est une cause fréquente de morbidité et de mortalité. Il peut survenir subrepticement ou dramatiquement. Sa prise en charge efficace nécessite la compréhension de la physiopathologie de ce syndrome, ce qui permet une réanimation rapide et adéquate. Il faut restaurer le volume sanguin agressivement, maintenir une pression de perfusion adéquate, administrer des inotropes et des vasopresseurs. Il faut aussi effectuer des cultures et administrer des antibiotiques quelquefois empiriquement. L'anesthésie doit comporter un monitoring hémodynamique minutieux. L'induction et le maintien de l'anesthésie doivent être adaptés à la gravité de l'instabilité hémodynamique du patient.

Conclusion : La gestion du patient septique à la période périopératoire présente un défi pour l'anesthésiste. L'instabilité hémodynamique et respiratoire devrait être anticipée. Le traitement nécessite une intervention sur plusieurs systèmes et une gestion anesthésique appropriée.

From the Department of Anaesthesiology, McMaster University, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario, Canada, L8N 4A5.

Address correspondence to: Dr. F.J. Baxter.

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I. Introduction

Sepsis and septic shock are commonly encountered by intensivists and anaesthetists. The yearly incidence of sepsis has been estimated at 400,000 cases in the United States.[1] Approximately half of these patients develop shock, with an associated mortality of 20 to 80%,[1] depending, in part, on the severity of underlying disease. The Society for Critical Care Medicine and the American College of Chest Physicians have jointly presented a series of definitions in an effort to standardize terminology relating to sepsis, (Table 1).[2]

It has been recognized that a number of clinical insults (sepsis, trauma, pancreatitis, burns) may result in a systemic inflammatory response. This response has been termed the 'Systemic Inflammatory Response Syndrome' or 'SIRS'.[2]

II. Pathogenesis

Septic shock is most commonly due to gram negative aerobic bacteria, particularly E. coli, Klebsiella and Pseudomonas.[3] Staphylococci, Streptococci, (particularly Streptococcus pyogenes) and other gram positive organisms also cause septic shock in both medical and surgical patients.[3,4] Fungi, particularly Candida species, are a relatively common cause of sepsis and shock in the ICU environment,[3] and viral infection can cause a similar clinical picture.[5] Bacterial toxins, in the absence of bactaeremia, can produce the clinical picture of septic shock.[6–8]

Host factors contributing to the development of sepsis include the extremes of age, chronic disease, substance abuse, immunosuppressive therapy, vascular catheterization, the presence of prosthetic devices and urinary catheters, and tracheal intubation.[3,6,9]

TABLE I Definitions

Infection Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
Bacteraemia Presence of viable bacteria in the blood.
Systemic Inflammatory Response Syndrome (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 bpm; respiratory rate >20 breaths·min or PaCO2 <32 mmHg; and white blood cell count >12,000·mm^{-3}, < 4,000·mm^{-3}, or >10% immature (band) forms.
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 bpm; respiratory rate >20 breaths·min^{-1} or $PaCO_2$ <32 mmHg; and white blood cell count >12,000 mm^{-3}, <4,000 cu mm^{-1}, 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 despite adequate fluid resuscitation along with the presence of perfusion abnormalities that 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.
Sepsis-induced hypotension = a systolic blood pressure <90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes for hypotension.
Multiple organ dysfunction syndrome (MODS) = presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

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III. Clinical Presentation

The presentation of sepsis and early septic shock may be subtle. The identification of sepsis before induction of anaesthesia is critical as its presence predicts haemodynamic instability, particularly on induction.

Fever is commonly present early in sepsis, stimulated by the release of cytokines such as Tumour Necrosis Factor, (TNF), and Interleukin 1, (Il-1).[10,11] Chills and rigors may be witnessed or described by the patient. Alternatively, normothermia or hypothermia may be present, particularly in debilitated patients, those at the extremes of age, or those receiving corticosteroids or other immunosuppressive therapy.

Confusion in a previously-lucid patient may be an early sign of sepsis. Tachypnea, with low PCO_2 and early widening of the alveolar-arterial, (A-a) gradient is often present,[10] and often precedes chest x-ray abnormalities.

The haemodynamic changes associated with sepsis include tachycardia, relative or absolute hypotension, associated with low systemic vascular resistance, and, in the volume resuscitated patient, increased cardiac

output. The extremities are often warm to touch, as opposed to the peripheral vasoconstriction seen in non-distributive shock.

Laboratory findings include leukocytosis with left shift and the presence of toxic granulations. Neutropenia may be present, predicting a higher mortality than leukocytosis. Thrombocytopenia is often present early in sepsis, and attributed to increased platelet loss and endothelial adherence.[13] Other disorders of coagulation are common in patients presenting with septic shock and will be reviewed.

