Reviews in Medicine

Intensive care

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Introduction

There can be few specialties over the last few years that have progressed as rapidly as intensive care. Considerable advances have been made in technology for both monitoring and patient support, in pharmacological treatments, and in the understanding of the pathophysiology of multiple organ failure with the development of specifically targeted therapies. The changes being wrought on the National Health Service are also having an implicit effect as the intensive care unit (ICU) is the most labour-intensive and, arguably, the most expensive hospital department. There is now a far greater awareness of cost and audit has become an integral part of a unit's work. This review, though not all-encompassing, will describe recent thoughts and innovations and allude to some potentially exciting ideas currently at various stages of development.

Multiple organ failure: (1) Pathophysiology

The major area of research in intensive care has undoubtedly been oriented towards the pathogenesis and management of multiple organ failure. The realization that infection ('sepsis') is but one insult that triggers an exaggerated, generalized, whole-body inflammatory response leading to the clinical and pathological sequelae of organ dysfunction and eventual failure has directed treatment towards attenuation, modification or blockade of various parts of this inflammatory response. The former concept of giving antibiotics and providing supportive therapy such as inotropes, mechanical ventilation and renal replacement until these antibiotics work has been replaced by a more sophisticated approach involving, for example, the rapid restoration of organ perfusion, the use of highly expensive monoclonal antibodies and the prevention of iatrogenically induced organ damage. Much still remains speculative and controversial yet there has been a perceptible improvement in patient outcome.

This excessive and nonspecific release of inflammatory mediators is in the response to an exogenous insult. Infection is by far the commonest cause though other insults such as severe trauma (including burns), pancreatitis, massive blood transfusion, smoke inhalation, drug overdose and a host of other aetiologies are also recognized. There need be no bacteria whatsoever present in order to produce a clinical picture of 'septic shock'. This late phase, which is usually indicated by cardiovascular collapse, is preceded by a collection of signs and symptoms which was coined the 'sepsis syndrome' (Table 1a).¹ However, confusion has arisen through the use of the word 'sepsis' in conditions where infection need not be present. As a result, this syndrome has recently been redesignated the 'systemic inflammatory response syndrome' (Table 1b)² in an attempt to emphasize the non-dependence on bacteria or other infectious organisms. Prompt recognition and management of the systemic inflammatory response syndrome will often halt progression to established organ failure with a consequent improvement in outcome. Various organ systems – cardiovascular, respiratory, renal, hepatic, gastroenterological, haematological, neurological, skin and muscle – are involved to varying degrees. The respiratory component of multi-organ failure is known as the adult respiratory distress syndrome whereas disseminated intravascular coagulation (DIC) is a haematological manifestation. Cardiovascular failure may either be peripheral,³ leading to widespread loss of microvascular regulatory tone and a consequent hyperdynamic circulation, or be central with myocardial depression.^{4,5} Gastroenterological failure may present as stress ulceration, acalculous cholecystitis or pancreatitis whereas neurological failure may result in central obtundation or encephalopathy,⁶ or in peripheral neuropathy.⁷ The greater the number of established organ failures, the worse the prognosis.

The biochemical and physiological factors leading to organ dysfunction and failure are related to activation of the various inflammatory pathways (Figure 1). Monocyte–macrophage activation leading to cytokine release, either directly from the

Table 1a Criteria for diagnosis of the sepsis syndrome (after Bone *et al.*¹)

Hypo- or hyperthermia (<35.6°C/96°F or <38.3°C/101°F)
Tachycardia (> 90 beats/minute)
Tachypnoea (> 20 breaths/minute)
Evidence of inadequate organ perfusion/function: Alteration in mental status Arterial hypoxaemia, (PaO ₂ < 9.6 kPa[72 mmHg]) An elevated plasma lactate level Urine output below 0.5 ml/kg/hour for at least 1 hour
The sepsis syndrome does not require the presence of a positive blood culture or hypotension

Table 1b Criteria for diagnosis of the systemic inflammatory response syndrome (after Consensus conference²)

Hypo- or hyperthermia (<36°C or > 38°C)
Tachycardia (> 90 beats/minute)
Tachypnoea (> 20 breaths/minute) or hyperventilation with a PaCO ₂ < 4.3 kPa
Alteration in WBC (<4,000/mm ³ , > 12,000/mm ³ , or 10% immature neutrophils

initiating insult or via complement and endotoxin, is currently considered central to this response.

Endotoxin

Endotoxin is a lipopolysaccharide derived from the cell wall of Gram-negative bacteria. It is a potent activator of the various cellular and humoral pathways involved in septic shock and its lipid A moiety is probably responsible for most of its toxicity. Endotoxaemia results from exogenous Gram-negative bacteria and, possibly, from intestinal flora as a result of translocation through the gastrointestinal mucosa though this has only been shown in animal models.^{8,9} Endotoxaemia has been demonstrated in patients with septic shock,¹⁰ even in the absence of a Gram-negative bacteraemia.¹¹ It has been linked to an increase in intestinal permeability,¹² reduced myocardial performance¹³ and activation with subsequent inhibition of the fibrinolytic pathway.¹⁴ Infusion of low dose endotoxin into human volunteers stimulated production of tumour necrosis factor with hypotension, tachycardia and pyrexia.¹⁵ Recognition of the importance of endotoxin, particularly in Gram-negative sepsis, has led to the development of a specific anti-endotoxin monoclonal antibody (*q.v.*). Inter-

Figure 1 Inflammatory pathways and their inhibition.

estingly, a recent *in vitro* study has demonstrated a greater release of endotoxin by ceftazidime compared to imipenem;¹⁶ if verified *in vivo* this may lead to a re-evaluation of current antibiotic practice.

