Part VIII: Shock

Chapter 61: Septic Shock

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This chapter and Chapter 63, Severe Sepsis, are related and should be read in sequence. Septic shock is a clinical syndrome characterized by a diversity of haemodynamic and metabolic abnormalities. The syndrome is associated with the presence in the blood of micro-organisms, their toxic products or both. Nevertheless, it is common to diagnose septic shock in patients with negative blood cultures, ie, the toxic shock syndrome, which is associated with isolation of *Staphylococcus aureus*, usually from the vagina.

While clinical features of septic shock may differ markedly from the classical hypovolaemic and cardiogenic varieties, one common feature is inadequate oxygen delivery to the tissues. In septic shock, total body O_2 delivery (DO_2) may be above normal, but any increase in O_2 demand by the tissues may not be met by the usual homeostatic mechanisms for O_2 delivery.

Microbiology

Gram-negative bacteria are the commonest causes of septic shock in the ICU. However, Gram-positive organisms, anaerobes and fungi (especially *Candida*) may also be responsible.

Pathogenesis

The clinical and physiological response to sepsis appears to be determined by the host, and is not peculiar to specific pathogenic micro-organisms. Patients with septicaemia caused by Gram-positive organisms, Gram-negative organisms, anaerobes and fungi, have shown similar fever, leucocyte, acid-base, and haemodynamic responses.

It seems that the host responds to the toxic products of these microorganisms (endo or exotoxins) by the release of mediators which produce the clinical syndrome. Currently, the monocyte macrophage system is under investigation as it appears to be the most important source of such mediators. Interleukin I and cachectin are just two such products of macrophage monocyte systems cited as playing central roles in this response. Indeed, synergism may exist between two cytokines. The response in humans to injected endotoxin is associated with a brief pulse of circulating cachectin (tumour necrosis factor) and the resultant responses are effected through the cyclooxygenase pathway. Tumour necrosis factor was detected in 10 of 11 patients who died with meningococcal infection but in only 8 of 68 who survived. Patients with the highest levels of tumour necrosis factor all died.

The septic patient usually exhibits a hyperdynamic response, when seen early. A hypodynamic response is usually due to pre-existing hypovolaemia, cardiac disease, or advanced septic response.

Vascular Effects

1. Peripheral Systemic Vascular Resistance (SVR)

Lowered SVR is a usual finding in septic shock and is independent of the type of invading organism. It is the dominant abnormality in patients dying of this condition. There is data to suggest that peripheral vascular failure, rather than cardiac failure, led to death in many patients with septic shock. Among postulated mechanisms of this response is incomplete catabolism of aromatic amino acids, leading to the production of vasoactive substances. Other mediator theories implicate histamine, beta endorphins, decreased C3 component of complement, C3 proactivator, and decreased prekallikrein.

2. Venous Capacitance

An increase in venous capacitance in severe sepsis from a relative hypovolaemia, will cause a fall in preload, and may adversely affect cardiac output.

3. Pulmonary Vascular Resistance (PVR)

This may be abnormal in septic shock. If PVR is not elevated initially, it frequently rises at a later stage. In one series 32% of patients were found initially to have pulmonary hypertension, increased PVR, and a pullmonary artery diastolic to pulmonary capillary wedge pressure (PCWP) gradient of greater than 5 mmHg (0.67 kPa). These findings were associated with an 83% mortality within 48 hours. Again, the mechanisms of an increased PVR are ill understood. Hypoxaemia and metabolic acidosis are well known causes. However, in septic patients, pulmonary hypertension may still be seen without the presence of hypoxaemia or acidosis. Other postulated mechanisms include micro-thrombi, vasoactive amine, endotoxin and angiotensin.

4. Capillary Permeability

In sepsis, capillary permeability may increase rapidly so that fluid is lost from circulation. The clearance of radio-iodinated serum albumin may increase from a normal of 5-10%/h to 20-35%/h in severe sepsis. Cachectin (a cytokine which can lead to fibronectin depletion and decreased cell to cell adherence) may be one of the factors mediating such a capillary leak. Activated leukocytes which release toxic factors such as superoxides, protease and leukotrienes may also increase capillary permeability.

5. Myocardial Effect

Myocardial dysfunction is a common finding in patients with severe clinical sepsis. In most instances, mortality was highest in patients with such dysfunction. Two distinct ventricular abnormalities have been demonstrated in patients with severe sepsis. In response to a volume load sufficient to significantly elevate PCWP, some develop ventricular dilation, while others do not. The former demonstrate an abnormality of ventricular contraction and the latter an abnormality of venticular compliance. Radionuclide scans detected a large sub-group of septic shock patients who developed substantial falls in acute phase ejection fraction,

associated with ventricular dilation and normal or high cardiac output. Most non-survivors in this study had normal ejection fractions but died of refractory hypotension due to low SVR.

