Management of Shock

R.G. Herkes and D.J. Bihari

Shock is the development of inadequate or inappropriate tissue perfusion, sufficient to cause cellular hypoxia, with the accumulation of toxic metabolites [15]. The aim of management must be the maintenance and restoration of a normal *milieu intérieur*. Therapeutic interventions aim to maintain O₂ delivery to cells and treat the underlying precipitant of shock, to prevent vital organ failure which is so often the harbinger of a fatal outcome [79,80]. The syndrome of shock, while having a common final pathway, has been classified into numerous forms; in this chapter attention will centre on the three conventional categories of hypovolaemic, cardiogenic and septic shock.

Shock is a dynamic process in which the measurable haemodynamic and metabolic variables are continually changing, and this betrays the simplistic nature of a formal classification. Immediate end-points of therapy remain the same whatever the cause, or category, and depend upon the maintenance of an adequate delivery of substrate to respiring tissues, with the prevention or reversal of anaerobic respiration [134]. Manipulations by altering blood flow, blood pressure, haemoglobin level and haemoglobin saturation aim to optimize haemodynamics and improve outcome.

The fundamental characteristic of the syndrome is cellular hypoxia due to an acute reduction in circulating blood volume (as in haemorrhagic shock); or to an acute deterioration in myocardial function (as in cardiogenic shock); or to a maldistribution of blood flow, which commonly occurs with a normal or raised cardiac output (as in septic shock). In the past, it has been assumed that the high cardiac output, maldistributive type of shock usually evolves into a more severe state with a low cardiac output; this is now open to question because a number of studies have demonstrated that patients who subsequently die from septic shock maintain a high cardiac output throughout their illness [56,112,130,133,135,139]. Hypovolaemia, absolute or relative, is common in all forms of shock.

Diagnosis of Shock

Shock can be thought of as any acute life-threatening circulatory failure, no matter what the precipitant. Diagnosis is a two-stage process which depends upon the recognition of the critical nature of the illness and the definition of the underlying cause. Clinical assessment aims to classify the shock syndrome into one of the three broad categories described: “primary pump failure”, “primary fluid loss” or “maldistribution of flow”. Attempts must be made to evaluate the four interacting circulatory determinants of blood volume, pressure, flow and tissue O₂ delivery.

Clinical Assessment

Careful clinical assessment allows a logical initial approach to therapy while other data is collected and considered. Most patients will be allocated to their diagnostic category by the context of their presentation. As in so much of medicine the clinician must integrate a carefully obtained history and physical examination with pertinent investigations to synthesize a plan.

Intravascular volume is difficult to assess non-invasively; initial pulse rate, pulse volume
and character, jugular venous pulse pressure and waveform, postural drop in blood pressure, urine output and skin turgor may be used as a guide to treatment while the history, fluid balance records and invasive monitoring are being considered. The most important observation in any shocked patient remains their clinical response to a fluid challenge; this allows the clinical signs to be interpreted dynamically. Hypovolaemia following surgery or trauma is usually obvious as a cause of circulatory collapse, and rapid resuscitation with fluid usually avoids further problems.

Perhaps the most significant difficulty in the clinical assessment of shock is determination of the adequacy of cardiac output. A clinical impression of this is gained from the patient’s temperature, the state of the peripheral vasculature, mean arterial pressure, and the urine output. However, the high cardiac output of maldistributive shock may not be recognized when it is associated with cutaneous and renal vasoconstriction, and “arteriovenous” shunting. The term “maldistribution” is used to describe a disturbance in the blood flow within the microcirculation, related to inappropriate vasoconstriction and dilatation. A breakdown of metabolic and myogenic autoregulation causes a pathological increase in the normal heterogeneity of capillary perfusion, the systemic effect of which is described as “shunting”. Inappropriate use of inotropes may result from a failure to recognize the high cardiac output of maldistributive shock. A source of sepsis must be sought in all patients and pre-existing disease excluded. A history of underlying disease processes is helpful in determining the likelihood of pump failure. Signs suggesting the cause of circulatory collapse, such as a new murmur following acute myocardial infarction, should be sought.

There are a number of other ways in which one can be misled about the state of cardiac function. The correlation between clinical signs of volume status and cardiac output with the adequacy of oxygenation judged from haodynamic and O₂ transport data is poor. Clinical assessment is further clouded by a “phase lag” of as much as 48 h between haodynamic stabilization and the resolution of abnormal physical signs, such as those occurring in pulmonary oedema [100]. Chronic underlying diseases may also cause clinical confusion, with chronic airflow limitation mimicking pulmonary oedema, for instance.

Intimately related to the estimation of cardiac output is the question of O₂ transport and the diagnosis of tissue hypoxia. While cyanosis indicates haemoglobin desaturation, anaemic patients may never develop cyanosis. Arterial hypoxaemia per se is not diagnostic of cellular hypoxia and must be related to total O₂ transport, consumption and extraction (see below). Almost as important in the clinical evaluation of a shocked patient is the assessment of the systemic consequences of shock and the signs of multiple organ failure (Table 18.1). Any cause of shock may lead to the development of acute respiratory failure, acute renal failure [22], hepatic dysfunction [25, 50], encephalopathy [63], coagulopathy [62] and acute myocardial failure [138]. Treatment of these secondary organ system failures should be instituted along with resuscitation of the patient, and often determine the ultimate outcome [79, 80].

**Haemodynamic Assessment (Table 18.2)**

Careful clinical examination in combination with simple investigations including an electrocardiogram, chest radiograph and gated blood pool scan to measure ventricular size and ejection fraction can adequately define haodynamics in many shocked patients and guide the choice of treatment. Clinical responses can often be used to evaluate therapy and avoid further investigation.

Invasive haemodynamic monitoring with flotation pulmonary artery catheters was seen in the late 1970s and early 1980s as a “quantum leap” in intensive care [132]. It was felt that the pulmonary artery occlusion pressure (PAOP)
Table 18.2. Haemodynamic variables

<table>
<thead>
<tr>
<th>Direct measurements</th>
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<tr>
<td>Pulse rate</td>
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<tr>
<td>Blood pressure</td>
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<tr>
<td>Central venous pressure</td>
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<tr>
<td>Pulmonary artery pressure</td>
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<tr>
<td>Pulmonary artery occlusion pressure</td>
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<tr>
<td>Cardiac output</td>
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<tr>
<td>Urine output</td>
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<tr>
<td>Peripheral and core temperature</td>
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<tr>
<th>Derived variables</th>
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<tbody>
<tr>
<td>Stroke volume</td>
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<tr>
<td>Rate pressure product</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
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<tr>
<td>Right and left ventricular minute work indices</td>
</tr>
<tr>
<td>Right and left ventricular stroke work indices</td>
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</table>

Corresponded with left ventricular end-diastolic pressure and that this reflected both preload and intravascular volume. This allowed a full haemodynamic assessment of a shocked patient with pulse rate, central pressures (CVP), mean arterial pressure and thermodilution cardiac output. Moreover, a vast array of derived variables were obtained from these direct measurements, including cardiac index (CI), stroke volume index (SVI), right and left ventricular stroke work indices (RVSWI, LVSWI) and pulmonary and systemic vascular resistance indices (PVRI and SVRI). These were used by the clinician as a guide to preload (CVP and PAOP), contractility (SVI for a given filling pressure) and afterload (SVR), with an assessment of the results of therapy [11].

Recent studies have questioned the widespread use of pulmonary artery catheters, particularly in patients suffering myocardial infarction. Evidence from one study [52] has been used in an accompanying editorial to argue that pulmonary artery catheters need to undergo a controlled trial, with a moratorium on their usage in the interim [127]. This controversy emphasizes the need for all clinicians to evaluate critically the use of expensive, invasive and potentially life-threatening tests.

Pressure measurements, on their own, have little to offer in predicting outcome. Parker [113], in a study of 48 septic shock patients with positive blood cultures, was unable to use conventional haemodynamics to predict outcome, although an initial heart rate of less than 106 was weakly predictive of survival.

Conventional haemodynamic monitoring with the measurement of pressures and flow clearly cannot predict outcome, but can be used intelligently to guide volume and vasoactive drug management. Shoemaker and his colleagues [137] have emphasized that monitoring alone cannot improve survival. He argues that values obtained from invasive haemodynamic monitoring must be manipulated in such a way as to increase the chances of an individual patient surviving. For this reason he has proposed that the patient be resuscitated to “optimal” values of wedge pressure, cardiac output and O₂ delivery rather than just “normal” levels. This resuscitation regimen does seem, in his hands, to improve survival and demonstrate the importance of haemodynamic monitoring. (See Therapeutic Goals below.)

Invasive pulmonary arterial monitoring also offers the possibility of either intermittent or preferably continuous measurement of mixed venous oxygenation, which is a useful guide to whole body O₂ delivery and utilization. The refinement of fiberoptic catheters continuously measuring saturation via light reflectance and absorption has allowed the “tracking” of changes in mixed venous oxygenation which would otherwise be unobserved. The administration of volume, vasoactive drugs, alterations in ventilation and a diverse range of stimuli including many normal nursing procedures can
cause dramatic changes in mixed venous saturation. These changes, which reflect alterations in O2 delivery and utilization occur with such rapidity that they would be difficult to observe using intermittent measurements or monitoring only bulk flow. Moreover, continuous monitoring of mixed venous oxygenation allows a more accurate assessment of therapeutic interventions. The combination of continuous arterial and mixed venous saturation measurements, so-called dual oximetry, allows even closer monitoring of the delivery/utilization equation and has been shown to facilitate changes in ventilation in the critically ill [125].

Assessment of Oxygenation (Table 18.3)

Careful consideration of oxygenation is paramount to the therapy of shock. Hypoxia in any clinical setting may occur at four different levels, as defined by Barcroft [8]:

**Hypoxic hypoxia**

**Anaemic hypoxia**

**Stagnant (low flow) hypoxia**

**Histotoxic or cellular hypoxia**

Hypoxic hypoxia resulting in arterial hypoxaemia is the form most readily identified. Pulmonary dysfunction as a result of ventilation-perfusion mismatching and frank pulmonary shunting is a common occurrence in the shocked patient. It may be the result of pulmonary oedema (left ventricular failure or low-pressure pulmonary oedema of the adult respiratory distress syndrome, ARDS), pulmonary infection, pulmonary embolism or a functional disturbance of the pulmonary circulation secondary to vasoactive factors. It is recognized by the measurement of the arterial PO2 and haemoglobin saturation. Arterial O2 content may be measured directly or calculated (Table 18.3.). A PaO2 of less than 8 kPa or a saturation of less than 90% is unacceptable and requires investigation and usually some form of intervention.