Liver function studies are often abnormal early in sepsis.[10] Metabolic acidosis due to lactate and other anions is often present, with increased mortality associated with elevated lactate levels.[14,15]

Hyperglycaemia is common in sepsis, resulting from increased secretion of catecholamines, cortisol and glucagon with resultant gluconeogenesis, glycogenolysis and insulin resistance.[11]

Hypoglycaemia may be present in late or severe sepsis.[10]

IV. Pathophysiology of Septic Shock

The shock state in sepsis is caused by the release of endogenous mediators, triggered by the presence of toxins produced by the infecting agent[1,16,17] (Figure 1). Endotoxin, (LPS), a component of the cell wall of gram negative bacteria, is the best-studied of the exogenous toxins. Its presence in the circulation triggers the release of Tumour Necrosis Factor (TNF), Il-1, and other humoral mediators, resulting in the clinical syndrome of septic shock.[1,16] Components of gram positive bacteria, fungi and viral elements also are capable of triggering this cascade.[16–18] Purified endotoxin, administered to animals and humans, is capable of initiating the clinical picture of septic shock in the absence of viable bacteria.[7,17]

The endogenous mediators of the syndrome of septic shock include TNF, Interleukins 1, 2, 6 and 8, interferon-γ and platelet activating factor, (PAF). These are released from monocytes, macrophages, neutrophils and endothelial cells.[1,17] Arachidonic acid metabolism is stimulated with the production of thromboxane A2 (TxA2), prostaglandins and leukotrienes. Mediators of myocardial depression are also present.[7] Complement activation occurs and the coagulation cascade is initiated.[1]

A number of mediators target the endothelial cell with a resultant increase in capillary permeability. These include endotoxin, TNF, PAF, the leukotrienes and TxA2.[16] Activation of complement directly affects endothelium and also activates neutrophils which damage endothelial cells. Aggregation factors are released,

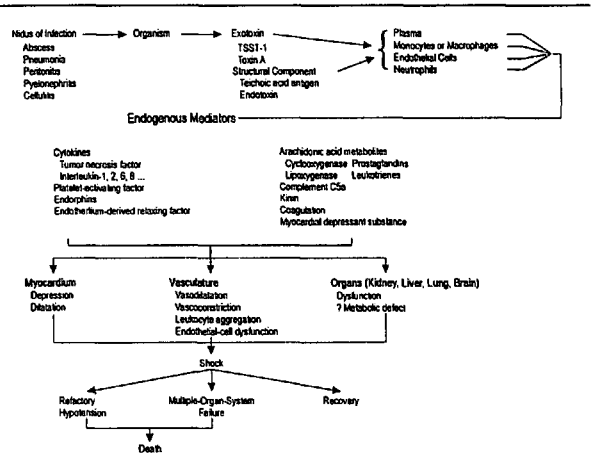

FIGURE 1 Pathogenetic Sequence of the Events in Septic Shock. TSST-1 denotes toxic shock syndrome toxin 1. Toxin A is *Pseudomonas aeruginosa* toxin A.

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enhancing platelet and neutrophil aggregation, with the formation of microemboli. Many of the mediators released cause vasodilation, resulting in hypotension.

1) Haemodynamic Variables:

The hypotension of septic shock results from a) hypovolaemia; b) impaired myocardial contractility and c) decreased systemic vascular resistance. Up to 50% of deaths due to septic shock are caused by refractory hypotension.[1]

A) HYPOVOLAEMIA

Patients in septic shock are commonly hypovolaemic.[19,20] Poor intake, inadequate replacement and excessive insensible losses all contribute to intravascular volume depletion. The generalized increase in microvascular permeability associated with sepsis results in a further decrease in intravascular volume.[21] Oedema formation is enhanced by low oncotic pressure due to hypoalbuminaemia, which is caused by disease, malnutrition, crystalloid infusion and decreased albumin production by the liver.[22] The hypovolaemia is exacerbated by the decrease in arterial and venous tone characteristic of the septic process, which results in expansion of the intravascular space with peripheral and splanchnic venous pooling. The hyperdynamic phase of septic shock depends on fluid repletion.[19] Without adequate volume replacement, a hypodynamic state will persist. Volume loading will dilute the haematocrit, coagulation factors and platelet count.

B) VASODILATATION

The characteristic haemodynamic pattern of septic shock in the volume resuscitated patient is that of a hyperdynamic circulation with tachycardia, increased cardiac output, decreased systemic vascular resistance, (SVR), and impaired responsiveness to vasopressor agents.[5] In some cases, vasodilatation is refractory to aggressive vasopressor therapy and volume infusion. Refractory hypotension may be the cause of death in these cases.