Complement pathway

Both classical and alternative complement pathways can be activated by bacterial cell wall components. The activated complement factors, C3a and C5a, are also potent activators of macrophages, neutrophils, platelets and endothelium. An increased concentration of activated complement has been related to a poor outcome in septic shock.¹⁷

Cytokines

Cytokines, released primarily by these activated tissue or circulating monocyte-macrophages, trigger a variety of other inflammatory cascades involving endothelium, neutrophils, platelets, complement, coagulation and contact systems. Cytokines currently attracting considerable interest are tumour necrosis factor (TNF) and the interleukins (IL), particularly IL-1 and IL-6.

Tumour necrosis factor, formerly known as cachectin, is a polypeptide cytokine which induces neutrophil activation to produce oxygen free radicals and proteases, platelet-neutrophil-endothelial interactions, and increased vascular permeability.¹⁸ It appears to be a central mediator in the pathogenesis of multiple organ failure. High plasma levels are found in the sepsis syndrome and the early phases of septic shock, and have been related to the severity of disease and the likelihood of death.¹⁹⁻²¹ Furthermore, similar clinical conditions have been recreated by injection into animal models²² and human volunteers.^{23,24} TNF production is not ubiquitous to infection; elevated plasma levels have been reported in a wide variety of other insults such as complicated *Plasmodium falciparum* malaria²⁵ and even chronic heart failure.²⁶

The interleukins, in particular IL-1 and IL-6, are also released in a variety of inflammatory conditions other than sepsis, for example, rheumatoid arthritis, haemodialysis and transplant rejection. Injection of IL-1 into rabbits induced a shock-like state²⁷ and outcome in some clinical studies was related not only to TNF levels but also to IL-1 and gamma-interferon.^{21,28} The encouraging response in animal septic shock models to specific blocking of IL-1 binding to its cell surface receptor²⁹ is also suggestive of a pivotal role of IL-1 in septic shock.

After TNF and IL-1, Interleukin-6 is the third cytokine described in the acute phase inflammatory response. It is probably a second messenger released within a few hours by macrophages, endothelial and other cells in response to TNF or

IL-1 β .³⁰ It appears to be a potent stimulator of acute phase protein production by the liver and of antibody production, and has an important role in the instigation and maintenance of the metabolic response to surgical stress. Very high serum levels have been detected in sepsis,^{31,32} these are much higher than those seen in other conditions such as acute graft rejection or surgery.

Neutrophils, platelets and endothelium

Activation of these cellular components of the inflammatory response occurs following release of complement, cytokines and endotoxin. Activated neutrophils will aggregate and obstruct the capillaries of lung, liver, splanchnic circulation and other organs. They then degranulate, releasing proteolytic enzymes and oxygen-free radicals which cause localized tissue damage. Interactions and adherence also occur between neutrophils, platelets and endothelial cells. As a consequence, endothelial integrity is lost, resulting in increased capillary permeability, increased leakage of proteinaceous fluid from intravascular into interstitial spaces, and the development of oedema.

Endothelial and platelet activation results in stimulation of the arachidonic acid cascade with production of prostaglandins, thromboxanes and leukotrienes. These are highly vasoactive substances which may cause either vasodilatation or vasoconstriction. Increased prostacyclin and thromboxane A₂ formation has been demonstrated in the human sepsis syndrome³³ and in the adult respiratory distress syndrome.³⁴ Cyclooxygenase inhibition has resulted in reductions in body temperature, heart rate, airway pressures and pulmonary artery pressures.³⁵

Recent interest has been expressed in the role of nitric oxide and endothelin in septic shock. Endotoxin and certain cytokines (TNF, gamma-interferon, and some interleukins) are known to enhance endogenous synthesis of nitric oxide via induction of nitric oxide synthase in both endothelial and vascular smooth muscle cells.³⁶ It has a crucial role in regulating visceral blood flow; in an animal model, inhibition of nitric oxide synthesis potentiated jejunal vasoconstriction produced by endotoxin and induced bowel wall haemorrhage.³⁷ It is nevertheless believed to be a major contributor to the marked vasodilatation and hypotension and decreased pharmacological responsiveness seen in septic shock.³⁸ On the other hand, endothelin is an extremely potent vasoconstrictor; it is five times more potent than angiotensin II on the renal vasculature.³⁹ Release of endothelin can be brought about by either endothelial damage or directly by endotoxin stimulation.⁴⁰ Preliminary studies in human sepsis syndrome and septic shock⁴¹⁻⁴³ have revealed an increase in plasma endothelin levels.

This release is associated with increased renal and splenic vascular resistances. It may help to maintain mean arterial pressure but, conversely, may contribute to microvascular vasoconstriction in some organ beds.

It is likely that local flow-dependent vascular regulation depends on the balance between release of endogenous vasodilators such as nitric oxide and prostacyclin, and of vasoconstrictors (for example, endothelin, thromboxane A_2). Disruption of this balance by an exogenous insult such as sepsis may result in loss of regulation so that some areas of the microcirculation are vasodilated while others are vasoconstricted. Blood may therefore be shunted through non-nutrient capillaries. The combination of obstructed capillaries, increased extravascular fluid and alterations in vascular tone results in tissue hypoxia. This leads to organ dysfunction and eventual failure.

Coagulation and contact system pathways

Bacterial cell wall components from both Gram-positive and -negative bacteria, as well as various cytokines will activate both intrinsic and extrinsic coagulation pathways. Activation of Factor XII (Hageman Factor) initiates the intrinsic pathway and, simultaneously, the contact system⁴⁴ (Figure

2). Conversion of prekallikrein to kallikrein cleaves high molecular weight kininogen to produce bradykinin, a potent vasodilator. It will also generate further neutrophil and complement activation and will stimulate fibrinolysis. The extent of complement and contact activation is related to outcome.^{45,46}

The coagulation cascade is activated leading to widespread formation of microvascular thrombin clots, depletion of clotting factors and, possibly, clinical and laboratory evidence of disseminated intravascular coagulation. At the same time the fibrinolytic pathway is activated, plasminogen being cleaved to plasmin which not only breaks down the fibrin clots but, in turn, will activate the complement cascade.