Arterial O2 content depends upon the quantity of haemoglobin available to take up and carry O2 to the tissues, and “anaemic” hypoxia may occur during and after blood loss. Shifts in the O2-haemoglobin dissociation curve may contribute to anaemic hypoxia, but usually they compensate for the reduction in bulk flow of O2 to the tissues. In haemorrhagic shock, the curve is shifted somewhat to the right, allowing delivery of more O2 to the tissues at any given PaO2. It appears that the shape of the curve, and the red cell 2,3-diphosphoglycerate (2,3-DPG) content are not disturbed, but paradoxically the red cell adenosine triphosphate (ATP) increases. Similar increases in the P50 value have been reported in cardiogenic shock and in the maldistributive form of shock associated with liver failure, and are considered to be a protective response [15,60,86].

Two other major determinants of the position of the O2-haemoglobin dissociation curve are pH and temperature. An acidosis shifts the curve to the right, while bicarbonate therapy reverses this protective effect, the resulting alkalosis producing a decrease in O2 delivery to the tissues. Hypothermia has two effects on O2 metabolism. Although the dissociation curve is shifted to the left, resulting in reduced O2 delivery, O2 consumption falls: requirements are reduced. The fall in consumption is much more marked than the reduction in delivery, and hypothermia is used therapeutically in bypass surgery and transplantation to protect organs from ischaemia. Hyperthermia is deleterious despite the rightward shift of the O2-haemoglobin dissociation curve because of the disproportionate rise in O2 consumption. While it is tempting to treat all temperatures aggressively with physical cooling and antipyretic agents, the beneficial affects of temperature on white cell function should also be remembered. In general, to avoid anaemic hypoxia it has been recommended that the haemoglobin concentration should be maintained above 10 g%, preferably using fresh blood, and the arterial pH should be maintained between 7.26 and 7.36 [15].

The third form of hypoxia is that associated with a low cardiac output. Despite a high PaO2 and an adequate concentration of haemoglobin, hypoxia may result secondary to pump failure.

<table>
<thead>
<tr>
<th>Table 18.3. Assessment of O2 transport</th>
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<tr>
<td>O2 delivery (DO2)</td>
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<tr>
<td>DO2 = arterial O2 content × cardiac output</td>
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<tr>
<td>where</td>
</tr>
<tr>
<td>arterial O2 content = Hb × 1.34 × Art sat. + 0.003 × PaO2</td>
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<tr>
<td>O2 consumption or utilization (VO2)</td>
</tr>
<tr>
<td>VO2 = (arterial/mixed venous oxygen content) × cardiac output</td>
</tr>
<tr>
<td>where</td>
</tr>
<tr>
<td>mixed venous oxygen content = Hb × 1.34 × MV sat. + 0.003 × P.O2 (vol. O2 in 100 ml blood)</td>
</tr>
</tbody>
</table>

Art sat., arterial saturation; MV sat., mixed venous saturation.
From the formula for O$_2$ delivery to tissues (Table 18.3) it can be seen that the cardiac output is a major determinant of O$_2$ delivery and a small reduction in its value has important consequences for tissue metabolism.

The final form of hypoxia in the shock syndrome is termed “histiotoxic” or “cellular”. O$_2$ consumption is reduced secondary to cellular poisoning due to circulating “toxins”. Other than poisoning with cyanide and 2,3-dinitrophenol, the nature of these toxins is obscure, and the diagnosis is presumptive, following the lack of response to an increase in O$_2$ delivery. It is difficult to distinguish this form of hypoxia from a reduced O$_2$ consumption secondary to arteriovenous shunting, but it probably occurs, if at all, only late in the course of shock, as a premortem phenomenon. Mitochondrial inhibition by endotoxin has never been demonstrated in vivo in shock, and remains an unsubstantiated hypothesis based upon in vitro findings. Vascular abnormalities are a much more frequent cause of a low O$_2$ consumption and low O$_2$ extraction ratio and a raised mixed venous O$_2$ tension. To our knowledge, cyanide poisoning is the only cause of histiotoxic hypoxia well recognized in the ICU.

Careful monitoring of the pH, base excess, lactate levels and the changes in O$_2$ consumption in relation to changes in O$_2$ delivery will give some clue to whether one is dealing with cellular poisoning (rare) or shunting. Since both of these phenomena occur in the later stages of shock and are difficult to manage, they tend to have a poor prognosis.

In conclusion, it is not possible to diagnose hypoxia using blood gas measurements alone, unless the problem is that of hypoxic hypoxia. The three other forms of hypoxia must be borne in mind, and O$_2$ delivery and extraction studies are essential. This has several practical implications for the physician. One must aim to maintain the haemoglobin concentration above 10 g%, the PaO$_2$ above (8 kPa), the haemoglobin saturation above 90%, and the CI above 4.5 litres/(min/m$^2$) [133]. The detection and treatment of arteriovenous shunting and cellular hypoxia are difficult and remain somewhat experimental; the former might respond to manipulations of the microcirculation (Table 18.4), whilst the latter, if it occurs at all, requires some form of “toxin removal” or a metabolic stimulant (Table 18.5).

**Effects on Other Organs**

The prevention of “multi-organ system failure” is another crucial aspect of the management of shock. Shock has a domino effect throughout the body, affecting all organ systems, precipitating initially reversible and later irreversible organ failure. The most commonly recognized primary manifestations of shock include acute respiratory failure, acute renal failure, acute liver impairment and encephalopathy. There are several hypotheses for the pathogenesis of multiple organ failure (Table 18.6), including maldistribution of flow within the microcirculation, inappropriate and uncontrolled release of cytotoxic mediators and specific defects in cellular metabolism due to a circulating “toxic factor” [14]. None of these theories is mutually exclusive, and all have animal and some human data to support them.

The prevention of multiple organ failure has necessitated the design of various therapeutic regimens such as early mechanical ventilation with positive end-expiratory pressure (PEEP), the use of mannitol, frusemide and low-dose dopamine, and aggressive haemodynamic support with inotropes and vasodilators and the like. Although there is little, if any, evidence from controlled clinical trials to suggest that any of these interventions improve survival, the most effective form of prevention remains the prompt identification and treatment of the initiating cause of shock, so minimizing the haemodynamic disturbance. Of prime importance in this respect is rapid diagnosis and accurate assessment of the degree of circulatory and metabolic derangement.

**Table 18.4. Manipulation of the microcirculation**

| Haemodilution and dextrans, e.g. Macrodex, Rheomacrodex PGI$_2$, PGE$_2$ Other vasodilators Calcium antagonists Anticoagulants, e.g. heparin |

**Table 18.5. Methods of “toxin removal”**

<table>
<thead>
<tr>
<th>Toxin removal</th>
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<tbody>
<tr>
<td>Plasmaphoresis</td>
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<tr>
<td>Haemofiltration</td>
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<td>Peritoneal dialysis</td>
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<tr>
<td>Monoclonal antibodies</td>
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<tr>
<td>Metabolic stimulant</td>
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<td>Dichloroacetate</td>
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### Table 18.6. Theories of multiple organ failure

- Maldistribution of flow within the microcirculation
- Inappropriate and uncontrolled release of cytotoxic mediators
- Specific defects in cellular metabolism due to a circulating “toxic factor”
Table 18.6. Possible pathogenesis of multiple organ failure

1. Mechanical factors producing a maldistribution of blood flow within the microcirculation:
   a) Microembolic phenomena:
      i) Rigid activated leucocytes
      ii) Decreased red cell deformability
      iii) Leucocyte and platelet emboli
      iv) Localized disseminated intravascular coagulopathy
   v) Accumulation of particulate matter
   iv) Increased capillary permeability leading to interstitial oedema and capillary compression
   b) Vasoactive compounds disturbing normal autoregulation:
      i) Endotoxin
      ii) Catecholamines
      iii) Opiods, serotonin, bradykinin
      iv) Eicosanoids (especially TXA₂ and the leucotrienes LTB₄, LTC₄, LTD₄)

2. Inappropriate and uncontrolled release of cytotoxic mediators directly damaging membranes and cells:
   a) O₂ free radicals, proteases, lysosomal enzymes and various eicosanoids from complement-activated neutrophils and stimulated monocytes and macrophages
   b) Various monokines inducing interleukin-1, tumour necrosis factor and proteolysis-inducing factor from stimulated monocytes and macrophages
   c) Thromboxane A₂ from activated platelets

3. Specific defect in cellular and mitochondrial oxidative capacity as a result of direct inhibition, possibly by endotoxin

Reproduced from Bihari [14].

**Irreversible Shock**

Prolonged shock, of any cause, can result in impaired myocardial function, and some authors have considered this to be of prime importance [87,112,120]. Animal studies have demonstrated the direct relationship between myocardial O₂ availability and ventricular performance in haemorrhagic shock [89]. While it is obvious that the balance between myocardial O₂ delivery and demand is of special relevance in shock following acute myocardial infarction, where limitation of infarct size (with preservation of jeopardized myocardial tissue) may determine both survival and later quality of life, optimization of this balance is also crucial to achieve maximal cardiac output in other forms of shock as well. Myocardial O₂ consumption is influenced by the same four major factors which set the cardiac output: preload, afterload, contractility and heart rate. A knowledge of the effect of an intervention on both cardiac metabolism and function is critical to therapeutic decision making.

**Blood Viscosity**

During the acute resuscitation of a shocked patient it is important not only to concentrate on cardiorespiratory support but also to consider haematological aspects of O₂ transport. Under normal circumstances the O₂ transport chain is a highly integrated, adaptable system which makes analysis and research on individual aspects difficult. The relative importance of red and white cell deformity, microcirculatory vaso-motion, alterations in plasma viscosity and even red cell 2,3-DPG are all clouded even in "normal" health. However, it is clear that the rheological aspects of blood flow in shock are important in determining the degree and severity of peripheral shunt. The major determinant of blood viscosity is the haematocrit. Certain forms of shock, such as that induced by thermal injury, are associated with intravascular aggregation of red cells, white cells and platelets, as well as profound salt, water and protein losses through the damaged capillaries. The combination of aggregates and haemoconcentration causes an increase in blood viscosity which can lead to thrombosis of vascular beds. Stored blood is another source of aggregates [99]. The role of these aggregates in the pathogenesis of ARDS following resuscitation with large volumes of unfiltered bank blood is controversial, but it would seem prudent to use effective blood micro pore filters to avoid increasing the risk of development of acute respiratory failure [50a,75].

