Care of the critically ill patient has considerably changed over the last decades with advances in ventilatory support, antimicrobial therapy, inotropic drugs and improved renal support. The survival, however, of patients presenting with major trauma or sepsis and developing the syndrome of multiple organ failure (MOF) remains poor, although this may partially be due to more severely ill patients being admitted to the intensive therapy unit (ITU).

In its final stages, shock, regardless of its primary pathogenesis, results in a picture of diffuse end-organ damage, coagulopathy, metabolic acidosis and hypotension. 'Septic shock', so called, is the commonest form of shock seen in hospitalized patients, and is the type of shock most studied in terms of pathogenetic mechanisms.

**Foci of infection**

The presence of possible or new septic foci must always be considered in the care of the critically ill patient and imaging techniques such as computed tomographic (CT) scans, ultrasound and white blood cell scanning can all be undertaken in the search for infection. The use of repeated laparotomy or laparoscopy should also not be discounted in the search for intra-abdominal sepsis in the critically ill. Patients in intensive therapy units have, inserted into them, a multitude of intra-vascular catheters, all contributing to possible infection risks. Pulmonary artery catheters appear to have the highest overall risk of catheter-induced infection. Parenteral nutrition, a common necessity in the critically ill, has always been regarded as having a high risk of infection. However, much of this risk can be reduced by careful preparation of the feeding solutions and the use of a separate intravenous line designated for feeding. A recent review article relating to catheter-induced infection encouraged the development of catheter care protocols. It was suggested that administration sets should generally be changed every 48 to 72 hours, unless fat emulsion or blood products have been used, in which case the administration set should be changed every 24 hours. In the absence of signs of infection, however, the length of time that a catheter should remain in place remains a contentious issue. The risk of repeated venepuncture has to be balanced against increasing risk of infection when lines have been in place for 4 or more days.

**Oxygen consumption**

In the septic patient there often seems to be a disparity between oxygen uptake by the cells and their estimated oxygen requirements. Recent clinical evidence suggests that inadequate oxygen uptake to cells is a major determinant of outcome, and in the critically ill patient a pattern of oxygen utilization can be demonstrated which has been termed pathological supply dependency. When oxygen delivery is decreased in animals, oxygen consumption/uptake remains constant or independent of delivery until a critical level is reached. Further decreases in delivery will then result in corresponding decreases in oxygen consumption, and thus oxygen consumption becomes supply-dependent. Studies of patients with pulmonary hypertension, impaired cardiac output and undergoing general anaesthesia are consistent with the supply-dependent pattern of oxygen consumption below critical levels of delivery. Critically ill patients, however, exhibit supply dependency over a much wider range of oxygen delivery levels than do normal subjects. Inflammatory mediators can cause increases in capillary permeability, interstitial oedema and lead to alterations in local flow. With cellular aggregates the fibrin emboli also causing alteration in local flow, and in experimental models of the above changes, pathological supply dependency can be demonstrated. Maldistribution of flow and increased diffusion distance from capillary to cell will lead to a situation where increased oxygen delivery is required to maintain oxygen uptake at the pre-maldistribution level.

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level, and thus supply dependency will be observed over a wider range of oxygen deliveries. Significant tissue oxygen debts were recently demonstrated in critically ill patients. Oxygen delivery was increased using the microvasodilator prostacyclin, and a greater oxygen debt was seen in nonsurviving patients as compared to survivors.17

The transport of oxygen from the atmosphere to the blood requires adequate alveolar ventilation, pulmonary perfusion, ventilation/perfusion ratio and diffusing capacity. In septic shock many of the above parameters may be abnormal and methods of improving arterial oxygenation may be required, with the aid of physiotherapy, increased oxygen tension, continuous positive airways pressure ventilation (CPAP), tracheal intubation, mechanical ventilation and the use of positive end expiratory pressure (PEEP). Although the above manoeuvres may improve arterial partial pressure of oxygen, the application of PEEP may impair cardiac output and thus decrease oxygen delivery. The management of patients with critical illness must therefore aim to optimize oxygen delivery and uptake, any intervention being assessed in terms of arterial oxygenation, cardiac output, oxygen delivery and oxygen uptake.