Protective mechanisms exist within the body to prevent released proteases from causing widespread tissue damage and disordered coagulation. Numerous naturally occurring protease inhibitors are recognized; many have primary functions, for example anti-thrombin III is the main inhibitor of the intrinsic coagulation pathway and the formation of thrombin. An alpha-1-antiprotease inhibitor will complex immediately with free elastase released by activated neutrophils while C_1 -esterase inhibitor has a potent inhibitory action on complement activation. Levels of these circulating protease inhibitors are recognized to fall in sepsis.^{47,48}

Figure 2 Coagulation, contact and fibrinolytic system activation and inhibition.

Multiple organ failure: (2) Treatment

The treatment of multiple organ failure has diversified greatly in recent years. This has been partially in response to new monitoring techniques, partially to changing philosophies and, primarily, to a greater understanding of the underlying pathophysiology with the subsequent development of directed therapies.

Prevention

A discussion on the treatment of multiple organ failure would be incomplete without mention of the efforts being directed towards prevention. Tissue hypoperfusion is now clearly recognized to be a virtual prerequisite for the development of organ failure. With the advent of better means of assessing regional perfusion at the bedside, such as blood lactate levels and gastric mucosal pH (*q.v.*), there has been an increasing appreciation of the importance of optimizing, if not supra-optimizing, circulatory status to ensure organ requirements are met.

In addition to maintaining organ perfusion, it is important to stress the importance of prompt removal of the insult wherever possible. For example, early fixation of major long bone and pelvic fractures has been shown to reduce significantly complement and macrophage activation, the incidence of subsequent organ failure and mortality.^{49–51}

The work of Shoemaker encouraged a major review of haemodynamic management of the critically ill patient. He found that routinely monitored variables such as heart rate, blood pressure and body temperature in a high-risk surgical population were poorly predictive of subsequent complications and outcome.⁵² However, those patients who spontaneously achieved higher levels of cardiac output and oxygen delivery (the product of cardiac output, arterial oxygen saturation, Hb and 1.34) fared markedly better. He developed the hypothesis that patients required a higher than normal cardiac output and oxygen delivery to cope with the metabolic stresses of dealing with both the precipitating cause and the surgery itself. He subsequently performed a prospective trial⁵³ where high-risk surgical patients were randomized to receive either conventional central venous pressure monitoring, pulmonary artery catheter monitoring, or pulmonary artery catheter monitoring with active 'driving' of the circulation using fluid and/or dobutamine to achieve a cardiac index (cardiac output corrected for body surface area) $> 4.5 \text{ l/min/m}^2$ and a tissue oxygen delivery $> 600 \text{ ml/min/m}^2$. This latter group only had a 4% mortality rate compared to 23–33% in the routinely managed patient groups.

This message of 'supranormalization' of cardiac output and oxygen delivery was strongly promulgated, albeit possibly confused by being adopted to patients in shock and established multiple organ failure. Schumacker and Cain had developed the concept of a critical oxygen delivery (DO_2);⁵⁴ decreases in oxygen delivery resulted in a greater oxygen extraction by the tissues in order to maintain similar levels of oxygen consumption (VO_2). Only when the DO_2 falls below a certain critical threshold will the VO_2 fall, resulting in anaerobic metabolism, lactate production and a metabolic acidosis. In septic patients, however, this critical threshold was found to be greatly elevated, giving rise to the notion of oxygen supply dependency^{55,56} (Figure 3). The hypothesis was developed that critically ill patients would require an increased oxygen delivery to cope with the recognized defective utilization of oxygen by the tissues and the greater metabolic demands. A suggested treatment endpoint was when no further rise in VO_2 occurred following an increase in DO_2 , that is, when the patient had reached the 'plateau' part of the oxygen supply–demand curve. Early uncontrolled studies of supranormalization of cardiac output and oxygen delivery—goal-directed therapy—in critically ill patients with septic shock claimed encouraging results.^{57,58} However, no large-scale randomized, controlled trial has been performed to verify efficacy in an intensive care population with established sepsis syndrome, shock or multiple organ failure. In view of the ever-increasing appreciation of the microvascular pathophysiology, it is perhaps too simplistic a concept in itself. Indeed, the oxygen supply dependency theory has been recently challenged as a methodological error.⁵⁹ Nevertheless, these studies have certainly succeeded in drawing attention to the importance of maintaining tissue perfusion as a means of preventing deterioration.⁶⁰ This theme is percolating from the intensive care to the operating theatre and recent, currently unpub-

Figure 3 Oxygen supply-dependency curve in septic and normal patients.

lished studies have found marked improvements in outcome following elective surgery.

Specific treatments

A host of new and speculative therapies are being studied; although no one agent is likely to prove a 'magic bullet' in itself, it is conceivable that a cocktail of antibodies, cascade inhibitors and modulators, substitution and supportive therapies will have a marked effect on altering prognosis.

Monoclonal antibodies: (i) Anti-endotoxin (HA-1A) monoclonal antibody The perceived importance of endotoxin as a potent activator of the various inflammatory pathways following Gram-negative sepsis led to treatments aimed specifically at attenuating or abolishing this response. Early and successful efforts included the use of pooled serum containing high titres of antibody to a mutant (J5) strain of *Escherichia coli*⁶¹ and polyclonal immunoglobulins containing high titres of antibodies against endotoxin determinants.⁶² However, the major problems associated with the widespread use of pooled serum in particular transmission of infection, has promoted the development of monoclonal antibodies.