**The Optimum Haematocrit**

Haematocrit is a reflection of red cell mass and plasma volume, and may change rapidly as fluid effluxes and influxes across peripheral capillary beds. The optimum haematocrit for maximum O₂ transport is 25% for the coronary circulation and approximately 45% for the systemic circulation in dogs with haemorrhagic hypotension. O₂ consumption of the myocardium increases with haemodilution to a peak at 25%, but total body O₂ consumption is constant over a wide range of haematocrit, between 25% and 45% [76]. While once again there is no universal agreement, the aim should be to maintain optimum O₂-carrying capacity with a relatively low viscosity, which can be obtained at a haematocrit between 30% and 40% [32,38,96].
Plasma Volume

Accurate assessment of plasma volume in critically ill patients is a difficult but crucial judgement. Lazrova et al. [85] have described a group of patients in whom cardiac output, CVP, pulmonary capillary pressure (PCP) and other vital signs were normal but who nevertheless were hypovolaemic when plasma volume was measured directly with $^{131}$I-labelled albumin. They emphasize that reliance on routine vital signs may give a false sense of security. Other studies by Shoemaker [134] have shown that a high percentage of surgical patients whose fluid deficits have been replaced according to conventional clinical criteria have significantly reduced plasma volumes. The routine measurement of plasma volume in the management of shock is not useful because the required plasma volume may be much greater than the predicted "normal". In general, measurement of cardiac filling pressures is an adequate and convenient guide to plasma volume, but the limitations must be remembered. The response of cardiac filling pressures to a small volume challenge is a particularly useful method of assessing the adequacy of plasma volume.

Metabolic Derangement

The difficulties in assessment of adequate oxygenation have been emphasized, and the complexity of the necessary measurements add to the clinical problem. The acid–base status of a patient is a convenient variable which can be monitored closely.

The form of acid–base disorder depends upon the severity and the stage of development of the shock syndrome. Moss and Saletta [106], in a study of trauma patients in Vietnam, found that one-third presented with an acidosis but that the other two-thirds had either normal or alkalotic pH because of respiratory compensation. A transient respiratory alkalosis (arterial $\text{CO}_2 < 4 \text{kPa}$) is also common in the early phase of sepsicaemia in association with hyperventilation [16,17,43].

Respiratory alkalosis is rapidly supplanted by a metabolic acidosis, caused by the accumulation of lactic acid as anaerobic metabolism becomes predominant and hepatic and renal clearance of lactate declines [27]. Lactate is a by-product of intracellular glucose metabolism with the only precursor being pyruvate. An elevated lactate usually indicates an imbalance between $\text{O}_2$ supply and demand. Shocked patients usually develop type A lactic acidosis [2,82]. The blood lactate level reflects the severity of circulatory shock, and has been correlated with prognosis [83,156,158].

The treatment of lactic acidosis in the intensive care setting ultimately depends upon the correction of the underlying cause rather than correction of the lactic acidosis per se [155]. Lactic acidosis appears to have a direct negative inotropic effect on myocardial function, especially when combined with hypoxia [3]. Rapid correction of acidosis has therefore been an aim of resuscitation, along with restoration of $\text{O}_2$ delivery. Unfortunately, sodium bicarbonate, the agent usually advocated to raise pH, has not consistently been shown to be effective in correcting either intracellular or intravascular acidosis. Graf [53] showed that infusion of bicarbonate resulted in an increase in lactate levels in hypoxic dogs to a higher level than sodium chloride infusion, with worsening in intracellular pH. Myocardial stroke volume decreased with bicarbonate infusion, worsening cardiac output and blood pressure. The same group demonstrated that portal blood flow decreases with administration of sodium bicarbonate to hypoxic lactic acidotic dogs, increasing the lactate produced in the gut and delivered to the liver. This extra load of lactate arrives at a time of decreased $\text{O}_2$ delivery, worsening intrahepatic acidosis and decreasing lactate extraction further [54]. Left shifts of the $\text{O}_2$–haemoglobin dissociation curve with a reduction in tissue delivery of $\text{O}_2$ are detrimental, and sodium overload is another consideration, especially in the presence of poor renal function.

Alternative therapy for correction of profound acidosis includes sodium dichloroacetate and carbicarb, an equimolar solution of sodium bicarbonate and sodium carbonate. Both have been shown to be more effective than bicarbonate infusion in correcting lactic acidosis in experimental animals [12,55,111], and early human evidence suggests similar results [145].

Abnormal carbohydrate metabolism is frequent in shock, especially when due to sepsis. Hypoglycaemia occasionally occurs in shock secondary to bacteraemia, partially due to depletion of hepatic glycogen stores, and inhibition of gluconeogenesis [62,70,84]. As outlined in the previous chapters, endotoxaemia interferes with the hepatic production of glucose from alanine, glycerol and lactic acid. This is apparently caused by depression of the rate-limiting enzymes (specifically phosphoenolpyruvate kinase and fructose diphosphatase) as...
well as an energy deficit, since ATP is necessary for converting these precursors into glucose [62]. In view of the central role of the liver in glucose homeostasis it is not surprising that hypoglycaemia is much more common in shocked patients with underlying liver disorders [108]. Hyperglycaemia is also seen in shock, although the aetiology is again disputed, with insulin resistance (reflecting glucocorticoid and catecholamine secretion) or deficient insulin secretion being proposed [33]. Hypoglycaemia secondary to the inhibition of gluconeogenesis requires an exogenous source of glucose. Glucose homeostasis, avoiding hyper- and hypoglycaemia, is an important aim in management.

Coagulation Status

Consumption coagulopathy or disseminated intravascular coagulation (DIC) plays an important role in the development of refractory unresponsive shock, especially in association with sepsis. It results from uncontrolled intravascular thrombin generation and fibrin deposition with consequent consumption of clotting factors and platelets, with secondary fibrinolysis. Its cardinal manifestation is the onset of severe, sudden abnormal bleeding which may appear from incisional margins of surgical wounds, or venepuncture sites. Haematuria, bleeding from the nose and gums, and ecchymoses are not uncommon, in association with a general reduction in organ function [29,97]. Laboratory tests of coagulation are essential for accurate diagnosis, but no single test is diagnostic. Prolonged prothrombin time, elevated fibrin degradation products and thrombocytopenia are usual, and a microangiopathic haemolytic anaemia may also be found. Therapy is currently limited to correction of the underlying precipitant, replacement of factors (blood, platelet and plasma transfusion) and support of the patient. The use of heparin and antifibrinolytics is controversial. Heparin should be reserved for patients who have predominantly thrombotic complications [45]. DIC usually indicates a grave prognosis unless the underlying illness can be corrected.

Other Organ Function

The development of multi-organ system failure is the hallmark of a deteriorating patient. Renal and pulmonary function may alter significantly, over short periods. Careful monitoring and treatment of abnormalities is of paramount importance.

Serial measurements of serum electrolytes are essential, and special attention should be paid to the serum potassium concentration in order to avoid cardiac instability. Hourly urine output, urinary electrolytes, and urine: plasma osmolality ratios are important indices of renal function. The creatinine clearance is the most commonly used measure of glomerular filtration; the blood urea is another useful measure but has more limitations.

Mechanical ventilatory assistance is often required in the management of these patients, and therefore monitoring must include the alveolar-arterial gradient, respiratory rate, tidal volume, vital capacity, effective compliance, PaO2 and PaCO2.

Therapeutic Goals

Shoemaker [18,133,134] has established a set of therapeutic goals, derived empirically, to guide treatment. These goals include:

1. CI 50% greater than normal – 4.5 litres/(min/m²)
2. O₂ delivery slightly greater than normal – 600 ml/(min/m²)
3. O₂ consumption 30% greater than normal – 170 ml/(min/m²)
4. Blood volume 500 ml in excess of norm – 3.2 litres/m² for males and 2.8 litres/m² for females

These increases over normal values are to allow for the metabolic demands of trauma, tissue repair and fever. Using these values as guidelines Shoemaker has been able to demonstrate a decrease in mortality in a prospective trial of critically ill postoperative patients from 35% in the control group to 12.5% [137].

Principles of Therapy

The principles of haemodynamic management depend upon a classification of patients into two groups: those with an inadequate cardiac output and impaired tissue perfusion (hypodynamic shock); and those with a high cardiac output, and impaired tissue perfusion due to maldistribution of flow, or metabolic block to
substrate utilization (hyperdynamic shock). Recognition of these two groups can only be made once hypovolaemia as a cause of shock has been treated, with the establishment of adequate cardiac filling pressure and hence preload.

**Volume Replacement Therapy – Optimization of Preload**

The objectives of IV fluid administration are two-fold: to replace body fluid, and to increase preload and cardiac output, which should increase $O_2$ delivery.

The haemodynamic hallmarks of a reduction in effective intravascular volume include: tachycardia, hypotension, arteriolar constriction, reduced systemic venous pressure, reduced ventricular filling pressures, and the concomitant reduction in cardiac output. Rapid and appropriate intervention will reverse hypovolaemic shock rapidly and completely with a good prognosis, provided the underlying cause is treated and the complications of transfusion are avoided. A delay in treatment may lead to multiple organ failure or a form of “irreversible” shock with hypotension persisting in the face of restitution of blood volume.

In many cases logic predicts the need for and type of volume replacement necessary. It is obvious that in frank haemorrhagic shock replacement of blood losses with blood is desirable, while shock associated with reduction in extravascular salt and water should be treated with salt-replete fluids. Similarly, in other forms of shock the fluid that is given should be selected in accordance with the pattern of fluid depletion, and so may be blood, colloid or crystalloid. In the case of water loss, with hypernatraemia and haemoconcentration, hypotonic sodium crystalloid replacement is indicated; shock due to sodium depletion requires repletion with normal saline.