It is important to remember that the myocardial dysfunction of sepsis is biventricular. Right ventricular (RV) afterload may increase as a consequence of elevated PVR. Increasing RV preload may maintain flow from right to left ventricle for mean pulmonary artery pressures up to 40 mmHg (5.3 kPa). Beyond this pressure, the increase in RV preload is insufficient to overcome the sequelae of depressed RV contractility, so that cardiac output and oxygen delivery will fall.

Possible causes of myocardial dysfunction in septic shock include a myocardial depressant factor (MDF) and diminished coronary blood flow. Systemic acidosis and hypoxaemia, if present, have added deleterious effects. Myocardial oedema will worsen cardiac compliance. There are circulating humoral factors in the plasma of septic patients which can depress myocardial function in vitro, but the concentration and ability to do so in vivo has yet to be elucidated. Abnormal calcium flux within myocardial cells and diminished alpha and beta adrenergic receptor response are also thought to be important.

6. Oxygen Transport and Consumption

Oxygen consumtion (VO_2) is frequently normal or decreased relative to metabolic demands and this situation occurs at or even prior to the initial hypotensive crisis. Other common findings in the hyperdynamic patient include "pathologically" increased mixed venous oxygen saturation and decreased arteriovenous (A-V) O_2 differences. Two major hypotheses have been proposed to explain this decreased O_2 extraction. The first is the existence of peripheral A-V shunts in severe sepsis and septic shock. This mechanism would explain the observation that at times, septic individuals with low VO_2 are capable of major increases in O_2 extraction. Such shunting and maldistribution of blood flow has recently been reviewed. Microemboli of platelets and white cells, oedema, localized intense vasoconstriction from Thromboxane release and other mediators, could all increase the diffusion distance from capillary to cell. The second view is that cellular and metabolic defects limit the cells' ability to utilize oxygen.

Although VO_2 in septic shock increases if DO_2 is increased, it is controversial whether this tissue demand for oxygen can always be satisfied. Studies in normal subjects in whom DO_2 was artificially manipulated, showed a biphasic response with respect to VO_2. As DO_2 was increased from low levels, a linear increase in VO_2 occurred until a plateau phase was reached where further increase in delivery did not result in increased consumption. However, in sick patients there is a linear relationship between those two variables over a wide range. Indeed, from mathematical analysis, this linear relationship was seen over the entire range of DO_2 recorded.

Clinical Presentation

Manifestations of septic shock cover a wide spectrum. In the classic presentation, the patient is febrile, vasodilated, tachypnoeic and has a hyperdynamic circulation despite a lowered blood pressure. Urine output may be normal, low or high. This is the classic picture of *"warm shock"*. As well as sepsis, other causes producing this picture include acute

pancreatitis and hepatic failure. It is also sometimes seen following cardio-pulmonary bypass and following resuscitation for multiple trauma.

If the septic patient was previously hypovolaemic, had poor myocardial function or was referred late, the picture may be one of hypotension, vasoconstriction and peripheral cyanosis. This has been termed *"cold shock"*. It is not unusual for such patients to be normothermic (or even profoundly hypothermic) and be labelled as having cardiogenic shock, pulmonary embolism, hypovolaemic shock and profound hypothermia. Respiratory failure (associated with the adult respiratory distress syndrome, ARDS), coagulopathy, renal failure, and glucose intolerance are common features (see below).

Management

Septic shock has a high mortality rate and efforts should be made to recognize and treat sepsis before shock occurs. Recognition of sepsis requires both a high index of suspicion and an awareness of conditions which predispose to sepsis. Fever, tachypnoea, glucose intolerance, increasing serum creatinine and altered mental state must always be investigated. Toxic granulations and a shift to the left of the neutrophils are supportive evidence of sepsis regardless of the total white cell count.

As with any shocked patient, management is carried out along lines which encompass:

1. Initial combined assessment and resuscitation.
2. Attempts to ensure adequate oxygen delivery so that O_2 demands are met. This may be guided by clinical, haemodynamic and laboratory monitoring.
3. Methods of diagnosing the cause of the shock, and where possible, eradication of that cause.

A practical set of management guidelines are set out in Tables 1 and 3.