Inotropic support

Since oxygen delivery is dependent on adequate arterial oxygen content and cardiac output, adequate systemic flow is necessary for tissue oxygenation. Although cardiac output may be normal or raised in the patient with septic shock, improvements of systemic flow may be useful in further improving tissue oxygenation and hence survival, due to the presence of pathological supply dependency. Work by Shoemaker has suggested improved survival if the following parameters were obtained: a cardiac index of greater than 4.5 litres/min and an oxygen delivery of greater than 600 ml/min/m² and an oxygen consumption of greater than 170 ml/min/m².7

A variety of inotropes are available. Dobutamine is predominantly a β₁ agonist. Dopamine stimulates both α and β receptors, the effect on the cardiovascular system being highly dose-dependent — at low doses dopamine has a direct renal vasodilatory effect, at somewhat higher doses it has an inotropic effect mediated through β₁ receptors and at larger doses the predominant effect is that of vasoconstriction. Dopexamine, a newer inotrope, stimulates dopaminergic and beta-adrenergic but not alpha-adrenergic receptors, and is said to cause an increase in renal blood flow and myocardial contractility associated with systemic vasodilatation.84 Adrenaline is a potent vasopressor, increasing heart rate, increasing the force of myocardial contraction and causing peripheral vasoconstriction, and also renal vasoconstriction. At an optimal infusion rate, peripheral resistance can fall due to β₁ effects, and an increase in cardiac output and stroke volume is seen. Noradrenaline stimulates both α and β receptors, increasing systemic vascular resistance and increasing myocardial contractility.

Myocardial oxygen demands are influenced by heart rate, contractility and left ventricular wall tension, thus, whilst inotropes may improve pressure and contractility they will also cause an increase in myocardial oxygen demands. Some agents may allow improvement in delivery but care must be taken that the increase in consumption that they may engender is adequately met. Roberts et al.18 reported significantly reduced inotropic requirements in the critically ill with ‘septic shock’ during continuous infusion of naloxone. The mechanisms remain controversial but may relate to potentiation or increased level of endogenous catecholamines.

Right ventricular dysfunction has recently been recognized as an important contributor to a fall in forward flow in the critically ill patient. The development of a thermodilution technique to assess right ventricular ejection fraction (RVEF) allows bedside evaluation of right ventricular function.19 Adult respiratory distress syndrome, commonly seen in the septic critically ill patient, is associated with the development of pulmonary hypertension, believed to be due to vasoconstriction, compression and destruction of pulmonary vessels and intra-vascular thrombosis.20,21 These changes can increase right ventricular (RV) afterload and thus impair right ventricular function. Frequently the addition of PEEP is required to maintain adequate arterial oxygenation, with PEEP itself causing increases in RV afterload, and potentially further impairment of RV function. Indeed, high levels of PEEP have been shown to decrease transpulmonary blood flow.22,23 The importance of the right ventricle was further emphasized in a recent paper showing that failure to improve forward flow, via fluid loading, in patients with septic shock was secondary to right ventricular failure in association with pulmonary hypertension and coronary hypotension.24 The effects of the inotropes, dobutamine and dopamine, were recently assessed with respect to RVEF. It was noted that dobutamine caused a significant decrease in pulmonary artery occlusion pressure and a significant increase in RVEF, suggesting that right ventricular function is improved with dobutamine as compared to dopamine in the critically ill patient, in the absence of profound hypotension.25 A balance needs to be struck between pressure and flow, achieved by the use of inotropic agents (dopamine, dobutamine, noradrenaline etc.), the vasodilators and appropriate fluid loading in order to maximize oxygen delivery and consumption.
Mediators

Our knowledge of the redistribution of blood flow in human septic shock is limited. Animal studies suggest that flow is preferentially directed to the heart, brain, and liver. Regulation of local blood flow is likely to be due to a balance between local regulation in arteriolar tone and the activity of central mechanisms such as the autonomic nervous system. The balance between these many, and often opposing, vasoactive forces ultimately determines flow to vital organs. Septic shock is often characterized by vasodilatation and a narrowed arterio-venous difference in association with elevated lactate levels, and tissue hypoxia in the face of normal or elevated cardiac output and oxygen delivery. Many of the features of shock—hypotension, acidosis, coagulopathy and renal failure can be induced in experimental animals by the infusion of tumour necrosis factor (TNF).