In the fully monitored patient fluid should be given, often as boluses until filling pressures are “adequate” (PAOP 12–15 mmHg) and further fluid boluses of 100–200 ml raise PAOP without increasing cardiac output – the so-called fluid flux test.

**The Colloid vs Crystalloid Controversy**

The rationale for fluid choice in septic or endotoxemic shock patients is complex. Early in the development of septic shock there is an increase in the fluid and protein flux of the pulmonary microcirculation related to pulmonary arterial vasoconstriction and increased protein permeability [20]. This occurs both centrally and peripherally in the lung causing the early appearance of peripheral pulmonary infiltrates, as opposed to the central infiltrates of hydrostatic pulmonary oedema. Many authors feel that the systemic circulation is similarly affected by endotoxin with patchy vasoconstriction and increased permeability leading to oedema [6]. Others report no direct effects of endotoxin on colloid and crystalloid resuscitators, with no final answer in sight. Many of the protagonists overlook the fact that without doubt the most important factor in the success of early treatment is the knowledge and experience of the nursing and medical staff, rather than their choice of fluid. Rapid and aggressive treatment is vital, and so an experienced team should be able to use both types of fluid with equal effectiveness [122].

The three major anatomical structures which control substrate transport to cells from the blood are the microvascular membrane, the interstitium and the lymphatics. Each acts dynamically in response to hypovolaemia and shock, to control fluid and protein transport and oedema formation [38]. A thorough understanding of the relationship between fluid resuscitation and these structures is as yet impossible, but it is clear that different precipitants of shock affect each differently.

Severe haemorrhagic shock appears to alter systemic and pulmonary microcirculations differently. There is little change in the protein permeability of the pulmonary microcirculation, while the systemic microcirculation on the other hand suffers an increase in both fluid and protein flux, frequently leading to oedema [39]. Crystalloid solutions used to resuscitate these patients will thus have little deleterious effect on the pulmonary circulation, but may lead to peripheral oedema, with protein from the interstitium being mobilized to make up for the plasma protein loss. This will lead to interstitial matrix oedema and hypoproteinaemia. Colloid resuscitation, on the other hand, has the advantage that interstitial protein washout is minimized and peripheral oedema is less likely. The importance of oedema in delivery of cellular nutrients is controversial, but certainly cannot help.
the peripheral microcirculation but speculate that decreased perfusion may be the real precipitant to the increased capillary permeability [40]. In this situation both crystalloid and colloid solutions will effectively restore circulating volume, with crystalloid resuscitation causing more hypoproteinaemia and oedema.

In the later stages of established septic shock where there is definite microcirculatory leak both in the lungs and systemic circulation, management should focus on adequately maintaining $O_2$ delivery by manipulation of blood volume and cardiac output, and for this colloids appear most suitable [38,77,133]. Any fluid should be used sparingly to avoid as much as possible further exacerbation of the interstitial and pulmonary oedema [93,94].

A prospective randomized trial to compare colloids and crystalloids was undertaken by Rackow et al. [119] in 26 consecutive patients with hypovolaemic shock; results with albumin, hetastarch and saline solutions were compared. Two to four times as much volume of crystalloid was necessary to maintain haemodynamic stability, and the crystalloid group experienced increased pulmonary oedema in comparison with the colloid groups. Studies by Modig [104] and Haupt et al. [64,65] achieved similar results in humans. In a definitive study of $O_2$ transport responses to colloid and crystalloid infusions in critically ill patients, Shoemaker’s group [66] demonstrated greater and more prolonged increases in plasma volume, CI, arterial pressure, and $O_2$ delivery and consumption in those hypovolaemic patients treated with colloid. Plasma expansion with lactated Ringer’s solution produced only a short-lived expansion of the plasma volume with a fall in $O_2$ consumption and pulmonary $O_2$ transport. There was no evidence of capillary leakage of albumin in these patients.

Studies in rats made hypotensive by exteriorization of the intestine suggest that five times the volume of crystalloid vs colloid must be given to maintain haematocrit values at pre-shock levels [36]. Animals infused with crystalloid show a 50% weight gain, with no improvement in survival. This is in contrast to those animals receiving colloid, who show only a 10% weight gain with high survival rates.

The place of dextran in the fluid resuscitation of shocked patients has received increasing attention. Dextran-70 has the advantage that it can be made up in 0.9% saline or in 5% dextrose. It has a colloid oncotic pressure of 268 mmH$_2$O and half-life of 12 h. Modig [104], in a study of 31 trauma victims in shock treated with either dextran-70 or Ringer’s lactate, has reported that CIs were higher in the dextran treatment group and that ARDS did not develop over the next 8 days. This finding compares with a 30% incidence of ARDS in the group treated with Ringer’s lactate. Similar data is available in a pig model of endotoxin shock [105]. It is interesting to note that some of the beneficial effects claimed for dextrans during shock may in fact be due to pharmacological actions. Dextran-70 has been shown to decrease granulocyte adhesiveness to endothelium and reduces platelet adhesiveness and aggregation. It is postulated that this leads to decreased fibrin trapping in the lung and may protect against the development of ARDS [23,24,103,129]. There is a reported incidence of serious anaphylactoid reactions of 1 in 6000 infusions, similar to that found when using altered gelatin (Haemaccel + Gelofusine), but higher than that found with plasma protein fractions.

### Other Crystalloids

Some authors have achieved success in the treatment of refractory hypovolaemic shock which has not responded to vigorous fluid replacement with hyperosmotic sodium chloride. These solutions have the advantage that small volumes of infused fluid can draw large volumes of intracellular water into the extracellular space [37,153]. The major limiting factors in their use include hypernatraemia, decreased intracellular volume and significant hyperosmolarity [38].

These solutions may reduce myocardial oedema and subendocardial ischaemia, an important factor in the pump failure associated with irreversible shock. Studies in dogs have shown that intracerebral pressure is lower following resuscitation with hypertonic saline than with Ringer’s solution but that cerebral blood flow is still depressed [118]. There is little evidence, however, that hyperosmotic solutions are more effective than more conventional fluid replacement.

The use of glucose-insulin-potassium solutions has been advocated in septic shock [21, 157]. Benefits described include an increase in cardiac output and blood pressure and a fall in filling pressures, especially in those patients with low cardiac output unresponsive to intravenous fluids and inotropes. The beneficial effect of these changes on survival remains to
be fully quantified, and as yet these solutions should remain for trials only.

**Fluid Choice in Shock**

Because of the absence of a consensus view, it is not possible to be dogmatic about fluid replacement. The primary aim of fluid therapy should include the rapid normalization of circulating blood volume, as measured by a PAOP of approximately 15 mmHg, the optimization of cardiac output, O₂ delivery and the survival of the patient [133]. Our knowledge is currently limited, but early data suggests that colloid solutions have many advantages over crystalloids, although they cost considerably more.

When neither clotting factors nor red cells are required, albumin preparations containing over 98% albumin are the colloids of choice. However, their cost is high, and hence their availability is frequently limited to those patients who are hypoproteinaemic, e.g. in acute hepatic failure or the nephrotic syndrome. Purified protein fraction contains 90% albumin and is free from viral and bacterial contaminants such as hepatitis B surface antigen (HBsAg) and human immunodeficiency virus (HIV). It is an excellent solution for volume expansion, but, again, use has to be restricted because of its short supply [119]. Various plasma substitutes are available for use, but all have disadvantages. An ideal plasma substitute should have an oncotic pressure similar to plasma, remain in the circulation long enough to exert its effect, and then be disposed of by metabolic degradation or excretion. Gelatins, dextrans and hydroxyethyl starches are all available and have been used with success. Obviously all these colloids have no O₂-carrying capacity and can only act through volume expansion [131].

**Therapy for the Failing Heart**

Pump failure as a primary cause of circulatory collapse, or as an end-point in the progression of shock, demands active intervention. Myocardial ischaemia, secondary to coronary artery disease, is the most common cause of defective heart function. Other primary causes of pump failure are numerous and include progressive chronic cardiomyopathies, mechanical factors such as valvular obstruction and regurgitation, intracardiac septal defects, and pericardial tamponade. “Cardiogenic shock” is the global term often given to these conditions and this defines a diseased heart as the source of the haemodynamic catastrophe. “Pump failure” is a less specific term, indicating circulatory collapse in association with failure of the heart to pump adequately. This may occur in individuals with previously healthy hearts [28].

Cardiogenic shock causes systemic hypoperfusion with reflex sympathetic cutaneous vasoconstriction and diaphoresis. Arterial hypoxemia secondary to pulmonary oedema may form a major component of the general hypoxic state. Cardiac signs may be minimal, but a gallop rhythm, a pericardial rub, or signs of acute mitral incompetence or ventricular septal rupture are occasionally found. Diminished urine output is characteristic, and acute tubular necrosis may develop.

Right ventricular infarction may cause shock due to a low cardiac output with raised right ventricular filling pressure, and a reduced left ventricular preload. An increase in left ventricular preload by volume loading is essential in management, and the general prognosis is better than in shock associated with left ventricular infarction.

Pump failure accompanying acute myocardial infarction is the paradigm of this form of shock and its therapy. Several workers have demonstrated that cardiogenic shock develops when greater than 45% of left ventricular myocardium is damaged by infarction or ischaemia [61,126]. Many of these patients exhibit triple vessel coronary artery disease with extensive involvement of the left anterior descending coronary artery, causing a large dyskinetic segment in the anterior, septal and apical regions of the left ventricle. This insult severely limits the function of the remaining myocardium, impairing stroke volume and cardiac output. Despite drug therapy with the use of inotropes, vasodilators and antiarrhythmics, 5%-15% of patients with acute myocardial infarction develop cardiogenic shock, carrying an in-hospital mortality of 80%-90% [58,72]. Over the last decade the therapy of ischaemic heart disease and myocardial infarction has been revolutionized as thrombolysis, angioplasty, intra-aortic balloon counterpulsation and aggressive cardiac surgery have allowed myocardial salvage. These forms of therapy, when instituted early, have partially addressed the problems of cardiogenic shock by limiting the extent of infarction [90].
A low cardiac output, secondary to myocardial dysfunction and pump failure, is the terminal event of all irreversible forms of the shock syndrome. The exact mechanisms which result in these profound functional changes in a healthy heart are unknown, but compromised coronary perfusion, increased metabolic requirements, a decline in the ratio of subendocardium to subepicardium perfused, and myocardial interstitial oedema all play some role. Therapeutic interventions in cardiogenic shock are geared to increasing cardiac output, restoring perfusion pressure and preserving myocardial tissue by limiting infarct size.