1. Adequate Oxygen and Ventilation

Hypoxaemia is common and in the early phase can usually be reversed by mask oxygen therapy. Should this be inadequate, then continuous positive airway pressure (CPAP) by mask may be employed. Where respiratory failure is severe, endotracheal intubation and either CPAP or mechanical ventilatory support is necessary. An adequate haemoglobin level must also be maintained.

2. Clinical Monitoring and Intervention

Basic monitoring involves repeated or continuous assessment of heart rate, rhythm, venous and arterial pressures. A central venous pressure (CVP) line and in selected cases, a balloon tipped thermodilution pulmonary artery (Swan-Ganz) catheter is inserted. The latter is especially useful if respiratory failure is evident or response to initial fluid loading is inadequate. Haemodynamic monitoring allows cardiac output as well as various pressure measurements to be obtained. Furthermore, the SVR, PVR and left and right ventricular stroke work can be derived. With additional data, DO_2 and VO_2 can be calculated.

Manipulation of the various determinants of cardiac output (Table 2) to attain or maintain the hyperdynamic state can then be made, as survival from septic shock can be directly related to cardiac output, DO_2 and VO_2.

Table 1. *General Measures - Septic Shock*

Administer oxygen, ventilatory support if indicated.
Basic clinical monitoring
- Pulse, systemic arterial pressure
- Central venous pressure
- Pulmonary artery pressure
- Pulmonary capillary wedges pressure (PCWP)
- Cardiac output
- Oxygen delivery (DO_2)
- Temperature, urine output

Chest x-ray
Basic laboratory monitoring
- Arterial blood gas/acid base
- Lactate
- Electrolyte, creatinine
- Blood sugar, haemoglobin
- Platelet and white blood cell count
- Prothrombin ratio
- Liver function tests.

Table 2. *Basic Determinants of Cardiac Output*

Heart rate
Stroke volume
1. preload
2. afterload
3. contractility.

(a) *Preload*

Preload is first manipulated by a colloid fluid "challenge" to a PCWP of 12 mmHg (1.6 kPa). The usual response is a prompt increase in cardiac output. This relatively low PCWP level of 10-12 mmHg (1.3-1.6 kPa) is associated with peak left ventricular stroke work and cardiac indices in patients with severe sepsis and septic shock. Further fluid loading beyond this level should only be used if improvement in cardiac output can be demonstrated and respiratory deterioration does not occur.

Table 3. *Specific Measures - Septic Shock*
Blood cultures
Gram stain and culture from possible sites of infection
Antibiotics
Surgical drainage
Other measures.

(b) *Contractility*

When fluid loading produces an unacceptable rise in PCWP without the desired increase in cardiac output, inotropic support or afterload reduction is then considered. As most of patients with septich shock have lowered SVR, afterload reduction is often inappropriate. An inotropic drug infusion (dopamine 5-10 microg/kg/min or adrenaline 1-15 microg/min) should be started. Often when systemic vascular resistance is profoundly depressed, noradrenaline by infusion is of benefit. A combination of noradrenaline and low dose dopamine is useful. Low dose dopamine prevents noradrenaline-induced renal hypoperfusion in dogs.

If no satisfactory response is obtained, a different inotrope or addition of other agents may be tried. Dobutamine may be used advantageous when one wishes to provide inotropic support whilst lowering both afterload and preload.

(c) *Afterload*

Afterload reducing therapy is conisdered in patients with "cold septic shock" who remain vasoconstricted despite volume loading and inotropic support. Topical nitroglycerine paste was used to treat 8 such patients of whom 5 survived. However, there was a coincident need for more volume expansion which implied an effect of venous capacitance also. Other agents which could be used in this setting include sodium nitroprusside (a vasodilator affecting both preload and afterload) or hydrallazine (affecting primarily afterload). Hydrallazine has also been used to lower PVR in patients with primary and secondary pulmonary hypertension. Pulmonary hypertension occurring in sepsis is associated with a high mortality.

(d) *Oxygen Delivery and Consumption*

DO_2 can be estimated from calculations utilizing the O_2 content of arterial blood (CaO_2) and cardiac output (CO). The measurement of VO_2 clinically is less reliable. VO_2 is most commonly calculated from the formula:

$$\mathbf{VO_2 = (CaO_2 - CvO_2) \times CO}$$

Apart from errors inherent in its calculation, the result reflects only overall VO_2 and not individual organ O_2 utilization. One is thus limited to optimizing DO_2 and VO_2 based upon probable inaccurate data.