The first major, double-blind, randomized, controlled trial of a monoclonal antibody (HA-1A) to endotoxin for the treatment of patients with systemic clinical evidence of presumed Gram-negative sepsis produced mixed results.⁶³ On an 'intention to treat' basis the drug showed no overall positive benefit; however, those patients with ultimately proven Gram-negative bacteraemia showed a reduction in mortality from 52% with placebo to 37% in the treated group. The mortality was more impressively reduced from 57% to 33% if the patients were shocked on admission to the study. A number of criticisms have been levelled, particularly the treatment failure when considering the patient group as a whole. Furthermore, Gram-negative bacteraemia was only confirmed in only 200 of the 543 (37%) patients studied; as the drug costs approximately £2,500 it has therefore been extrapolated that £25,000 will be needed to save one extra patient life. Although this is cheap in terms of life years saved when compared with anti-hypertensive therapy, long-term haemodialysis and other such treatments, the cost implications have aroused deep concern. Most hospitals have drawn up their own protocols regarding use and this usually includes approval from intensive care and microbiology consultants. Recent and as yet unpublished data (Centocor, personal communication) appear to indicate that early administration is necessary for efficacy. A rapid bedside (or laboratory) test to confirm Gram-negative bacteraemia or endotoxaemia would greatly aid patient

selection; however, this is not likely to be realized in the short-term. To dispel lingering doubts a second large placebo-controlled multi-centre study is currently in progress in the United States; this should ascertain whether this antibody has a viable future.

Monoclonal antibodies: (ii) Anti-TNF antibody Antibodies directed against TNF improved early survival and reduced hypoxaemia in various animal studies.⁶⁴ However, other studies have been more ambivalent.⁶⁵ A genuine concern voiced regarding anti-TNF antibody treatment is the potential effect of blocking the body's natural physiological inflammatory response to infection and other insults. Among other functions, TNF (and other cytokines) upgrades white cell, complement and macrophage activation and blockade may possibly prove deleterious. Nevertheless, two large multi-centre, placebo-controlled studies of anti-TNF antibody treatment in patients with sepsis syndrome or established septic shock are currently in progress and results are eagerly awaited.

Monoclonal antibodies: (iii) IL-1 receptor antagonist IL-1 receptor antagonist is a naturally occurring inhibitor of IL-1 which has been successfully cloned. This monoclonal antibody, that blocks the cell-surface receptor to which IL-1 binds, is another putative therapy currently being evaluated in critically ill patients. Experimental studies have also been highly encouraging.^{66,67}

Steroids Two large placebo-controlled multi-centre trials^{68,69} assessing the effect of high-dose methylprednisolone in a total of 605 patients failed to show any improvement in outcome and this was regarded as definitive evidence that steroids are ineffective in septic shock. However, closer examination of the results generated several questions: the first study made no differentiation between Gram-positive, Gram-negative and culture-negative sepsis syndrome whereas the other study documented the steroid-treated group as having a 75% reduction in mortality in those with Gram-negative bacteraemia but a 50% increase in those with Gram-positive bacteraemia. Both of these findings were non-significant and it may well be that the study design was inadequate with regard to patient numbers. Secondly, was the dose adequate? The first gave four doses of 30 mg/kg methylprednisolone 6 hours apart while the other gave a 30 mg/kg bolus followed by a 5 mg/kg infusion over 9 hours. Although large doses in conventional terms it may be that these were still insufficient as corticosteroid binding activity is reduced in sepsis.⁷⁰

Since publication of these studies, there has been a gathering consensus that although steroids are

inappropriate for routine treatment there are certain subgroups where they may prove beneficial. Treatment in patients in the fibroproliferative phase of late adult respiratory distress syndrome (ARDS) showed a marked and rapid improvement to corticosteroids.^{71,72} There may also be covert adrenocortical insufficiency which may result in marked hypotension and be mistaken for vasodilatation induced by the septic process.⁷³ Even though basal cortisol levels may be normal, a poor response to corticotrophin was often found and this correlated strongly with poor outcome.⁷⁴ A number of studies in patients requiring high doses of catecholamines to maintain blood pressure showed marked responses to corticosteroids with abrupt haemodynamic improvement.^{75–78}

As a final comment on steroid therapy, it is worth commenting on some studies which reveal an important role of steroids in inhibiting various pathways involved in the pathogenesis of sepsis. Early administration of dexamethasone in bacterial meningitis showed a reduction in cerebrospinal fluid lactate, tumour necrosis factor and interleukin-1.⁷⁹ Dexamethasone was also shown to inhibit endotoxin-induced TNF mRNA, irrespective of whether the dexamethasone was given before or during endotoxin stimulation.⁸⁰ However, when given 2 hours after endotoxin, that is, after macrophage stimulation had occurred, there was no effect of dexamethasone on TNF levels. A recent study⁸¹ examined the cytotoxic effect of endotoxin on incubated vascular endothelial cells; this was inhibited both by N^G -monomethyl-L-arginine (L-NMMA), an inhibitor of nitric oxide synthesis, and by dexamethasone and hydrocortisone which are also known to inhibit expression of inducible nitric oxide synthase which synthesizes nitric oxide.⁸² On the other hand, another study⁸³ has suggested that methylprednisolone had an injurious effect on rabbit endotoxaemia by increasing release of toxic oxygen metabolites. Clearly, the steroid debate has yet to be fully resolved.

Other therapies: (i) Plasma exchange A number of studies have suggested that plasma exchange may be beneficial in the management of septic shock; circulating mediators will be removed⁸⁴ and replacement by fresh frozen plasma will enable substitution of protease inhibitors whose levels are usually depleted.⁴⁸ Patient studies to date have been either anecdotal^{85,86} or small in number; the most encouraging to date is one showing a reduction in mortality from 87% in a conventionally treated group to 36% treated by sequential plasma filter-dialysis with slow continuous haemofiltration.⁸⁷ A large-scale controlled study is obviously required to validate these findings.