Though poorly understood, it has been hypothesized that the low SVR of septic shock results from adrenergic receptor down regulation, endogenous vasodilatory mediators released during the septic process, and exogenous vasodilators.[3,23] Endogenous vasodilators probably play a role in the hypotension of septic shock. Phospholipase A_2 (PLA_2) levels are elevated and correlate directly with the degree of hypotension in human septic shock.[24] This suggests the possible role of eicosanoids and lysophosphatides in the hypotension of sepsis. Tumour Necrosis Factor, (TNF), causes direct vasodilation in vitro.[25]

More recently, it has been proposed that the excess production of nitric oxide (NO) by the inducible form of nitric oxide synthase may be the final common pathway to the hypotension of septic shock.[5,26] Nitric oxide is a potent vasodilator, acting to increase cyclic GMP (cGMP) levels in vascular smooth muscle cells.[27] Increased levels of products of NO metabolism have been found in adults[28] and newborns[29] with sepsis. Ng-monomethyl-L- arginine (L-NMMA), an inhibitor of both the inducible and constitutive forms of NO synthase has been used in experimental septic shock, with reversal of hypotension and restoration of responsiveness to norepinephrine demonstrated in one animal model.[30] This effect is species specific and may be dosage specific, as L-NMMA is deleterious in endotoxin shock in some animal species.[31,32] Total inhibition of both the constitutive and inducible forms of nitric oxide synthase may prove to be harmful, resulting in end organ damage.[31,32]

Nitric oxide synthase inhibitors have been used in the management of human septic shock, with reversal of hypotension and improved systemic vascular resistance.[33,34] The safety of this approach has been questioned[35] on the basis of animal studies demonstrating poor outcome with non-specific NO synthase inhibition. A controlled trial of NOS inhibition in human septic shock currently is underway.

C) MYOCARDIAL DYSFUNCTION

The most common haemodynamic pattern seen in volume resuscitated patients with septic shock consists of an elevated cardiac index, primarily due to tachycardia, and low systemic vascular resistance. Nevertheless, both left and right ventricular dysfunction have been observed during septic shock.[26,36]

Left ventricular (LV) dysfunction in sepsis and septic shock has been demonstrated by radionucleotide cineangiography[19,37] and transoesophageal echocardiography.[38] Systolic LV dysfunction has been observed in human volunteers during endotoxin infusion.[7] Ejection fraction is depressed and LV end diastolic volume index increased. Right ventricular (RV) dysfunction also has been demonstrated in patients with septic shock.[39]

The aetiology of myocardial dysfunction in septic shock is unclear. Myocardial ischaemia does not appear to be a major cause of ventricular dysfunction. Myocardial lactate production, measured in blood from the coronary sinus during sepsis, was not demonstrated in most patients,[40,41] suggesting that LV coronary flow usually is maintained. A subgroup of patients with decreased coronary perfusion pressure did exhibit myocardial lactate production.[41] It has also been suggested that RV coronary perfusion pressure may be a major determinant of RV function in septic shock, and may determine the ability of the heart to respond to a volume infusion.[42] These observations highlight the importance of maintaining adequate coronary perfusion pressure in patients with septic shock.

Circulating myocardial depressant factors have been implicated as a cause of ventricular dysfunction in septic shock. Serum from patients with septic shock depresses myocyte contraction in vitro.[43,44] Endotoxin and *Il*-2, infused into humans, results in myocardial depression in vivo.[7,44] The negative inotropic effects of TNF-alpha, *Il*-6 and *Il*-2 may be mediated through production of myocardial nitric oxide.[45]

Nitric oxide is synthesized in the heart and has a negative inoptropic effect on myocardial function.[46] Improved LV function has been demonstrated in patients with septic shock treated with methylene blue, an inhibitor of guanylate cyclase.[4,47] Nitric oxide stimulates soluble guanylate cyclase. These studies suggest that increased NO production in the heart may contribute to the depression in myocardial contractility seen in septic shock.

2) Oxygen Delivery and Uptake:

A controversial area in critical care management relates to the debate over criteria for adequacy of oxygen delivery (DO_2). Experimental models of shock have demonstrated that above a critical point of DO_2, (DO_2 crit) oxygen consumption ($\dot{V}O_2$) remains con-

stant despite further increases in DO_2. Below DO_2 (crit), VO_2 begins to decrease, thus becoming "supply dependent."

The concept that supply dependency and, therefore, oxygen debt, may coexist with relatively normal conventional haemodynamic variables, (MAP, urine output, CVP) was initially proposed by Shoemaker. He hypothesized that therapeutically driving DO_2 and VO_2 in critically ill patients to higher than normal ("supranormal") levels, using aggressive volume loading and inotropic agents, would improve survival. His goals of therapy were obtained from a previous study and consisted of averaged values of DO_2, VO_2, and blood volume from ICU survivors. His results, in post-operative patients, showed benefit in terms of survival in patients where DO_2 was driven up to 600 $ml \cdot m^{-2} \cdot min^{-1}$ and VO_2 to 170 $ml \cdot m^{-2} \cdot min,^{-1}$ [49] but his methodology has been challenged.[50]

Subsequent studies of driving DO_2, using similar endpoints, have shown conflicting results. A recent metanalysis of these studies[50] concluded that therapy targeted to achieve supranormal levels of DO_2 did not improve mortality, when all studies were considered. Two studies, which initiated therapy to achieve supranormal DO_2 preoperatively showed an improvement in survival both individually and when their data was combined.[50]

Clearly, it is imperative to maintain adequate blood volume, haemoglobin concentration, oxygen saturation of haemoglobin and perfusion pressure, using volume and vasopressors.[36,51] The addition of dobutamine, as a means of further increasing DO_2 once optimization of volume status has been achieved, should probably be based on evidence of ongoing inadequacy of tissue oxygenation such as elevated serial lactate levels,[51,52] or oliguria. Inotopic therapy should be tailored to the patient rather than managed on the basis of fixed goals.[51]

3) Nervous System:

Central nervous system dysfunction is often an early presenting symptom of sepsis, particularly in the elderly.[10,53] Central nervous system infection is not a prerequisite for CNS dysfunction in sepsis.