It is suggested that optimal goals of therapy in critically ill postoperative patients should be: cardiac index (CI) 50% in excess of normal (ie, 4.5 L/min/m^2), a blood volume 500 mL greater than normal (provided PCWP , 20 mmHg, 20.1 kPa), DO_2 greater than 600 mL/min/m^2 and VO_2 greater than 170 mL/min/m^2. Severely traumatised and septic patients may require greater increases. However, one cautions against sustaining high levels of PCWP as respiratory problems will result.

(e) *Urine Output*

A urine output in excess of 0.7 mL/kg/h should be maintained. If severe oliguria persists despite appropriate fluid loading and adequate peripheral perfusion, a low dose dopamine infusion, IV bolus mannitol (25 g) and IV frusemide (250-500 mg) are commonly employed. There is evidence that all of these agents increase renal blood flow and promote diuresis. Frusemide by its venodilator effect can reduce preload and precipitate hypotension. It may also worsen toxic nephropathy.

3. Chest X-ray

An early erect chest X-ray may show evidence of raised pulmonary venous pressure. In severe sepsis (eg, in any patient with early ARDS) considerable tachypnoea and hypoxaemia may exist despite a deceptively normal-looking chest X-ray.

4. Laboratory Monitoring

This will detect biochemical and haematological abnormalities (Table 3, see also Chapter 63, Severe Sepsis).

Rises in blood lactate suggest severe tissue hypoxaemia and as such, may indicate an advanced stage of decompensation. However, in severe sepsis, lactate may be elevated by mechanisms other than hypoxaemia. Increased circulating catecholamine, by augmenting levels of glycogen phosphorylase (through stimulation of cyclic AMP), lead to increased glycolysis. The pyruvate produced may exceed its ability to enter the TCA cycle. Conversely, in malnourished patients with low glycogen stores, the rise in lactate for a given level of hypoxia may be less. As tissue pH falls, glycogen flux is inhibited. Hence lactate may be an insensitive marker of tissue hypoxia.

Complications and Other Treatment

1. Metabolic Acidosis

This is commonly present as a result of lactic acidaemia due to anaerobic metabolism. Measures to correct hypoxaemia and improve cardiac output will usually reverse this. However, severe metabolic acidosis may lead to further depression of myocardial function, increased PVR and venoconstriction. For these reasons, bicarbonate in aliquots of 50 mmol may be given with close monitoring, although its value in this setting is controversial.

2. Hyperglycaemia

Acute glucose intolerance is commonly precipitated by severe sepsis. Steroids, if employed, may also induce this state. Hypertonic glucose solutions will aggravate the problem. If severe, a low dose insulin infusion is started. Hypoglycaemia may occasionally be seen, especially in the very young and those with severe hepatic dysfunction.

3. Coagulopathy

Disseminated intravascular coagulation (DIC) may occur in septic shock, ranging from a mild, barely detectable disorder to the full-blow syndrome. Management is directed towards reversal of the shock and removal of the septic source. Platelets, fresh frozen plasma and other factors are given if necessary (see Chapter 88, Haemostatic Failure). Vitamin K and folate are routinely given if no contraindication exists.

4. Gastrointestinal Bleeding

This is common in severe uncontrolled sepsis. Antacids, H_2-receptor blockers and cytoprotective agents such as sucralfate are effective in reducing the incidence of this disorder. The aim is to maintain the intragastric pH above 4.0 when antacids and H_2-blockers are used. This necessitates 1-4 hourly monitoring of the pH of gastric fluid. Sucralfate has minimal effect on intragastric pH and has antimicrobial properties. Gastric colonization and nosocomial pneumonia in ventilated patients are less likely to occur when this agent is used.

5. Other Organ Failure

Septic shock can result in failure of virtually any body organ or system. Sepsis is one of the commonest causes of acute respiratory failure (including ARDS), acute renal failure and multiple organ failure seen in the ICU.

6. Adequate Nutrition

Severe sepsis is associated with a hypercatabolic state. Accelerated muscle wasting is frequently alarmingly obvious. Negative nitrogen balance can be minimized by providing nutritional support. This often necessitates intravenous feeding, while avoiding excessive glucose loads. (See Chapter 82, Parenteral Nutrition.)

7. Steroids

The use of high dose steroids (examples: methylprednisolone 30 mg/kg and dexamethasone 6 mg/kg) in septic shock cannot be recommended. Shumer in both retrospective and prospective trials reported lower mortality in those treated with high dose steroid. However, a later prospective study concluded that steroids do not improve the overall survival rate of patients with severe, late septic shock, but may be helpful early in the course and in certain subgroups of patients. More recent controlled clinical trials also demonstrated no benefits from high dose steroids in severe sepsis and septic shock. Moreover, of those treated with steroids, significantly more deaths were related to secondary infection.