Other therapies: (ii) Pentoxifylline Pentoxifylline

is a xanthine analogue structurally related to aminophylline. It has been used for a number of years for the treatment of peripheral vascular disease; however, the belated discovery of its potent effects on inhibition of neutrophil activation^{88,89} turned attention to its use in sepsis. It has since been found to have prostacyclin-like properties,⁹⁰ to inhibit the release of TNF after administration of endotoxin,⁹¹ and to inhibit TNF and interleukin-1-induced neutrophil activation^{92,93} and endothelial cell cytotoxicity.⁹³ Its precise mode of action is still unclear; however, its inhibitory role on neutrophils appears paramount in providing protection or attenuating injury. Its phosphodiesterase inhibitory action is not considered important in this context. Various experimental models of septic shock have shown beneficial effects with pre-treatment such as increased survival,⁹⁴ reduced albumin leak and oedema formation,^{95,96} and improved haemodynamics with greatly reduced histological damage.^{88,96} So far there is only anecdotal evidence of pentoxifylline use in patients with multiple organ failure.⁹⁷

Other therapies: (iii) Arachidonic acid cascade modulators—ibuprofen, prostacyclin, prostaglandin E_1 The importance of the arachidonic cascade in the inflammatory response, with the production of highly vasoactive prostaglandins, thromboxanes and leukotrienes, has led to the investigation of a number of modulatory agents. Cyclooxygenase inhibitors, such as the non-steroidal anti-inflammatory agents ibuprofen and indomethacin, have been shown in animal models to improve the survival rate,^{98,99} attenuate the degree of lung injury,¹⁰⁰ and improve haemodynamics and mesenteric perfusion.⁹⁹ Ibuprofen decreased shock-related damage following infusions of TNF and IL-1, inhibiting the production of toxic oxygen metabolites.¹⁰¹ It has clinical benefits, reducing temperature, heart rate, and maintaining cardiac output and blood pressure.¹⁰¹ When ibuprofen was given to human volunteers given an endotoxin challenge it did not prevent the rise in plasma TNF α but did prevent the rise in temperature and heart rate.¹⁵ To date, clinical data is scanty though a recent pilot study in septic patients¹⁰² revealed clinical improvement in haemodynamics, temperature, pulmonary mechanics, and the frequency of shock reversal (88% vs 43%). Obviously there are the risks of renal impairment, gastrointestinal haemorrhage and platelet dysfunction and these will no doubt be scrutinized in a large-scale multi-centre study currently under way.

Prostaglandins such as prostacyclin (PGI₂) and prostaglandin E_1 have also been studied in septic animal models and patients as these appear to have the reverse actions of the thromboxanes and leukotrienes and could thus prove beneficial. A

placebo-controlled pilot study¹⁰³ of PGE₁ in 41 patients with ARDS revealed improvements in gas exchange and doubled the 30-day survival rate. However, a larger study¹⁰⁴ of 100 patients failed to show any benefit on outcome though cardiac output did improve. Other studies have concentrated on prostacyclin; it increased survival rate in canine endotoxaemia¹⁰⁵ and recent human trials have shown improvement in pulmonary function.¹⁰⁶

Other therapies: (iv) Protease inhibitor substitution, protease inhibition and oxygen radical scavengers The inflammatory response includes complement activation, neutrophil activation with release of supraoxide radicals and proteases such as elastase and catalase, contact system activation with production of kinins, and the coagulation cascades which, via proteases, may result in stimulation of intravascular coagulation and depletion of clotting factors. Circulating protease inhibitors are nature's way of protecting the body from the excesses of protease action. Antithrombin III (ATIII) is a potent inhibitor of the intrinsic coagulation pathway, thrombin, trypsin and the contact system. C₁-esterase inhibitor (C₁-INH) will also attenuate contact activation as well as the classical complement pathway while α_1 -proteinase inhibitor will complex immediately to any free elastase released by neutrophils.

In an animal model of sepsis, pretreatment with ATIII concentrate prevented DIC and death.¹⁰⁷ When administered after endotoxin challenge there was a marked attenuation in DIC.¹⁰⁸ There have been anecdotal patient studies also showing attenuation of DIC by ATIII concentrate.^{109,110} Likewise, there have been early encouraging reports of C₁-esterase inhibitor substitution in human sepsis.^{111,112} An alternative means of countering the effects of circulating proteases is to administer nonspecific serine protease inhibitors such as aprotinin. This is a polypeptide derived from bovine lung which has activity against a variety of proteases such as trypsin, chymotrypsin, plasmin as well as kallikrein.¹¹³ At lower doses it is probably more effective against other proteases; however, at higher doses, there seems to be significant plasma kallikrein inhibition.¹¹⁴ It may also inhibit neutrophil-derived proteases.¹¹⁵

Antioxidants are agents that can scavenge superoxide, hydrogen peroxide or xanthine oxidase which are produced following reperfusion injury and cause marked endothelial damage. Various agents have been studied in sepsis and burn injury including superoxide dismutase^{116,117} and allopurinol.¹¹⁸

Other therapies: (v) Nitric oxide blockade Recent discoveries of the role of nitric oxide (NO) in

mediating the marked vasodilatation and hypotension seen in septic shock has led to investigation of blockade of NO production. Inhibitors of NO synthesis (via inducible NO synthase) such as N^G-monomethyl-L-arginine (L-NMMA) or N^G-nitro-L-arginine methyl ester (L-NAME) has reversed endotoxin-induced hypotension in rats¹¹⁹ though larger doses of the antagonist accelerated the hypotension. Clearly a dose-dependent effect was witnessed. An early anecdotal report in humans¹²⁰ showed rapid reversal of hypotension and suggested that these agents may be a new therapeutic option. However, concerns have been voiced¹²¹ that NO may be protective in terms of regulating visceral blood flow, platelet aggregation and antimicrobial activity; inhibition of production may in fact prove deleterious. Paradoxically, nitric oxide is also being investigated as a treatment in the adult respiratory distress syndrome as NO inhalation (at non-toxic levels) appears to result in preferential vasodilatation of ventilated regions of lung, producing marked improvements in gas exchange.¹²²

Noninvasive monitoring

Cardiac output

Pulmonary artery catheterization (PAC) has become the established bedside technique in the ICU for measurement of cardiac output (by the thermodilution technique) and intracardiac pressures. It will also allow calculation of oxygen delivery and consumption. However, it is an invasive technique requiring expertise in insertion and management, it does carry a recognized complication rate¹²³ and there are recognized pitfalls in measurement.^{124–127} A recent editorial has even suggested that this technique may be responsible for a covert increase in mortality.¹²⁸ Usage in British intensive care units was considerably lower than that of their American counterparts;¹²⁹ insertion was mainly indicated by clinical need. This delay in insertion may be primarily responsible for the inability of invasive monitoring to improve outcome on the ICU patient.