The aetiology of septic encephalopathy remains unknown. Possible aetiologic factors include alteration in the blood-brain barrier, toxins, alterations in neurotransmitter levels, changes in receptor function and changes in energy availability.[54] Bowton[55] found depressed cerebral blood flow in eight of nine patients with septic encephalopathy, without evidence of central nervous system infection, and not related to hypotension. Cerebral blood flow CO_2 responsiveness was preserved. Oxygen uptake, measured in three patients, was markedly depressed. The presence of intact CO_2 responsiveness coupled with low cerebral blood flow and cerebral oxygen uptake suggests that aggressive hyperventilation may be hazardous in this population,[55] although data to document this are not available.

Unsuspected microabscess formation has been found at autopsy in some patients with septic encephalopathy[56] and may account for some cases of CNS dysfunction.

A polyneuropathy associated with sepsis and multisystem failure has recently been reported.[57,58] This is associated with axonal degeneration of motor and sensory nerves. Muscle atrophy, including the respiratory muscles, was present at autopsy. The aetiology is unclear.[58]

There have also been a number of reports of prolonged muscle weakness following neuromuscular blockade with non-depolarizing relaxants in critically ill patients in the ICU. This has recently been reviewed.[58,59]

4) Respiratory System:

Tachypnea is an early clinical sign of sepsis, probably stimulated in part by endotoxin or other mediators of sepsis.[10] Hypoxaemia often precedes chest X-ray evidence of Adult Respiratory Distress Syndrome (ARDS). Subsequently, the development of ARDS, with widespread alveolar oedema results in a shunt fraction as high as 50%.

Sepsis is the most common cause of ARDS.[60] Adult Respiratory Distress Syndrome is diagnosed by the presence of widespread alveolar infiltrates on chest x-ray, associated with hypoxaemia and lack of evidence of cardiogenic pulmonary oedema (pulmonary artery occlusion pressure <18 mmHg). Adult Respiratory Distress Syndrome develops in 29–41% of patients with sepsis syndrome and predicts a higher mortality.[61] Sepsis-related ARDS carries a poorer prognosis than other causes of non-cardiogenic pulmonary oedema.[61]

The pathophysiology of sepsis-induced ARDS is related to the elaboration of humoral and cellular mediators of sepsis, resulting in a generalized increase in capillary permeability and increased extravascular lung water.[61] Neutrophils are recruited to the lung where they release proteases and oxygen radicals with subsequent tissue damage.[62] Pulmonary microemboli and platelet aggregates may also contribute to lung injury.[61]

Fluid in alveoli and in the interstitial space results in alveolar collapse and surfactant loss. Hyaline membranes, consisting of fibrin, plasma proteins and cellu-

lar debris, form in alveoli. Using CT scanning, it has been demonstrated that ARDS does not involve all alveoli equally.[63] Thus, relatively normal alveoli coexist with fluid-filled non-ventilated alveoli, resulting in a decrease in compliance, decreased functional residual capacity, total lung capacity and vital capacity. Work of breathing is markedly increased. Pulmonary hypertension develops, probably as a result of both neurohumoral and structural mechanisms. Interstitial oedema and pulmonary microthrombi contribute to the increase in pulmonary vascular resistance.[61]

Experimental evidence has accumulated which implicates ventilator-induced trauma in the exacerbation of lung damage in ARDS.[64–7] Animal studies suggest that overdistension of alveoli, high alveolar pressures and cyclic collapse and reopening of alveoli during the inspiratory cycle exacerbate lung injury. This has led to an approach to mechanical ventilation which limits alveolar pressure, often at the expense of hypercapnia (permissive hypercapnia).[64–7] One randomized, controlled trial[66] and one trial using historical controls[68] suggest benefit using this approach.

5) Gastrointestinal System:

The GI tract has been implicated as both a target and a cause of sepsis and multiorgan failure. Clinical evidence of liver dysfunction is a common and early finding in sepsis[69] with moderate elevation of alkaline phosphatase and transaminase levels sometimes preceding the diagnosis of infection.[70] Liver biopsy may reveal hepatocellular swelling and intrahepatic cholestasis with or without necrosis.[69]

Ischaemic hepatitis or "shock liver" has been reported in septic shock.[69] It is characterized by a sudden, massive increase in transaminase and lactate dehydrogenase levels.[71] Cholestasis is not usually present. Centrilobular necrosis with little or no inflammation is seen on histological examination.