**Limitation of Infarct Size**

In any discussion of the minimization of myocardial damage some general principles should be kept in mind. As in all tissue, stress on myocardium is a result of an imbalance between substrate delivery and utilization. Unlike other tissue, the heart extracts 65% - 75% of the available $O_2$, so an increase in the extraction fraction is not an option. Therapeutic manoeuvres can be aimed at increasing substrate delivery or minimizing substrate utilization. Substrate delivery to the heart, mainly $O_2$ transport, may be manipulated by changes in diastolic blood pressure, $O_2$ saturation, haemoglobin level and alterations to afferent vessels via thrombolysis, angioplasty or surgery. $O_2$ utilization may be minimized by arrhythmia prophylaxis, alterations in inotropic and chronotropic state, vasodilation and sedation [107].

Each of these mechanisms of altering the balance between supply and utilization has been recently addressed. Large multicentred trials have demonstrated the benefits of thrombolysis with either streptokinase or tissue plasminogen activator, achieving recanalization of about 75% of recently occluded vessels, with decreased short- and long-term mortality, and smaller infarct size [57,78,148,161]. Other studies have shown the efficacy in acute myocardial infarction of beta blockade, which limits myocardial $O_2$ demand and thus infarct size and decreases the risk of arrhythmias [74,101]. Vasodilators, including nitroglycerin and nitroprusside, have been shown to diminish the mortality in acute myocardial infarction to some degree, while calcium antagonists give acutely have been shown to increase mortality slightly [161]. As a group these trials fail to address the problems of shocked patients, who are often not entered into study protocols because they may be disadvantaged by therapy.

**Pharmacological Agents in Cardiogenic Shock**

In the shock syndrome secondary to pump failure, there are two major methods of reducing myocardial work, and hence myocardial $O_2$ consumption: the control of inappropriate and disruptive tachyarrhythmias, and the reduction of afterload [126].

If after attempts to optimize preload and improve myocardial contractility the haemodynamic state remains unsatisfactory, then reducing ventricular afterload may be helpful. Such vasodilator therapy has been described by Braunwald as a “physiological approach to heart failure”. Myocardial systolic tension is a major determinant of myocardial fibre shortening and $O_2$ consumption, and a reduced afterload permits greater ventricular muscle shortening with an increase in ejection fraction and cardiac output, usually with reduced myocardial $O_2$ consumption and heart size. In a normal left ventricle reduction of afterload does not greatly augment left ventricular stroke volume, and arterial blood pressure may fall. Reflex tachycardia compensates for the fall in peripheral resistance by increasing cardiac output and maintaining arterial pressure. The more abnormal the function of the left ventricle, however, the greater the stroke volume will rise as afterload is reduced, and thus a smaller fall in arterial pressure is observed, often without tachycardia.

The main indications for reduction of afterload include:

1. Evidence of vasoconstriction and oliguria in the presence of a systolic pressure of greater than 90 mmHg
2. Pulmonary oedema with a low cardiac output
3. Pulmonary oedema in association with acute mitral incompetence, or a ruptured interventricular septum

Caution should be exercised because severe hypotension, with concomitant decreases in coronary, cerebral, and renal blood flow, is a major hazard. As nearly all vasodilator drugs cause some venodilation, preload may fall precipitously necessitating volume expansion.
Careful haemodynamic monitoring is essential because the response to such drugs as nitroprusside and nitroglycerin is sometimes unpredictable. A high filling pressure is essential at the start of therapy in order to minimize the drop in preload. Tachycardia may indicate inadequate preload and must be avoided in order to minimize myocardial O₂ consumption. Nitroprusside or an angiotensin converting enzyme (ACE) inhibitor are the agents of choice.

Nitroprusside remains the more suitable agent for acute afterload reduction because it has a lesser effect on the venules and produces a rapid and predictable response, which is easily terminated [72]. It has been suggested that increases in subendocardial blood flow are more profound with nitroglycerin, but there is no good evidence of this in man. Nitroglycerin has an important role in the management of patients with a low output state and pulmonary oedema. In this situation, reduction of preload and afterload is indicated and is best achieved with this drug [91].

The effects of the various inotropes on the imbalance between myocardial O₂ supply and demand are somewhat variable. Any increase in cardiac output achieved through increasing myocardial contractility is associated with an increase in myocardial O₂ consumption, which needs to be met by increased coronary perfusion. An alpha-adrenergic agent may improve myocardial perfusion but be insufficient to increase other vital organ perfusion adequately. A beta-adrenergic agent will increase peripheral perfusion at the cost of higher myocardial O₂ requirements in excess of increased supply [107].

Dopamine, a precursor of 1-noradrenaline, has specific dopaminergic, beta-adrenergic and alpha-adrenergic effects depending upon the infusion rate. At low doses of <4.0 µg/(kg/min) it acts only on dopaminergic receptors, causing an increase in renal and splanchnic blood flow, with little effect on systemic blood flow. As the infusion rate is increased to doses of 5–10 µg/(kg/min), the drug has a positive inotropic effect by stimulating beta-1 receptors on the myocardium directly, increasing cardiac output and blood pressure, with only moderate increases in myocardial O₂ consumption. Increasing the dose to 10–15 µg/(kg/min) increases the beta-1 effect with positive chronotropic effects. It has less chronotropic effects than isoprenaline. At high doses of >15 µg/(kg/min), alpha vasoconstriction and the generation of arrhythmias becomes more prominent. It is difficult to predict its effects on the balance between myocardial O₂ demand and supply, but comparison with dobutamine suggests that the latter is superior in this respect [49,92].

Dobutamine is the result of systematic modification of the chemical structure of isoprenaline and is now recommended by many as the inotrope of choice following myocardial infarction. It acts directly on the beta-1 receptors in the myocardium to produce an increase in contractility, with only a weak chronotropic effect. Peripheral vasoconstriction is unusual even at maximal doses. In acute myocardial infarction in man it augments left ventricular performance without increasing enzymatically estimated infarct size [51]. At high doses of >10 µg/(kg/min) dobutamine causes tachycardia, deterioration of myocardial metabolism and frank myocardial ischaemia [107].

Comparison of dobutamine and dopamine in patients with low output cardiac failure demonstrates that for the same increases in cardiac output and heart rate, dobutamine decreased mean arterial and pulmonary capillary pressures, whereas dopamine does not change arterial pressure, and increases pulmonary capillary pressure. Similar findings were demonstrated in a crossover study of dopamine and dobutamine in patients with congestive cardiomyopathy and heart failure. Dobutamine produced a progressive rise in the cardiac output by increasing stroke volume, while simultaneously decreasing systemic and pulmonary vascular resistances and filling pressures. There was no increment in heart rate or premature ventricular contractions. As arterial pressure rose with increased doses of dopamine, pulmonary capillary pressure also rose, and the incidence of ventricular extrasystoles increased. Dobutamine would seem to be the inotrope of first choice following myocardial infarction [107].

Isoprenaline consistently increases heart rate, produces arrhythmias, lowers aortic diastolic pressure, and further impairs myocardial metabolism, as evidenced by increases in coronary sinus lactate concentrations. Isoprenaline’s main use is to increase pulse rate in bradycardic patients, when used at low doses [68].

Noradrenaline, a potent alpha agonist with mild beta effects, increases myocardial O₂ demand, but this increase may be equalled by an increase in delivery secondary to an increase in aortic diastolic pressure, particularly if profound hypotension exists [9a,68].

It seems likely that inotropes seldom improve the imbalance between myocardial O₂ supply and demand, and frequently aggravate it, em-
phasizing the role of mechanical support of the circulation in the post-infarct situation. Inotropic agents have the reputation of “thrashing the myocardium to death”, but are invariably required in pump failure states. Suffice it to say that there are no magic potions available and all such agents have their disadvantages. There is sometimes value in combining two inotropes in the management of the critically ill patient, and a low-dose dopamine infusion to protect renal perfusion is often of value in combination with another catecholamine, such as dobutamine or noradrenaline, which provides full inotropic support. Early introduction of mechanical support, before the myocardium is “thrashed to death”, is recommended, with subsequent reperfusion of jeopardized myocardium or repair of mechanical abnormalities.

Mechanical Support of the Circulation

The development of temporary mechanical methods of circulatory assistance has been an important priority in cardiovascular research. Mechanical support of the circulation allows patients to settle following cardiac bypass, acts as a temporary bridge to definitive repair of a mechanical defect (such as mitral valve incompetence or atrial septal defect) or buys time in which to find a suitable donor for cardiac transplantation. The most widely used device is the intra-aortic balloon counterpulsator (IABCP). The balloon pump augments diastolic pressure and reduces afterload. Resnekov [126] has demonstrated that left ventricular end-diastolic pressure is reduced by about 20%, while cardiac output rises by 40% in patients with cardiogenic shock.

The best-defined indication for the use of IABCP is after cardiac surgery to assist a patient off cardiopulmonary bypass, when a limited period of pumping may allow the myocardium to recover from the intraoperative ischaemic damage. In the preoperative setting the balloon pump has a role in stabilizing patients needing surgery for mitral incompetence or repair of an atrial or ventricular septal defect.

The role of IABP in patients suffering acute myocardial infarction is only now being fully evaluated. Large multicentre trials using pharmacological and balloon pump support for cardiogenic shock suggest a survival rate of less than 20%, when no underlying lesion is corrected [42,58]. DeWood [42] demonstrated that pharmacological and balloon support, when combined with early surgical revascularization (within 16 h of infarction), reduced mortality to 25%. Lee and coworkers [90] have demonstrated a 23% mortality in patients with infarct-related cardiogenic shock using IABCP, inotropes and vasodilators with subsequent successful angioplasty. This finding compared with an 82% mortality in those in whom angioplasty was unable to re-establish perfusion. It would seem that IABCP can be used successfully to resuscitate a patient until other procedures are undertaken to rectify the precipitant of shock.

In conclusion, the available evidence suggests that IABCP should be used early in the development of cardiogenic shock, in those patients likely to have reversible causes. Without reversible underlying causes for cardiogenic shock the prognosis is grave, with at best 20% survival to discharge. Using myocardial salvage and repair of mechanical lesions, survival is considerably improved.