On the other hand, it is probably not justifiable in terms of cost–benefit analysis to insert pulmonary artery catheters routinely in every ICU patient. For this reason, major efforts are being made to develop noninvasive monitoring techniques including thoracic bioimpedance and Doppler ultrasound. These have the advantage of safety though reliability has been questioned (*q.v.*). Nevertheless, the merit of noninvasiveness should lead to earlier recognition and management of alterations in haemodynamic status. This may then impact on outcome statistics. Blood pressure is a

late indicator and active treatment is usually delayed until sometimes catastrophic falls in blood pressure occur. It would therefore appear entirely rational that a simple, safe, easy-to-use technique would serve as an early-warning system and serve as an adjunct to invasive monitoring. This section will deal briefly with thoracic bioimpedance but will concentrate primarily on Doppler ultrasound measurement of aortic blood flow which we believe to be the best noninvasive option currently available.

Thoracic bioimpedance This technique utilizes the pulsatile change in resistance to injected microcurrents to measure stroke volume. Four pairs of surface electrocardiogram (ECG) electrodes are placed on the neck and chest, the outer pairs injecting a 70 kHz, 2.5 mA current into the thoracic tissue which is then sensed by the inner electrodes. The resistance to this current depends upon the fluid characteristics of the thoracic volume. Pulsatile changes in this thoracic resistance – the bioimpedance – are then then timed to ventricular electrical depolarization and mechanical systole. The following equation¹³⁰ is then used to calculate stroke volume (SV):

$$SV = \frac{L^3 VET \, dZ/dt_{\max}}{4.25 \, Z_0}$$

where L is derived from a nomogram that adjusts for ideal body weight; VET = ventricular ejection time; $dZ/dt_{\max}$ = maximum time of impedance change; and Z_0 = baseline impedance.

A considerable number of clinical and experimental validation studies have been performed using this technique; results have been somewhat variable with the majority in the critical care setting being negative. It appears to be satisfactory in following changes in cardiac output in normal, healthy resting subjects, however, in conditions of stress this accuracy wanes markedly. Studies in

patients with sepsis, low and high cardiac output states, hypotension, tachyarrhythmias, valvular disease, and variable haematocrits have all given unreliable results and, as the machine simply provides a digital readout of stroke volume, it is difficult to place sufficient confidence in the technique for it to be used as a stand-alone instrument.^{131–134} The technique and equation are undergoing regular refinements; perhaps its place is as a trend-monitoring device rather than a cardiac output monitor as which it is currently marketed.

Doppler ultrasound Doppler ultrasound was first used to measure aortic blood flow in the 1960s. Initially this was from a parasternal approach¹³⁵ but a suprasternal technique was developed soon after.¹³⁶ This technique relies upon measurement of blood flow velocity from Doppler frequency shifts produced as a result of backscattered ultrasound waves from moving blood corpuscles. A probe containing either a single piezoelectric crystal both emitting and receiving ultrasound frequencies (pulse wave Doppler) or two crystals, one emitting and the other receiving (continuous wave Doppler), is directed towards the aorta until sharp audio and/or visual signals of aortic blood flow are obtained. Correct orientation is important as the cosine of the angle between the direction of the ultrasound beam and that of blood flow has to be considered in the Doppler equation. The Doppler frequency shift corresponds to blood flow velocity, and this can be analysed by a variety of techniques, the most sensitive being Fast Fourier Transform spectral analysis. Velocity–time waveforms are produced (Figure 4), the area of which can be integrated to provide the ‘stroke distance’ – the distance moved by a column of blood through the aorta with each stroke of the left ventricle. The product of stroke distance and aortic cross-sectional area is the left ventricular stroke volume. The assumption can be made in adults that there are minimal changes in aortic cross-sectional area during systole therefore changes in stroke distance will reflect proportional changes in stroke volume. Favourable comparisons were made against thermodilution, initially for following trends in cardiac output¹³⁷ and subsequently, by measuring the aortic diameter ultrasonically, for actual measurement of cardiac output.^{138–139}

Difficulties experienced with the suprasternal approach included the inability to fix the probe in a correct position to enable continuous beat-by-beat monitoring, and the confounding effects of blood flow turbulence produced by aortic valve abnormalities. Approximately 5% of patients cannot be assessed from this route because of anatomical (short neck) or pathological (hyperinflated lungs, mediastinal air post-cardiothoracic surgery) reasons. Some operator variability exists though with

Figure 4 Aortic flow velocity waveform.

sufficient experience (> 20 subjects) this was relatively minimal (7%).¹⁴⁰ One of the major problems of this technique gaining widespread acceptance has been the inadequacies of the manufactured machines. For a variety of reasons substandard equipment and/or probes were marketed which only served to undermine.

In terms of the critically ill patient in the intensive care unit a device providing continuous monitoring would be far more desirable. As the suprasternal approach cannot provide this, alternative routes have been explored, namely transtracheal and oesophageal. The transtracheal probe is incorporated into a specifically designed endotracheal tube such that blood flow in the aortic arch will be measured in ventilated patients.¹⁴¹ Unfortunately this device has also been launched prematurely without sufficient validation;¹⁴² means of assessing correct placement are inadequate and the assumed angle of insonation may well be inaccurate depending on the orientation and/or unfolding of the aortic arch.