Stress ulceration of the stomach and duodenal mucosa occurs in virtually all critically ill, septic patients.[10] Recent data suggests an incidence of 1.5% for bleeding[72] in ICU patients, primarily in patients with coagulopathy or who are on mechanical ventitation. The pathogenesis of stress ulceration is probably related to impaired mucosal blood flow with mucosal tissue hypoxia and systemic acidosis.[73] Gastric acid also plays a role in ulcer formation[73] and prophylactic antacids, Histamine-2 receptor blockers or sucralafate are commonly used in high risk patients.

6) Coagulation:

Abnormalities of coagulation are common in patients with sepsis presenting for surgery. Vitamin K deficiency, due to poor dietary intake, liver dysfunction, impaired absorption and antibiotic-induced inhibition of gut flora results in decreased activity of the vitamin K dependent factors II, VII, IX and X. This results in prolongation of the INR with relative preservation of PTT, unless the deficiency is severe.

Haemodilution may contribute to the coagulopathy and thrombocytopenia. Platelet counts and INR and PTT should be followed during the initial phase of resuscitation from septic shock.

Thrombocytopenia due to increased platelet destruction is a common finding in patients with sepsis and septic shock, even in the absence of DIC.[10] This is likely due to an immunological mechanism as platelet-associated IgG often is elevated.[74] Dilution also may contribute to thrombocytopenia if large volumes of crystalloid, colloid and packed red blood cells are used during resuscitation.

Platelet dysfunction is common in uraemic patients. The aetiology is unclear but appears to be related to a defect in adhesion.[74] Platelet dysfunction due to previous use of acetylsalicylic acid (ASA) and anti-inflammatory drugs (NSAID) also may be present if these agents have been used in the previous week.

Sepsis and septic shock result in direct activation of the coagulation cascade and simultaneous fibrinolysis. The fibrinolytic system is, however, impaired by inhibitors of fibrinolysis, resulting in a procoagulant state.[75] Endothelial cells normally provide an anticoagulant barrier. Endotoxin, TNF and IL-1 stimulate endothelial cells and monocytes to elaborate tissue factor, which, in turn, binds factor VII, thus initiating the coagulation process.[76] It is speculated that these changes may contribute to widespread microembolization with subsequent multiple organ dysfunction.

Disseminated intravascular coagulation (DIC), occurs in the setting of sepsis and septic shock. The aetiology of DIC in sepsis recently has been reviewed.[75,76] Diagnosis is based on a constellation of abnormal laboratory tests in the setting of clinical evidence of abnormal bleeding with or without evident thrombosis. The blood smear reveals microangiopathic red blood cells. A low, or decreasing, platelet count; low or decreasing fibrinogen level; and elevation of the INR, PTT and thrombin clotting time in an appropriate clinical setting, suggest DIC. Confirmation is made by demonstrating fibrinolysis, usually by means of the D-dimer assay.[76]

Resuscitation and Management

The following recommendations for therapy are graded by levels of available evidence (TableII).[77]

TABLE II Levels of evidence and grades of recommendations for therapy.

Level of Evidence	*Grade of Recommendation*
Level 1	Grade A
Level 1	Results from a single RCT in which the lower limit of the CI for the treatment effect exceeds the minimal clinically important benefit
Level 1+	Results from a meta-analysis of RCTs in which the treatment effects from individual studies are consistent, and the lower limit of CI for the treatment effect exceeds the minimal clinically important benefit
Level I-	Results from a meta-analysis of RCTs in which the treatment effects from individual studies are widely disparate, but the lower limit of the CI for the treatment effect still exceeds the minimal clinically important benefit
Level II	Grade B
Level II	Results from a single RCT in which the CI for the treatment effect overlaps the minimal clinically important benefit
Level II+	Results from a meta-analysis of RCTs in which the treatment effects from individual studies are consistent and the CI for the treatment effect overlaps the minimal clinically important benefit
Level II-	Results from a meta-analysis of RCTs in which the treatment effects from individual studies are widely disparate, and the CI for the treatment effect overlaps the minimal clinically important benefit
Level III	Grade C Results from nonrandomized concurrent cohort studies
Level IV	Grade C Results from nonrandomized historic cohort studies
Level V	Grade C Results from case series

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1) Respiratory Management:

The management of septic shock should begin with assurance of oxygenation, ventilation and airway stability, followed by aggressive haemodynamic resuscitation. Increased diaphragmatic oxygen consumption plus decreased supply in the haemodynamically unstable patient predicts respiratory failure which may occur suddenly. Early tracheal intubation and mechanical ventilation are therefore indicated unless rapid stabilization is expected.

Hypotension often occurs or worsens and should be anticipated following endotracheal intubation and the institution of positive pressure ventilation. Positive pressure ventilation with the resultant increase in intrathoracic pressure, results in a decrease in venous return which may exacerbate hypotension.[65]

Adult Respiratory Distress Syndrome results in decreased alveolar volume with decreased total lung compliance.[63] Conventional tidal volumes of 10–15 $ml \cdot Kg^{-1}$, delivered by volume cycled ventilators, may result in dangerously-high peak inflation pressures with overdistension of ventilated lung units. Decreased tidal volumes ≤ 6 $ml \cdot Kg^{-1}$) with an increase in respiratory rate to maintain CO_2 removal and/or changes in respiratory flow rate or I:E ratio, may allow adequate oxygen and ventilation at lower inflation pressures. It may be necessary (and reasonable) to tolerate hypercapnia with a decreased pH in order to avoid inflation pressures higher than 30–35 cm H_2O[60, 64–8] (Grade B–C).