8. Agents of Experimental Interest

(a) *Prostaglandins* are known to participate in the pathophysiology of endotoxic and septic shock in both animals and man. Prostaglandin cyclo-oxygenase inhibitors (eg, indomethacin, a non-steroidal antiinflammatory drug) improves survival in animal septic shock models, even when administered after the onset of shock. However, these cyclo-oxygenase inhibitors interfere not only with the formation of the stable prostaglandins, but also with

thromboxane A_2 and prostacyclin (PGI_2). Inhibition of prostacyclin synthesis in septic shock may be undesirable. Prostacyclin is a vasodilator, an antagonizer of Thromboxane A_2, an inhibitor of platelet aggregation and granulocyte adherence. It increases red cell deformability (thereby increasing blood flow through the microcirculation), inhibits gastric acid secretion and stimulates the rening-angiotensin-aldosterone system. Prostacyclin infusion has increased survival in dogs with endotoxaemia. In a recent study of prostacyclin administered to critically ill subjects, the majority who increased their VO_2 had increased the peripheral extraction rate.

(b) *Endogenous opioid peptides* derived from beta-lipotropin are released in septic shock as well as in many other stress states. Experiments in dogs with septic shock have shown that the opioid receptor blocker naloxone can raise blood pressure and improve survival. There are also reports of improvements following the administration of naloxone to humans suffering from septic shock, though more recent reports are not as encouraging.

(c) *Corticosteroids* inhibit beta-lipotropin and therefore endorphin release, and abolish the pressure response to naloxone in septic shock. This suppression of pituitary endorphin release may explain part of their apparent beneficial effect in shock. However, such theoretical benefits do not appear to improve mortality in clinical trials. Also, if interleukin I and cachectin do play a central role in the pathophysiological and clinical response to severe sepsis, then high dose steroids would be expected to be beneficial, as steroids suppress the production of these cytokines. However, circulating cachectin is only detected at the onset of clinical responses to endotoxin. In clinical practice, steroids have been given at the height rather than the beginning of the clinical response and this may explain their ineffectiveness.

(d) *Thyrotropin releasing hormone (TRH)* a tripeptide from the hypothalamus and other sites, has many physiological effects. It opposes many opioid-mediated actions and like naloxone, has been used to treat endotoxic shock in animals. Both TRH and naloxone improved cardiovascular function in experimental endotoxin shock, but TRH also increased the mean arterial pressure of control animals who were not in shock. Another important difference between TRH and naloxone is that TRH does not reverse opioid-induced analgesia.

(e) *Antibodies to lipopolysaccharide (LPS).* Two prospective, randomized clinical trials have demonstrated improved survival time after the administration of antibodies to LPS during sepsis.

(f) *Monoclonal antibody against cachectin.* The haemodynamic collapse, metabolic acidosis and tissue injury stimulated by infusion of recombinant cachectin can be inhibited by monoclonal antibody against cachectin. Pretreatment of baboons with similar antibodies prevented their death after injection with a lethal dose of *E. coli.* Such antibody administration, directed against either the circulating cachectin or peptide receptor binding, has been suggested as a possible new therapeutic modality in the management of clinical endotoxaemia. However, passive immunization against cachectin has a negative effect on survival in murine malarial infection.

Currently, cyclo-oxygenase inhibitors (eg, indomethacin), prostacyclin infusions, naloxone and TRH are not recommended in the management of septic shock at our present state of knowledge. Similarly, whilst cachectin has deleterious effects when produced in

excessive quantities, it has protective effects when produced on a smaller scale in the course of a limited infectious process.

Prognosis

Mortality rate generally remains about 50% in septic shock. Factors discussed in relation to prognosis in Chapter 63, Severe Sepsis, are equally applicable to septic shock. Mortality can be directly related to age and the severity of underlying illness. Origin of the sepsis is also important. Urological cases with septic shock have a better prognosis than sepsis in other organ systems. Haemodynamic findings associated with a favourable prognosis include the ability to maintain an elevated cardiac output and DO_2. Pulmonary hypertension is an averse factor.

When cardiac index decreases in septic shock, survivors are more able to augment SVR than non-survivors. Peripheral vascular failure may thus be a major haemodynamic determinant of mortality in septic shock.