IABCP may have a role in the management of septic and anaphylactic shock, especially where myocardial depression is the prominent feature. Coexisting coronary artery disease and myocardial ischaemia is an important element in this form of myocardial depression, particularly in the elderly patient, and the maintenance of coronary blood flow is a fundamental consideration. Berger et al. [10] employed IABCP in two patients in advanced septic shock and coronary artery disease, reversing the shock state with survival of both patients [112]. Raper and Fisher [123] have used IABCP successfully in anaphylaxis following bee sting, with demonstration of return of left ventricular function, in an otherwise normal heart.

“Paracorporeal left ventricular support” is a blanket term used to describe a variety of mechanical support measures which have been employed in desperation, usually in order to take a patient off cardiopulmonary bypass or as a bridge to cardiac transplantation. These methods are designed to unload the damaged left ventricle totally while also maintaining adequate levels of systemic blood flow. In the post-bypass setting left ventricular contractile function will show a significant improvement in the first 72 h, if any significant recovery of cardiac function is going to take place at all. [102,115] Others have successfully used a mechanical heart such as the Jarvik as a bridge to transplantation [69]. The implications of successful paracorporeal support are as extensive as they are expensive, but the widespread application of
this form of therapy awaits further investigation and technological advance.

Heart Transplantation

Cardiac transplantation has become the standard form of aggressive treatment for irreversible cardiac failure of almost any cause, with over 90% 2-year survival. The main limiting factors remain the availability of suitable donors and of the resources needed to carry out such a program [28].

Management of High Cardiac Output "Distributive" Shock

Hypotension with reduced peripheral resistance due to physiologically inappropriate regional vasodilatation characterizes this alternative form of shock. Of all patients with bacterial sepsis 40% suffer profound hypotension and shock, with a mortality of about 50% [147]. Although this clinical entity usually occurs in association with sepsis, it is also seen following anaphylaxis, as a sequel to a neurological insult, or in association with toxic, metabolic and endocrine depression of vasomotor tone. Systemic hypotension with its impaired perfusion pressure, compromises perfusion of vital organs [62]. Although flow has been emphasized as the essential determinant of O2 delivery and substrate supply to tissues, it is vital to remember that autoregulation of blood flow to the cerebrum and the kidneys, and within the coronary circulation can only compensate for a limited range of perfusion pressures. At low levels of arterial pressure, flow is dependent entirely on pressure. Reduction of mean systemic arterial pressure below about 50 mmHg is accompanied by a marked decline in cerebral blood flow, as autoregulation is inoperative. Similar pressures have been established for flow in the renal vascular bed [146]. Therefore, in order to maintain perfusion of these vital organs, therapy must be aimed at the maintenance of systemic arterial pressure as well as flow.

The initial lowering of arterial blood pressure in septic shock, is accompanied by a reduction in O2 consumption (or inadequate O2 consumption for demands), despite a raised cardiac output and O2 delivery [5,133,134,140]. These changes are not explained exclusively by a decline in total peripheral vascular resistance and perfusion pressure of vital organs. Experimental evidence suggests that distribution of flow may vary greatly during shock, with maldistribution of flow to areas of low O2 demand such as the splanchnic bed, while other areas of high demand are poorly perfused, with consequent lactic acidosis. Changes in the microcirculation may also contribute to the narrow arteriovenous O2 content difference [73,121]. Therapeutically increasing DO2 causes an increase in O2 utilisation in septic shock with subsequent fall in lactate levels, a phenomenon called flow (or delivery) dependency [5,65,160]. Furthermore, myocardial dysfunction often becomes prominent in both early and late stages of this form of shock, but is completely reversible [112]. Ellrodt [44], in a series of 35 septic shock patients, demonstrated abnormalities in left ventricular function in all but one patient, with 74% suffering segmental wall dyskinesis. There was no correlation, however, between ventricular dysfunction and outcome. Some authors attribute mortality in septic shock to continued inappropriate vasodilation, despite increased cardiac output, rather than dying from myocardial failure [147].

Most studies of sepsis and trauma have shown that survival correlates with high cardiac output on arrival, high O2 delivery and O2 consumption, and higher blood volumes [1,121]. Shoemaker [133,134] has proposed that "physiological goals" for the optimal treatment of septic shock should include values of cardiac output, O2 delivery and O2 consumption higher than "normal" for non-septic survivors of postsurgical critical illness. These values, as outlined above, include CI 50% higher than normal (4.5 litres/(min/m2)), O2 delivery >600 ml/(min/m2) and O2 consumption >170 ml/(min/m2).

As with any form of shock, hypovolaemia plays a major role in the aetiology of hypotension and should be addressed early in therapy. Haupt [65] has demonstrated an increase in O2 delivery, O2 consumption and a reduction in lactic acidosis in septic patients treated with fluid repletion. Once again haemodynamic data obtained from a pulmonary artery catheter is generally used to guide therapy, aiming for a PAOP of 12–16 mmHg. The choice of fluid for resuscitation is again largely a matter of personal preference, in the light of evidence to support both crystalloid and colloid solutions, and arguments as to which solution worsens oedema both in the lung and peripherally [38].
Adequate fluid resuscitation should be achieved prior to further vasoactive therapy.

Role of Vasoactive Drugs

Once preload has been assessed and deemed to be sufficient, attention must turn to pharmacological methods of manipulating organ blood flow in order to maintain cerebral, coronary and renal blood perfusion. General supportive measures should not be forgotten, i.e. maintenance of arterial $O_2$ content, correction of a severe metabolic acidosis, optimization of the haematocrit, correction of electrolyte and blood sugar abnormalities, and attention to clotting abnormalities. This will ensure the best possible circumstances in which pharmacological intervention may act. If systemic hypotension persists despite these measures, in combination with adequate fluid replacement, there are a number of possible approaches.

Inotropes

Therapy with inotropes is primarily aimed at increasing cardiac output, and thus $O_2$ delivery, while maintaining blood pressure. There is little direct evidence to favour the use of any one agent over the others, although dopamine and dobutamine have theoretical advantages. The pharmacology of these drugs is well known, but it should be emphasized that during sepsis there is down-regulation of adrenergic receptors, necessitating larger doses of these drugs than in other forms of shock [26]. Most authors favour the initial use of dopamine in beta-adrenergic doses of 5–15 μg/(kg/min) with use of alpha-adrenergic doses of $>20$ g/(kg/min) if the patient’s mean blood pressure is not maintained at greater than 60 mmHg [114]. Should this be insufficient to maintain perfusion pressure, the use of vasoconstrictors is indicated.

Vasoconstrictors

There is no doubt that arterial pressure can be restored to satisfactory levels using alpha agonists (noradrenaline, high-dose dopamine, metaraminol). Recent studies have demonstrated that noradrenaline may produce increases in CI and myocardial blood flow and a decrease in pulse rate. Renal vasoconstriction may be prevented by a simultaneous infusion of low-dose dopamine (2.5 μg per kg/min), and urine flow may even increase [41]. In the face of profound, persistent hypotension, the judicious administration of noradrenaline is justifiable. It must be emphasized that continuous monitoring of cardiac filling pressures, cardiac output, $O_2$ delivery and $O_2$ extraction is essential in order to assess this potentially hazardous pharmacological intervention. The potentially severe complications of vasoconstrictor therapy, with the development of acute renal failure, ischaemic digits and skin, must be weighed against the severity of illness.

Vasodilators

The rationale for the use of vasodilators, including nitroprusside, nitrates, hydralazine and prostacyclin, rests on the accepted theoretical consideration that the observed systemic hypotension is partly induced by arteriolar vasoconstriction with the opening up of many low-resistance arteriovenous shunts. Vasodilators may improve actual tissue perfusion by increases in cardiac output and correction of vasoconstricted beds. The essential prerequisite for the use of vasodilators is normovolaemia, with adequate preload, otherwise profound hypotension will ensue. There is little substantial evidence to support the widespread use of vasodilators at present, especially in the face of hypotension [14].

In conclusion, the management of the patient with profound hypotension and a normal or raised cardiac output is extremely difficult. If severe vasoconstriction is present and an adequate arterial pressure maintained, vasodilatation in association with fluid replacement is the treatment of choice. Frequently, however, arterial pressure is so low that a further reduction in peripheral resistance, cannot be contemplated and vasoconstriction is indicated. Finally, alpha agonists can be used and, when administered with due care, produce good results.

Diagnosis and Management of Sepsis

Sepsis continues to be a major cause of death in critically ill patients, despite advances in its management, with the use of specific antibiotics, aggressive surgical intervention, and intravenous/enteral hyperalimentation. Moreover, sepsis may be not only the final insult in patients
dying of profound underlying disease, but also, all too frequently, the only insult to otherwise young healthy individuals. Recent trends in modern medicine, leading to liberal use of immunosuppressive agents and increasingly invasive procedures, have increased the risk of infection, often with otherwise minimally pathogenic organisms. Aggressive treatment of both "benign" and malignant diseases, not to mention transplantation, has salvaged numerous patients, allowing them to go on and live prolonged, productive lives. But this achievement is at the cost of compromised host defences. Frequent instrumentation and the widespread practice of extensive abdominal and pelvic surgery have contributed to an increasing incidence of septic shock. The development of invasive monitoring in the treatment of the critically ill has also allowed a portal of entry directly into the vasculature for many organisms, while the use of broad-spectrum antibiotics in a seemingly random manner has facilitated the development of multiresistant strains of bacteria. The use of devices such as indwelling intravenous catheters (especially those used long-term for parenteral nutrition) and bladder catheters markedly increases the risk of sepsis developing in the critically ill [34,109]. Despite the advances in therapy for septic shock, most research groups still report a mortality in excess of 40% [1,56].