The use of positive end expiratory pressure (PEEP), in patients with ARDS, is well established.[60] PEEP functions by recruiting alveoli, thereby improving oxygenation, ventilation and compliance.[78] It limits its O_2 toxicity by decreasing the FiO_2 required to maintain an adequate PaO_2, with a goal of maintaining oxygenation with an FiO_2 of 0.5 or less, and may prevent alveolar collapse followed by re-opening, which has been implicated as a cause of lung injury[66] (Grade C).

2) Haemodynamic Management:

The haemodynamic goals of therapy for the patient with septic shock are:

1. A perfusion pressure that provides adequate organ blood flow, and
2. Optimal oxygen delivery.

The mainstay of management of hypotension and DO_2 maintenance is aggressive intravenous volume loading.[20,79] Septic patients are both absolutely and relatively volume depleted. Their resuscitation may require very large volumes of fluid. There is little data to favour colloid over crystalloid as the solution of choice[20] although rapid infusion of colloidal solutions will achieve a more sustained vascular expansion. It has been recommended that colloid osmotic pressure be maintained during resuscitation[79] (Grade C).

Frequently, the haemoglobin concentration and haematocrit decrease with haemodilution. It is useful to crossmatch several units of packed red blood cells early in the resuscitation period to ensure availability of blood and blood products. Blood products, other than albumin, carry the risk of viral infection and should only be given to treat unacceptable anaemia and coagulopathy.

The optimal haemoglobin concentration is controversial and should be individualized based on the assessment of the patient's reserve to maintain oxygen delivery in the face of reduced O_2 carrying capacity. A reasonable goal, in most critically ill patients, is to maintain haemoglobin at or near 100 $g \cdot L^{-1}$.[79] Rarely is transfusion indicated to levels above 100 $g \cdot L^{-1}$ [80] (Grade B–C).

Volume resuscitation should be titrated, initially to blood pressure and subsequently to central venous (CVP) or pulmonary artery occlusion pressure (PAOP). An arterial line, CVP line and, frequently, a pulmonary artery (PA) catheter are inserted for this purpose. Recommendations for PA catheterization have recently been published[81] and support the perioperative use of the PA catheter in patients where haemodynamic stability is compromised (Grade C).

Optimization of cardiac filling pressure is dependent on cardiac compliance, which is not measured in the clinical setting. A target PAOP of 16–18 mm Hg is reasonable in most patients.[79] Further increases in filling pressure may be necessary to optimize the Starling effect in patients with a non-compliant left ventricle but run the risk of lung water accumulation.[20]

Vasopressor therapy is frequently required to maintain perfusion pressure. Vasopressor therapy should be used in conjunction with, but not as a substitute for, adequate volume resuscitation, although it may be used to quickly restore perfusion pressure while rapid volume infusion is being carried out. Vasopressors should be weaned as soon as possible.

Data to support the choice of any specific vasopressor do not exist.[82] Recommendations for specific vasopressor use are therefore Grade C.

Dopamine is often used to initiate vasopressor therapy.[51] It contains alpha (vasoconstrictive) and beta (inotropic) activity with activation of dopamine 1 and 2 receptors. Dopamine 1 receptor activation occurs at doses of 0.5–3 $\mu g \cdot Kg^{-1} \cdot min^{-1}$ and results in vasodilatation of renal and mesenteric vessels which may benefit organ perfusion, particularly when more potent vasoconstrictors are being used simultaneously.[36,51] Dopamine may fail to produce the required increase in blood pressure despite doses of 20–30 $\mu g \cdot Kg^{-1} \cdot min^{-1}$ or may cause unacceptable tachycardia, predisposing the patient to myocardial ischaemia. A more potent vasopressor is usually started if this occurs and dopamine is either continued or weaned to levels thought to provide renal and splanchnic protection (2–4 $\mu g \cdot Kg^{-1} \cdot min^{-1}$).[83] The benefit from low-dose dopamine has not been clearly demonstrated.[51,79]

Norepinephrine may be used in cases where dopamine fails to achieve adequate blood pressure control without excessive tachycardia. Its powerful alpha adrenergic effect counteracts the vasodilatation of septic shock and frequently results in slowing of heart rate and improved urine output.[83] Cardiac index usually increases or is unchanged. Norepinephrine usually is started at 0.5–1 $\mu g \cdot min^{-1}$ (in adults) and is quickly titrated upward to achieve pressure control.

Epinephrine has been used in septic shock, with improvement in CI, DO_2 and MAP.[84] Because of its potent beta effect, it may be a better choice in the presence of inappropriate bradycardia or low CO. Dosage is the same as norephinephrine.

Phenylephrine, an alpha agonist, has been used successfully as a means of increasing perfusion pressure in septic shock.[85] It is started at a dose of 20 $\mu g \cdot min^{-1}$ and titrated to effect.