Endotoxin itself will alter vascular responsiveness to catecholamines and can decrease the number and affinity of $\alpha$ receptors, thus altering microcirculatory flow.

Endotoxin release, whether from bacteria or viruses, can cause activation of macrophages with subsequent release of TNF and leukotrienes. Endotoxin infusion in healthy human volunteers has been demonstrated to cause peaks of TNF at 90 minutes, myalgia, headache and elevation of ACTH. Recent work has raised further questions relating to synergy between TNF and interleukin. Leukotrienes have been demonstrated to decrease renal blood flow and glomerular filtration rate in animal studies, and work has now shown a close correlation between urinary leukotriene levels and progressive renal dysfunction in patients with liver failure. The role of TNF blocking agents has been assessed in animal studies, and pretreatment with such agents has demonstrated protection. Infusions of interleukin I alone can induce a shock-like state in rabbits.

Renal replacement

The development of acute renal failure in the critically ill patient continues to carry a poor prognosis, with a mortality of around 30%. The methods of renal replacement therapy have extended over recent years, and the introduction of continuous haemofiltration and haemodialysis allow adequate renal support and early institution of parenteral nutrition fluids without the risks of hypotension and the rapid electrolyte shifts sometimes seen during haemodialysis in the haemodynamically unstable patient.

Gastrointestinal

The occurrence of gastrointestinal bleeding, secondary to gastric erosions is a problem in the critically ill patient, often contributing to increased morbidity and mortality. Both $H_2$ antagonists and antacids are effective in controlling gastric pH, and these agents and sucralfate are effective in controlling gastric erosions. Some studies suggest that antacids, frequently administered, are somewhat more effective in control of pH alone. An increase in secondary respiratory infections in $H_2$ antagonist or antacid treated patients has been noted that was not seen in those receiving sucralfate. This finding is probably related to the effect of alkalinating the stomach and thus compromising a first line of defence against bacteria. The alkalized gastric contents of the critically ill will be rapidly colonized by coliforms, which may then pass beyond the endotracheal balloon, leading to secondary lung infection. Methyl substituted prostaglandins will soon be introduced, and their role will need assessment.

Head injuries

Frequently patients with head injuries will be found on the ITU. Assessment of outcome in individual patients usually utilizes the Glasgow coma scale devised by Jennett and Bond in 1975. In head injured patients there is considerable evidence that raised intra-cranial pressure (ICP) is associated with poor prognosis. However, ICP should not be considered alone. The relationship between mean arterial pressure (MAP) and ICP (MAP minus ICP) gives rise to the cerebral perfusion pressure (CPP), a normal value being 80 mmHg and a critical level of CPP of less than 40 mmHg being associated with a significant risk of secondary brain damage. Poor outcome has been associated with the development of secondary ischaemic/hypoxic brain damage, which is related to alterations in cerebral haemodynamics and may be due to several factors: intracranial hypertension, systemic hypotension, hypoxia and anaemia. Thus the maintenance of reasonable levels of CPP is crucial. Cerebral blood flow (CBF) shows immense variation in post-trauma patients and initial CBF values are not predictive of outcome, whilst cerebral metabolic rate (CMRO$_2$) appears to be a better predictor with uniformly low levels being seen in non-survivors. When serial measurements are performed CBF is seen to decline to very low levels in patients who die, whilst in survivors, a coupling of CBF and CMRO$_2$ is seen, with increases in both values accompanying neurological improvement; however, on a practical level the measurement of CBF and CMRO$_2$ is often not feasible.
Management of such patients often includes prophylactic hyperventilation, cerebrospinal fluid drainage, osmotherapy and the administration of anaesthetic agents and steroids. The components of such regimes have different mechanisms of action and their individual effect on brain homeostasis varies according to the state of the cerebral haemodynamics and metabolism. For perhaps this reason several randomized trials have failed to show an improved prognosis with the prophylactic use of barbiturates, hyperventilation or steroids. The routine administration of neuroprotective agents (corticosteroids, barbiturates, and anaesthetic substances) has not been shown to improve outcome in large randomized clinical trials. A more selective choice of treatment for cerebral protection based on bedside evaluation of the state of the cerebral metabolism, vascular auto-regulation, ICP and CPP is required, and the effects of such therapies require assessment in carefully selected homogeneous groups of head injured patients. Improved pre-hospital care and rapid transport has been shown to decrease mortality in patients with head injuries, and the aim should be to improve primary resuscitation at the site of the accident, and to improve nutritional flow as rapidly as possible and thus reverse the microcirculatory defects and avoid local ischaemia which may otherwise lead on to the development of multiple organ failure.