Any microorganism capable of infecting the human host ultimately may produce an overwhelming septicemia that evolves into septic shock. The haemodynamic response to shock is essentially the same, no matter what the underlying organism. Fungal organisms, viruses, rickettsiae, Gram-positive aerobic bacteria, and the Gram-negative anaerobic bacteria have all been incriminated in causing this form of circulatory collapse, but the organisms of major importance are the Gram-negative aerobic rods, which produce endotoxin [62,121]. In several large series, the most commonly isolated pathogen was *Escherichia coli*, followed by *Klebsiella pneumoniae*, *Proteus* sp. and *Pseudomonas aeruginosa* [9]. *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most frequent Gram-positive causes of septic shock. Anaerobes, particularly *Bacteroides*, are responsible for about 10% of cases following abdominal surgery. Shock is thought to develop in 25%–50% of patients who develop Gram-negative bacteremia. The genitourinary tract is the most common source of infection, while the gastrointestinal and respiratory tracts are also frequently sources [121].

Many bacterial substances have been shown to have vasoactive properties. Endotoxin, a lipid-A moiety of lipopolysaccharide found in the cell wall of all Gram-negative organisms, and peptidoglycan of Gram-positive cell walls have been shown to elicit many of the features of sepsis when injected into experimental animals and human volunteers. Endotoxin can damage capillary and post-capillary venular endothelium, and the lipid-A of endotoxin is recognized as one cause of vasospasm and intravascular coagulation. Endotoxin is able to produce a rapid release of cachectin/tumour necrosis factor from monocytes and tissue macrophages and this is believed to mediate most of the manifestations of shock [13,35,46,150,152]. Animal studies demonstrate a protective effect of anti-cachectin antibodies when used in endotoxic shock induced in mice, rabbits and baboons, with improved survival [98,151]. Studies have clearly demonstrated that massive leak of endotoxin through the intestinal wall is able to overwhelm the ability of liver to clear endotoxin and allow cachectin production, leading to the symptoms of septic shock. This has led to the recent widespread interest in the administration of selective parenteral and enteral antibiotics (SPEAR) in an attempt to eliminate Gram-negative flora of the gastrointestinal tract, and thus potentially improve survival [88].

Although the clinical picture of septic shock depends in part upon the nature of the causative organism, it frequently entails chills and rigors, in association with a pyrexia, which rapidly evolves over a few hours into the full-blown hypotensive syndrome of septic shock. Fever may be absent, particularly in the elderly or immunosuppressed, necessitating a high index of suspicion in any shocked patient. Hyperpyrexia may occur and cerebral function is commonly impaired. Vasodilatation with a warm and dry skin may be prominent during the initial phase, but later, as shock progresses and becomes refractory, vasoconstriction occurs, and there is a decline in cardiac output. Oliguria is also noted at this stage, but polyuria may occur in association with the vasodilatation and go on to high urine output renal failure. Hyper- and hypocoagulability occur with these clinical manifestations. The disorders of glucose metabolism have already been described [117].

As with any patient a careful clinical history and examination is the vital step in directing investigations and treatment until laboratory studies are available. Particular attention should
be placed on excluding genitourinary infection, which can remain undetected without formal pelvic examination.

The microbial investigation of such patients depends upon immediate culture of blood, urine, sputum, cerebrospinal fluid (in those with signs of meningism) and, where present, wound exudates. Specimens of sputum, urine, cerebrospinal fluid and any other secretions should undergo Gram staining, in an attempt to identify pathogenic organisms early. Blood cultures remain the most important investigation, as true pathogens are identified and sensitivity to antimicrobial agents documented [7]. Anaerobic and aerobic media should be used, and a Gram stain of a turbid broth often gives valuable information about the likely microbial diagnosis. Most bacteria can be isolated from the blood culture broth after only 1 day’s incubation, and so a routine 24-h subculture is recommended. As in all aspects of intensive care, close liaison with laboratory staff is necessary to ensure rapid and thoughtful processing of specimens [4].

The detection in the circulation of antigens may allow early commencement of specific therapy. Counter current immunoelectrophoresis and latex agglutination are able to detect the presence of a few bacterial species even without viable organisms in the blood, including *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis* group A + C and *Klebsiella aerogenes*. Immunofluorescence is highly sensitive for the detection of many viruses including cytomegalovirus, herpes simplex and influenza A and B. Enzyme-linked immunoabsorbent assays (ELISA) and radio-immunoassay techniques can detect the presence of many viruses, including hepatitis A and B, varicella-zoster virus, rotavirus and Epstein–Barr virus, and show promise for the future in the early identification of bacterial organisms. These techniques should not be considered as an alternative to culturing, which remains the mainstay of identification.

Radiographic studies are playing an increasingly important role in the evaluation of the patient with septic shock. A conventional chest radiograph will provide evidence of a primary pulmonary infection; it may demonstrate the presence of septic pulmonary emboli, show subdiaphragmatic air from a perforated viscus and give some indication concerning the development of ARDS. Plain x-ray films of the abdomen, while often difficult to obtain and interpret, may reveal evidence of mechanical bowel obstruction, intestinal perforation, or a soft tissue density with gas, suggesting a localized abscess. An ultrasonic examination of the abdomen may reveal intra-abdominal or pelvic collections, demonstrate obstruction of the biliary tree, or acalculous cholecystitis, as well as providing useful information about the presence of ascites, pleural effusions and renal size. Computerized tomographic (CT) scanning of the chest and abdomen often reveals unsuspected collapse of the lung bases with overlying pleural effusions, which may represent the focus of infection, as well as subphrenic collections. If at all possible it is wise to attempt fine needle aspiration and drainage of collections under ultrasound or CT control to allow appropriate antibiotic treatment to be instituted early, with later formal surgical drainage. Although gallium-67 citrate and indium-111-labelled white cells may localize inflammatory foci, they do not differentiate sterile from septic collections, or provide enough anatomical information to enable safe percutaneous needle aspiration. In this respect, ultrasonography and CT scanning are superior.

**Therapy of Septic Shock – Drainage of Collections and Administration of Antimicrobial Drugs**

The first priority in the management of septic shock is the establishment of haemodynamic stability through the use of fluids and inotropes, as outlined above, with the early identification of septic foci and their treatment. It is important to realize that even the most powerful antibiotics will not cure a septic collection, because of poor antibiotic penetration of pus and inactivity in acid collections. Surgical intervention for the drainage of localized septic foci must be considered a first priority, and often, septic shock responds to the drainage of pus alone. Removal and, if necessary, replacement of infected catheters or prostheses is an integral part of therapy. The old adage that the sun should never set on an undrained collection of pus is still appropriate today.

In the absence of specific antimicrobial therapy, or relief of an infected collection, mortality is almost inevitable within 48 h, and survival may be enhanced as much as three-fold by using appropriate and vigorous antimicrobial agents [81]. Therapy is by necessity situational and empirical; that is, at the time of prescription, the organism is unknown, and informa-
tion on its sensitivity to antimicrobials is unavailable.

The choice of antimicrobial agents before an organism is identified depends upon a number of considerations. Of great importance is the setting of the infection and knowledge of local epidemiology. Was the infection acquired in hospital, or in the community, and has the patient been on antibiotics?

The second consideration relates to the anatomical site of infection, if one can be detected. Infections that develop below the xiphoid are frequently caused by Gram-negative organisms, either alone or in concert with anaerobic organisms. Anaerobic infection is common in two situations: spillage of bowel contents into the peritoneal cavity, and female pelvic infections. In these instances, and in the case of septic shock associated with pulmonary aspiration, broadening antimicrobial coverage to include anaerobes is justifiable. Community-acquired infections occurring above the xiphoid are usually caused by Gram-positive organisms, and are sensitive to the penicillins or early-generation cephalosporins. The child with meningitis deserves special consideration as Haemophilus influenzae must be covered using chloramphenicol or a third-generation cephalosporin such as cefotaxime. Pneumonia in the alcoholic or in the elderly debilitated patient may be caused by Gram-negative organisms, and so requires broader spectrum cover. A Gram stain examination of sputum is useful in detecting Gram-negative rods.

A third consideration is the increasing recognition of “atypical” pneumonias caused by previously unrecognized organisms such as Mycoplasma pneumoniae and Legionella pneumophila. If Legionella is suspected, high-dose erythromycin or rifampicin is indicated. Legionella should be suspected following an epidemiologic in the geographical region (especially in relation to air-conditioning equipment) or in pneumonia in the middle-aged. A history of recent travel, diarrhoea, encephalopathy, relative bradycardia in association with a pyrexia, leucocytosis, hyponatraemia, hypertransaminasaemia and renal failure in association with pneumonia are all suggestive of Legionella infection.

Recent hospitalization or prolonged antibiotic administration is commonly seen in cases of septic shock, suggesting nosocomial infections. Gram-negative organisms are involved in the majority of nosocomial infections, regardless of site. Gram-positive organisms can also cause nosocomial septicaemia, most commonly multi-resistant Staphylococcus. Infection due to Staphylococcus may be controlled by an aminoglycoside, but in the case of septic shock, specific antistaphylococcal therapy with two antimicrobial agents is indicated, using high doses of cloxacillin/flucloxacillin, or vancomycin with fucidin for methicillin-resistant S. aureus. Pseudomonas is an important pathogen in the critically ill and must also be covered. Carbenicillin, one of the semisynthetic penicillins (ticarcillin, azlocillin), which contain less sodium, or a third-generation cephalosporin with enhanced anti-pseudomonal activity such as ceftazidime should be used initially.

The importance of intravenous cannulae in the pathogenesis of septicaemia cannot be overemphasized. Recent studies [59,95] suggest that 5.7% of all admissions suffer nosocomial infection, while 5% of these have positive blood cultures, and that the bulk of these result from infected cannulae. The US Public Health Service Centers for Disease Control have strongly recommended that no peripheral cannulae remain in situ for more than 72 h and that they should be examined daily for signs of inflammation and removed earlier if necessary [141]. The relative risks of the development of infection following rewiring of existing catheters remains controversial, but, if possible, rewiring should be avoided [30,109,116].

The above considerations also apply to the immunologically compromised host, but such patients demonstrate exceptional susceptibility to certain organisms, related to their specific immunological defect. Those patients with ineffective humoral immunity or recently splenectomized are unusually susceptible to encapsulated organisms, such as Streptococcus pneumoniae, H. influenzae and N. meningitidis. Patients with defective T-cell function, including the transplant population and the acquired immune deficiency syndrome (AIDS) population, are unusually susceptible to cytomegalovirus, Toxoplasma gondii and Pneumocystis carinii. Experience in the diagnosis and treatment of pneumonia in AIDS patients is expanding rapidly, and includes early staining of sputum, washout and bronchoscopy specimens to identify Pneumocystis cysts. High-dose cotrimoxazole causes an increased incidence of rash and hepatitis in AIDS patients and may need changing to pentamidine, which is also effective [67].