Normalization of blood pressure does not guarantee adequacy of tissue perfusion. While the hypotensive patient is clearly in shock, it is now recognized that normotension may coexist with inadequate tissue perfusion. Inadequate DO_2 may cause, or contribute to, the subsequent development of multisystem failure.

Optimization of DO_2 is difficult without clear endpoints to define 'adequacy' of DO_2. Resolution of tachycardia and improved urine output are indirect measures of adequacy of DO_2 and tissue perfusion. Decreased lactate concentrations also suggest improved tissue perfusion, although other factors affect lactate during sepsis.[5]

Once volume status, oxygenation and haemoglobin concentration have been optimized, further increases in DO_2 can be obtained by inotropic therapy, usually using dobutamine, starting with a dose of 2–4 $\mu g \cdot Kg^{-1} \cdot min^{-1}$.[86] Addition of dobutamine may result in a decrease in MAP, often as a result of relative hypovolaemia. Dobutamine may be added if evidence of tissue hypoperfusion persists (elevated lactic acid, low urine output) associated with low or low normal CO, despite normalization of perfusion pressure.

As the patient's clinical condition improves, it is important to wean vasopressors as quickly as possible to avoid the consequences of unnecessary vasoconstriction. In general, the most potent vasopressors should be weaned first, followed by inotropic agents and, finally, the low dose infusion of dopamine (Grade C).

Other possible causes of haemodynamic instability should be considered. Gastrointestinal bleeding may complicate sepsis, and serial measurements of haemoglobin and haematocrit should be followed. Cardiogenic shock secondary to myocardial ischaemia or infarction may complicate a septic episode.

Routine steroid therapy for septic shock is no longer recommended. Two recent, well designed, trials demonstrated a lack of efficacy of high-dose steroid therapy in the management of septic shock. Two recent meta-analyses support this conclusion[87,88] (Grade A). Adrenal insufficiency may, however, mimic septic shock in its clinical presentation.[89] Adrenal

insufficiency may result from adrenal atrophy caused by previous steroid therapy. Acute adrenal insufficiency may be caused by autoimmune destruction of the adrenal glands, haemorrhage (anticoagulation, meningococcaemia and after surgery) or in association with infection (tuberculosis), AIDS and pregnancy.[90]

Adrenal insufficiency may present during septic shock and result in unresponsiveness to catecholamine infusions. If suspected, an abbreviated ACTH stimulation test may be done, with glucocorticoid replacement therapy started before results are available.[91] Short-term, high-dose steroid therapy was not associated with any increased risk of complications during septic shock.[87]

3) Gastrointestinal Management:
Patients in septic shock frequently develop ileus.[92] Nasogastric drainage should be instituted early, before regurgitation and aspiration occur.

Though less common than previously thought, GI bleeding from stress ulceration occurs most frequently in critically-ill patients with coagulopathy or who require mechanical ventilation for respiratory failure.[72] Intravenous ranitidine or sucralafate by nasogastric tube are commonly used for prophylaxis.

The details of nutritional management of patients with sepsis are beyond the scope of this paper, and the reader is referred to a recent review.[92]

4) Management of Infection:
Septic shock mandates a search for the cause, which includes a thorough physical examination, appropriate cultures (preferably taken before antibiotics are administered), relevant diagnostic imaging and early, empirical antibiotic therapy. Antibiotics should be chosen based on presumed site of infection and anticipated organism sensitivities. Broad spectrum coverage may be appropriate, with modification when culture reports and sensitivities become available.

Patients with undifferentiated sepsis should receive antibiotic treatment which covers S. aureus and gram negative organisms.[93,94] A first-generation cephalosporin plus an amino-glycoside or, alternatively, a third generation cephalosporin and an antistaphylococcal penicillin, or vancomycin would provide this coverage.[93,94] If a gastrointestinal or female pelvic source is suspected, anaerobic coverage should be included, using metronidazole or clindamycin.[93,94]

Pneumonia requires consideration of Legionella as a possible pathogen. Undifferentiated community-acquired pneumonia often is treated initially with a second or third generation cephalosporin plus erythromycin.[95] Antipseudomonal coverage should be considered in patients with hospital-acquired pneumonia.[96]

The immunosuppressed patient should receive broad spectrum antibiotics which include antipseudomonal coverage. Antifungal and antiviral therapy should be considered.[97] The possibility of line-related sepsis should be considered if indwelling vascular catheters are present.[9] If line sepsis is suspected, lines should be removed and cultured and vancomycin and an aminoglycoside should be administered.[94]

5) Correction of Coagulation Abnormalities:
Abnormalities of coagulation require correction before surgery. Vitamin K deficiency causes elevation of the INR/PT and can be corrected with vitamin K, given sc or iv but may take up to 24 hr.

Practice guidelines for blood product therapy have recently been published.[80] Fresh frozen plasma is recommended for:

1. Urgent reversal of warfarin therapy
2. Correction of microvascular bleeding with elevation of INR/PT or PTT >1.5 times normal (10–15 $ml \cdot kg^{-1}$)
3. Correction of coagulation factor deficiencies where appropriate concentrates are unavailable
4. When one blood volume has been replaced and coagulation variables cannot be obtained rapidly (Grade C).