The oesophageal approach is currently attracting the most attention and we must at this point declare a personal interest.^{143–145} The close proximity of the oesophagus to the descending thoracic aorta allows high quality signals to be obtained with minimal artefact. Just above the stomach, at a probe insertion depth of 35–40 cm, the oesophagus runs parallel with the aorta. The angle of insonation of the ultrasound beam to blood flow is therefore assumed to be 45°.

Measurement of aortic blood flow from this

route was first described in 1971.¹⁴⁶ A commercial machine was launched in the 1980s¹⁴⁷ but this too suffered from inadequate machine and probe design, and insufficient validation. As a consequence, it was withdrawn from the market. However, a recently launched machine (ODM, Abbott) overcomes many of these previous faults by incorporating sophisticated waveform-measuring software, a superior probe design, and an on-line monitor which allows visual verification of a correctly oriented probe. Finally, it incorporates a nomogram which translates the Doppler-derived data of blood flow in the descending thoracic aorta into an estimate of total volumetric cardiac output. Assumptions are made that: (1) the angle of insonation is 45°; (2) that blood flow down the descending thoracic aorta is a relatively fixed proportion of total cardiac output and that this proportion does not change much despite large changes in cardiac output, blood pressure or body temperature; and (3) that aortic dimensions change little during systole despite the changes described in (2) above. Studies have shown this noninvasive device to be 85–90% accurate when compared against thermodilution.¹⁴³ Perhaps more importantly, trends are followed closely.

Another useful facet of having a monitor to view the velocity waveforms is the ability to make assessments of circulatory status from the waveform shape (Figure 5). The peak velocity decreases with age as the aorta widens and the left ventricle becomes less contractile. A normal range of peak velocities exists for each age group thus a value

Figure 5 Alteration in velocity waveform shape following haemodynamic interventions.

above or below the expected range is indicative of a hyperdynamic (for example, sepsis) or a hypodynamic (for example, left ventricular failure) circulation. Addition of an inotrope will result in an increase in peak velocity as the ventricle becomes more contractile. On the other hand, an underfilled left ventricle, as seen in hypovolaemia, will produce a narrow, peaked waveform with a relatively normal peak velocity. The effect of giving fluid challenges can be immediately assessed and a Starling-type curve produced. Initial experience has been highly encouraging.^{145,148}

Regional organ perfusion – gut tonometry

Critically ill patients are being increasingly managed with reference to haemodynamic flow variables. However, the ultimate goal at which all therapy should be directed is the preservation of tissue oxygenation and the rapid correction of any oxygen debt. Global indices such as base deficit and lactate which indicate global hypoperfusion and a metabolic (lactic) acidosis are useful indicators. However, confounding influences exist in critically ill patients, such as an acidosis produced by concomitant acute renal failure or the variable degree of lactate uptake by the liver.

Gut tonometry represents a potentially important new technology for monitoring of tissue oxygenation, that is, regional organ perfusion.¹⁴⁹ The tonometer consists of a fine bore tube around the end of which is wrapped a thin silicone balloon. The balloon is inserted either into the sigmoid colon or, more commonly, the stomach, and is then filled with 2.5 ml n-saline. Carbon dioxide released from the gut mucosa crosses the semipermeable membrane into the saline with which it equilibrates over a minimum period of 15 minutes. The saline can be withdrawn and injected into most standard blood gas analysers for determination of $p\text{CO}_2$. This value is then placed into a modified Henderson–Hasselbach equation for calculation of the gut mucosal pH (pH_i):

$$p\text{H}_i = 6.1 + \log_{10} \frac{\text{arterial HCO}_3^- \text{ concentration}}{F \times \text{tonometer saline } p\text{CO}_2}$$

where F is a time-dependent factor for partly equilibrated samples. The arterial bicarbonate concentration is assumed to be in steady state with gut intramural bicarbonate.

This technique was originally developed to investigate the role of reduced blood flow and tissue acidosis in the pathogenesis of stress ulceration¹⁵⁰ but its potential role in the critically ill patient was quickly realized. Whether a low pH_i is an indication of hypoperfusion in other organ beds, or relatively gut-specific has yet to be elucidated. Perhaps intestinal mucosal ischaemia itself will allow trans-

location of gut microorganisms and endotoxin with subsequent amplification of the inflammatory pathways. This has been demonstrated in animal work though remains to be proven in humans. The gastrointestinal tract does, however, appear to be highly susceptible to alterations in oxygen supply. A direct correlation was found between the levels of splanchnic oxygen delivery and gastric intramucosal pH_i .¹⁵¹ Early clinical work suggested that gastric mucosal pH_i monitoring significantly improved the prediction of complications in patients undergoing aortic¹⁵² or cardiac¹⁵³ surgery. In the latter study the sensitivity of the technique approached 100% when the gastric mucosal pH_i fell on the day of surgery.

The most significant work to date on patients in intensive care is a study from Argentina.¹⁵⁴ Patients had their pH_i measured on ICU admission and were then randomized to be in either control group (that is, receiving standard ICU therapy) or protocol group (where systemic oxygen delivery was increased, or demand reduced, whenever the pH_i fell below 7.35). Those admitted with a $\text{pH}_i < 7.35$ showed similar survival, whether they were in protocol or control groups (37% vs 36%). However, those with an admission $\text{pH}_i \geq 7.35$ showed a significantly higher survival in the protocol group compared to controls (58% vs 42%, $P < 0.01$). This work needs to be repeated in a multi-centre environment where a greater degree of monitoring is used other than central venous lines to see whether pH_i -directed treatment, after conventional resuscitative measures have been taken, will improve outcome.