Nutrition

Nutritional support should be instituted early in the course of critical illness. Many would suggest that enteral feeding is the preferred method if possible, avoiding the extra risks of central venous access and infection. Absence of bowel sounds in the critically ill, however, does not correlate well with ileus. Feeding should be commenced initially as small volumes, preferably a nasoduodenal or nasojejunal tube should be used, as these patients often demonstrate gastric atony despite having a normally functioning small bowel. The composition of parenteral feeding fluids allows the tailoring to an individual patient’s needs, and most studies have demonstrated an improvement in the patient’s nitrogen balance. The use of branched chain amino acids feeding solutions, has shown an improvement in half life plasma proteins and lymphocytes function, but this finding has not been confirmed by other workers.

Scoring in the ITU

The development of physiological scoring systems such as APACHE II and SAPS should allow the ITU physician to monitor the degree of physiological disturbance in their patients both over time and following a variety of interventions. Scoring systems, when combined with an accurate description of disease can accurately stratify patients with respect to prognosis. This should not, however, be taken as a justification for discontinuing treatment, but should allow therapeutic methods to be critically assessed with respect to outcome for various disease states in multiple centre trials.

Selective gut decontamination

Recent articles have described the development of selective elimination of oropharyngeal and gastrointestinal flora in the critically ill patient with a reduction in secondarily acquired infections. This is achieved by elimination of the aerobic potentially pathogenic organisms from the throat and gastrointestinal tract whilst preserving the indigenous mostly anaerobic flora. The initial studies involved trauma patients requiring prolonged mechanical ventilation, with an ITU stay of greater than 5 days. They received a mixture of tobramycin, polymyxin and 2% amphotericin via a nasogastric tube. A paste of amphotericin was applied to the buccal mucosa and parenteral antibiotic in the form of cefotaxime was given for a period of 4 days. The investigators noted an 18% decrease in infection rate and their conclusions were that secondary endogenous infections by yeasts and aerobic Gram-negative potentially pathogenic organisms are almost completely prevented by this regime and that primary endogenous infections can also largely be prevented by systemic antibiotic prophylaxis. The selection of resistant strains causing superinfection was not a problem. A further study, using a similar regime also showed a decrease in acquired infection in the treated groups, and a significant reduction in mortality was noted in various subsets of patients: those with polytrauma, relatively long stay patients and those with middle range APACHE II scores.

Conclusions

The use of corticosteroids in the treatment of adult respiratory distress syndrome and septic shock has been reported as showing no benefit with respect to outcome. However a vast array of potential therapeutic interventions is becoming available, such as TNF and endotoxin antibodies, oxygen radical scavengers, cyclo-oxygenase inhibitors and microvasodilators. The role of such agents in the critically ill patient will need to be assessed, in addition to that of present therapy.

Sadly, however, in many hospitals the ITU can
become a battlefield between the warring factions of anaesthetist, physician and surgeon with the patient the potential loser — we must strive to improve this with better inter-specialist communication, not only within the medical groups but also including the nurses, physiotherapists and physiological measurement technicians who play such a vital role in the survival or otherwise of patients, and who are so often overlooked.

References