The previous discussion renders impossible a recommendation concerning the exact antimicrobials to use in septic shock, and many
ICUs have their own antimicrobial policy. Liaison with local microbiological staff will allow a good working knowledge of resistance and prevalence patterns in each area. As a general rule, however, aminoglycosides remain the mainstay of treatment of Gram-negative septicemia, despite their well-recognized ototoxic and nephrotoxicity [7]. Blood levels are readily available, and should be monitored daily to ensure adequate peak levels with low troughs. A dose of 2.5 mg/kg of gentamicin should be given initially with subsequent doses tailored to renal function and drug levels, usually 1.5–2.0 mg/kg/dose. This should be combined with a cephalosporin, with metronidazole added if anaerobic infection is suspected. Most organisms are covered by this regimen, but staphylococcal infection would require the introduction of a beta-lactamase stable penicillin and fucidin. The third-generation cephalosporins are in ascendance in the treatment of septicemia, since they have not been reported to cause significant renal impairment. Newer drugs such as imipenem (a carbapenem derived from thienamycin) used in combination with cilastatin (an inhibitor of dehydropeptidase-I in the renal brush border, thus preventing inactivation of imipenem) have been advocated as initial therapy for septic patients, but they are expensive, and widespread experience is only now being obtained.

Obviously, once a causative organism is established, therapy should be tailored to cover it adequately, and vigilance should be maintained to watch for emergence and selection of resistant organisms. Fungal overgrowth, especially with Candida, is becoming an increasingly acute problem with the use of broad-spectrum antibiotics, and may require treatment of its own accord.

Secondary Therapy in Septic Shock

General supportive measures, with the prevention of multi-organ failure, remain central to management. As with any form of shock, sepsis produces effects on all body systems. The treatment of acute respiratory failure, acute cardiac failure, acute renal failure, coagulopathy and alterations in carbohydrate metabolism remains the same no matter what the underlying precipitant, and is responsible for much of the underlying mortality. Prevention, as always, is both better and cheaper than cure, and so infections should be treated aggressively from the start with both surgical and medical measures to minimize the risk of shock.

Role of Steroids in the Management of Shock

The use of high-dose corticosteroids in septic shock is one of the few areas of critical care medicine which has been subjected to rigorous double-blind, placebo-controlled trials. Numerous animal trials had suggested a protective effect from high-dose corticosteroids given early in the course of septic shock [71]. Bone et al. [19] reported a study of 382 patients who fulfilled criteria for the clinical suspicion of sepsis (fever >38.3 °C or hypothermia <35.6 °C, tachypnoea >20 breaths/min, tachycardia >100 beats/min and the presence of one of the following: change in mental status, hypoxaemia, elevated blood lactate or oliguria). Patients received either methylprednisolone sodium succinate (30 mg/kg) or placebo given in four infusions commencing within 2 h of diagnosis. There was no difference demonstrated in the prevention of shock, reversal of shock or overall mortality. However, there was a significant increase in mortality at 14 days in patients with elevated creatinine (>2 mg/dl) at enrolment in the steroid-treated group (46 of 79; 59%) compared with the placebo group (17 of 58; 29%; P < 0.01). More deaths were associated with secondary infection in the steroid-treated group, although secondary infection rates did not vary. In a study by The Veterans Administration Systemic Sepsis Cooperative Study Group [154], 223 patients with clinical sepsis were randomized to receive glucocorticoid or placebo. Treatment began within 2.8 h of diagnosis. Mortality at 14 days was similar in placebo (22%) and steroid (21%) groups, and did not vary in those with Gram-positive bacteraemia, Gram-negative bacteraemia or all Gram-negative infections. Resolution of secondary infections within 14 days was significantly higher in placebo-treated patients (12 of 23) than in those receiving steroids (3 of 16; P = 0.03).

These studies reinforce the findings of Sprung et al. [144], who noted that steroids given to patients with late, severe septic shock did not alter the rate of hospital mortality despite significantly improving short-term survival. They contradict the earlier report by Schumer [128] of a favourable effect in septic shock.
Management of Shock

It is clear that corticosteroids as currently administered have no role in the treatment of septic shock. They remain vital in the treatment of Addison's disease and transplant rejection, both of which can present with profound shock. The adage that no patient should be allowed to die without the benefit of steroids is no longer true!

How to Manage the Profoundly Shocked Patient

In practice the treatment of a profoundly shocked patient rests on two primary therapeutic aims which should be undertaken together. The first is to maintain and maximize perfusion and oxygenation, while the second involves establishing and treating the precipitant of shock. In our hands this is achieved by the rapid infusion of colloid (usually human plasma, or blood if the haemoglobin is less than 10 g/100 ml) while the patient is intubated, ventilated and "lined". For difficult cases a pulmonary artery catheter, preferably one with oximetry, is inserted, and the patient's filling pressures pushed to a wedge of 15 mmHg. A pulse oximeter is used to allow minute-to-minute changes in arterial oxygenation to be observed. Cardiac output is measured, with further boluses of fluid given whenever the cardiac output increases, without raising the PAOP above 15 mmHg. A pulse oximeter is used to allow minute-to-minute changes in arterial oxygenation to be observed. Cardiac output is measured, with further boluses of fluid given whenever the cardiac output increases, without raising the PAOP above 15 mmHg. Inotropes are administered depending on the arterial blood pressure and cardiac output. We favour noradrenaline if mean blood pressure is less than 60 mmHg in patients with high cardiac outputs and low systemic vascular resistance. Adrenaline or dobutamine are used for inotropic effects if blood pressure is adequate. The regimen for patients commences with "renal dose" dopamine of 2.5 μg/(kg/min). If blood pressure will allow, a vasodilator such as nitroprusside is added to the inotrope. At the same time the patient is ventilated with enough PEEP to maintain arterial saturation greater than 90%, using as low an inspired O₂ as possible (and usually < 60%). The patient undergoes an informal PEEP trial, using arterial oxygenation, mixed venous oxygenation and cardiac output measures to optimize ventilation and O₂ delivery. As a rule, attempts should be made to avoid paralysis, by using spontaneous forms of ventilation such as pressure support or synchronized intermittent mandatory ventilation, to minimize the hemodynamic effects of ventilation. At times, however, paralysis with its decrease in O₂ utilization may be useful. All procedures such as rolling or washing the patient and therapeutic changes are undertaken with one eye on the mixed venous oximeter to avoid precipitous and prolonged desaturation.

Concurrent with an attempt to perform rapid resuscitation the patient is assessed to establish the most likely precipitant to their shock. This involves careful and thorough physical examination and baseline investigations – arterial and mixed venous blood gases, electrolytes, urea and creatinine, full blood count and differential, chest radiograph, blood, sputum, urine and other appropriate cultures. If surgery is necessary to drain or correct a septic focus it can usually be undertaken shortly after initial resuscitation, which can continue under anaesthetic.

Patients believed to be septic begin receiving antibiotics after reasonable resuscitation and multiple cultures have been taken. The usual regimen is gentamicin 2.5 mg/kg, a third-generation cephalosporin such as cefotaxime 2 g and metronidazole 500 mg. If Staphylococcus aureus is likely, penicillin and flucloxacillin or even vancomycin should be given instead of the cephalosporins. The benefits of antibiotics are unlikely to be seen for at least 24 h. Steroids and naloxone are not used.

The importance of maintaining O₂ delivery to tissues dictates that haemoglobin levels should be maintained at greater that 10 g/100 ml while the patient is shocked. This has the added advantage that haemoglobin is unlikely to leak into alveolar spaces to exacerbate ARDS. Coagulopathy is aggressively treated with coagulation factors and platelets, while bleeding is treated surgically if possible.

Respiratory management is crucial. During the stages of frothing ARDS, PEEP should not be interrupted, necessitating a sealed suction system to maintain endotracheal tube patency. The chest should only be suctioned often enough to guarantee tube patency, usually only each 8 h or so, because more frequent suctioning will result in continual alveolar fluid leak. Chest suctioning and moving the patient often produce marked falls in mixed venous O₂ saturation, and the oximeter should be used to limit these procedures. As the patient progresses from interstitial oedema, PEEP can often be decreased. Barotrauma should be expected and should be treated immediately it is suspected with large-bore intercostal drains.
Frequently patients suffer a rising creatinine despite adequate blood pressure and blood volume. Renal dopamine has proved to be useful in our hands and should be continued while the patient is on other inotropes. Oliguria is the warning sign of more severe renal dysfunction, which warrants large doses of frusemide, in an attempt to increase water and urea clearance. Often 500 mg of frusemide will produce an ongoing diuresis, which can be chased with fluid. Renal ultrasound should be performed at the same time as any upper abdominal ultrasound to exclude calyceal obstruction and document renal size. Depending on the availability of dialysis facilities, either conventional haemodialysis or continuous arteriovenous haemofiltration/dialysis is undertaken in oliguric patients early in their course to maintain the urea level at less than 30 mmol/litre and to control fluids, electrolytes and acidosis.

Prophylaxis for gastric ulceration is begun early, with antacids, sucralfate (Carafate, Boots) or H₂ antagonists. Disturbances in hepatic metabolism are common, with prolonged prothrombin index, elevated bilirubin levels and climbing transaminases. It is often difficult to know how to deal with these problems apart from excluding hepatic obstruction and acalculous cholecystitis with an ultrasound or CT scan. Renal dopamine undoubtedly increases splanchnic blood flow, and is continued for this reason. Paralytic ileus often resolves in the first few days, needing only intermittent nasogastric emptying to decompress.

Nutrition, while important to the long-term survival of patients, is left until haemodynamic stability has been achieved, usually 24 h after arrival in the ICU. Where practical, this should take the form of enteral feeds.

Undoubtedly, good intensive care requires obsession on the part of medical and nursing staff. It should be emphasized that ventilation and inotrope changes are made by the minute during the first few hours, by medical and nursing staff experienced in acute resuscitation. This is not the time for the intensivist to delegate responsibility to junior staff.

Failure to find an underlying cause for shock should be attributed to occult septic collections, and investigations to find a source should be undertaken. Given time, the source of many of these occult problems becomes clear, and appropriate treatment becomes obvious.

References

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