The platelet count below which bleeding is increased is unknown. Practice guidelines[80] suggest that platelet replacement is rarely indicated if the platelet count is $>100 \times 10^9\ L^{-1}$ and should usually be given in surgical patients, if the platelet count is $< 50\ 10^9\ L^{-1}$. In anticipation of haemorrhage during surgery and in view of the haemodilution of fluid resuscitation an initial target of $100 \times 10^9\ L^{-1}$ is reasonable (Grade C).

One unit of transfused platelets increases the platelet count by approximately $10{,}000\ \mu L^{-1} \cdot m^{-2}$ body surface area.[74] Platelets must be pooled proir to transfusion and often are not immediately available. The hospital blood bank should be warned when a need for platelets is anticipated.

The platelet dysfunction of uraemia can be corrected rapidly with cryoprecipitate (10 units *iv*) or 1-Deamino-8 arginine vasopressin (DDAVP) 0.3 $mg \cdot Kg^{-1}$ *iv* in 50 ml of saline over ½ hour.[74] The platelet dysfunction caused by ASA and NSAIDs can be corrected by an infusion of normal platelets capable of releasing ADP. It has been rec-

ommended that enough platelets be transfused to increase the level by 50,000 $u \cdot L^{-1}$ [74] for complete correction.

The treatment of DIC is controversial. Management of the underlying condition is the primary treatment goal. Factor replacement may be appropriate and necessary. Heparin therapy is controversial.[76] Indications for heparin in DIC are beyond the scope of this paper. Consultation with Haematology is recommended.

VI. Anaesthetic Management

In addition to the usual pre-operative assessment, a number of issues must be clarified when planning anaesthesia for the septic patient. Assessment of haemodynamic stability is of major importance. A "normal" blood pressure does not ensure adequate volume status. Assessment of HR, urine output and mentation, and a review of pre-septic blood pressure may indicate a state of occult hypoperfusion. The patient with frank hypotension presents no diagnostic challenge. Stabilization with volume and vasopressors should usually be carried out before induction of anaesthesia.

Patients in shock or with sepsis should usually be considered to have a full stomach and should be managed accordingly. Assessment of pre-operative respiratory status, including ventilatory variables and recent blood gas analysis are important in predicting intra- and post-operative respiratory problems. As discussed earlier, sepsis and shock warrant consideration of post-operative ventilation. PEEP is not available on all anaesthetic ventilators. Patient dependence on PEEP may require a change of ventilators or addition of a PEEP valve. Adequate ventilation of patients who are dependent on modes of ventilation unavailable on the anaesthetic machine may necessitate transfer of the patient's ventilator to the OR.

In general, infusions of vasoactive agents should be continued until the patient is monitored in the OR. Patients receiving TPN may develop hypoglycaemia if TPN is stopped. Total parentenal nutrition should, therefore, be continued or 10% dextrose infused at the same rate and blood glucose concentration assessed intraoperatively. Insulin infusions may be continued if TPN is continued, but blood glucose should be measured every one to two hours. Tight control of blood sugar may not be appropriate with the patient during anaesthesia because of the inability to identify clinical signs of hypoglycaemia.

Plans for monitoring should include an arterial catheter, placed before induction under local anaesthesia and, at least, CVP monitoring, with preference for a pulmonary artery catheter in patients who are unstable (Grade C). Adequate venous access with large bore *iv* lines should be obtained before induction.

Guidelines for the transport of critically ill patients between hospitals and within the hospital have been published.[98] The transport should be co-ordinated to ensure readiness at the receiving site. Monitoring should be maintained during transport and appropriate personnel should accompany the patient. This should include a physician if the patient is unstable. Adequate equipment and medication should accompany the patient during transfer to ensure the ability to resuscitate during transport, should the patient deteriorate.

There is no specific anaesthetic induction technique for patients with sepsis syndrome or in septic shock. Avoidance of sudden afterload reduction and relative preservation of sympathetic drive makes ketamine attractive in patients with questionable haemodynamic stablity.[99] The use of succinylcholine has been reported to cause hyperkalaemia in patients with prolonged intra-abdominal sepsis,[100] and in other critically ill patients.[101] In an animal model of sepsis, MAC isoflurane was found to be decreased when compared with non-septic controls.[102] Blood product availability should be ensured before anaesthesia. Inotropic and vasopressor agents should be prepared in anticipation of their need during induction.

Post-operative management should be carried out in the ICU. Post-operative ventilation is usually appropriate and is recommended if haemodynamic instability persists or if inotropes must be used in excess of renal protective doses of dopamine.

Conclusion

Optimal anaesthetic management of the patient with septic shock requires an understanding of the pathophysiology of sepsis. Early identification of the septic patient may be difficult and requires a high index of suspicion and a search for clinical signs of sepsis. Haemodynamic instability and respiratory compromise are to be expected if sepsis is present.

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