Management of severe respiratory failure

The aetiology of severe respiratory failure is often that of the generalized inflammatory response leading to the adult respiratory distress syndrome (ARDS) and multiple organ failure. ARDS was first described in 1967.¹⁵⁵ The pathogenesis of ARDS is multifactorial and is viewed as an acute non-cardiogenic oedematous lung injury. The phenomena¹⁵⁶ associated with ARDS include neutrophil degranulation with release of oxygen free radicals, endotoxaemia, alveolar macrophage activation, lipid-derived mediator release and defective surfactant function. Management is aimed at resolution of the primary cause and supportive therapy until that resolution can be obtained.¹⁵⁷ Thus many of the therapeutic endeavours aimed at controlling the septic response are applicable here, but in addition there are interventions specifically tailored to ameliorate the lung injury.

Treatment specific to the management of severe respiratory failure include physical measures to support gas exchange, alternative ventilation

modes such as inverse ratio ventilation (IRV) and high-frequency ventilation (HFV), and extra-corporeal respiratory support (ECRS) such as extra-corporeal membrane oxygenation and carbon dioxide removal (ECMO and ECCO₂R). In addition there has been the recent development of an intravenous oxygenation device (IVOX).

ECMO, ECCO₂R and IVOX

ECMO can be defined as an extracorporeal system requiring 50% of the cardiac output to pass via a venoarterial circuit, thus providing oxygenation support and some carbon dioxide clearance.¹⁵⁸ The patient still requires ventilation to complete oxygenation, and allow for carbon dioxide removal. There have been tremendous practical problems to overcome, the most important being that of blood loss related to the extracorporeal circuit requirement for anti-coagulation, thrombocytopenia, and blood sampling.^{159,160} It appears possible to overcome this problem to a large extent with the use of heparin-bonded circuits and gas exchangers.¹⁶¹

Despite the difficulties, there have been successes in maintaining patients upon an extracorporeal oxygenation system from as early as 1972.¹⁶² Unfortunately, these early encouraging results in adults have not been repeated, and the technique still has to prove that it increases survival in ARDS. The only controlled prospective trial¹⁶³ of ECMO in adults to date, while demonstrating that the technique is feasible, failed to show any improved survival in the ECMO group over the control group treated with conventional ventilation. This study contained a salutary lesson for clinicians treating this condition, as 34 of the 38 deaths in patients who received ECMO occurred in patients who, at the time of death, showed no resolution of their lung injury. The findings were similar in the patients receiving conventional treatment. It would seem that unless the underlying pathology can be improved there is little benefit using more sophisticated support systems. This is supported by the apparently greater success found using the same principles in neonatal intensive care,¹⁶⁴ where there is evidence of resolution of the pulmonary disease as the lung matures. Analysis of data is further complicated by the fact that it appears that survival of patients with ARDS may be improving in all treatment groups as compared with controls.¹⁶⁵ This makes interpretation of uncontrolled trials unreliable if results are compared with historical controls.

The alternative approach of ECCO₂R¹⁵⁹ was based upon the principle that if the lungs were physically rested by reducing their motion, they may stand a better chance of healing. The fundamental difference between ECCO₂R and ECMO

is that, with the former, ventilation of the lungs can be substantially reduced. Oxygenation is maintained via insufflation of the lungs with 100% O₂ while low frequency ventilation (3–4 breaths/minute) maintains the functional residual capacity and lung movement is reduced to a minimum. Carbon dioxide removal can be achieved through the low blood flow–high gas flow extracorporeal circuit as carbon dioxide has a much higher solubility coefficient than oxygen. A further advantage of the lower blood flow in this veno-venous system is that it reduces the potential for blood loss and may reduce pulmonary blood stasis as compared with the veno-arterial system. The early results were encouraging with improvements in pulmonary function demonstrable in survivors within 48 hours.¹⁵⁹ However, there have been no trials since that have repeated these results. Preliminary results of an ongoing trial¹⁶⁶ that compares ECCO₂R and pressure controlled-inverse ratio ventilation (PC-IRV) (*q.v.*), demonstrate a survival of 37%, but in both groups. The ECMO criteria that previously gained patients access to this treatment may have been too rigid, and excluded all but those who are in the poorest prognostic category already. This may well be another technique that could be used more prophylactically in the future.

IVOX, the intravenous oxygenator, is described as a device consisting of approximately 1,000 hollow polypropylene fibres¹⁶⁷ that may be introduced so that it lies the length of the major venous drainage system from the confluence of the iliac vessels to the right atrium and superior vena cava. When unfurled, 100% oxygen is drawn through the fibres allowing exchange of oxygen and carbon dioxide along their concentration gradients. Clinical investigation is still at an early stage, the first patient to receive this therapy was only reported in 1990.¹⁶⁸ Further anecdotal cases were reported recently from Britain.¹⁶⁹ The efficacy of the technique is still being evaluated though it does not appear to have major effects on either removing CO₂ or improving oxygenation. The first abstract¹⁶⁸ from the ongoing Food & Drug Administration approved trial describes some of the practical difficulties encountered. These relate to the size of the device in relation to the inferior vena cava, and the rise in central venous pressure that the presence of the device causes that in itself seems to reduce the capacity for gas exchange. However, future refinements and improvements in technology are likely to enhance the technique.

Alternative modes of ventilation

In recent years, the clinical approach to the management of patients with severe respiratory failure

Table II Modes of high frequency ventilation

<i>Mode of ventilation</i>	<i>Respiratory rate (breaths/minute)</i>	<i>Hz</i>
High-frequency positive pressure ventilation (HFPPV)	60–100	1.0
High-frequency jet ventilation (HFJV)	110–400	1.8–6.7
High-frequency oscillatory ventilation (HFOV)	400–2,400	6.7–40

has been aimed at developing different modes of ventilation that will maintain oxygenation while minimizing iatrogenic trauma (such as high peak inspiratory pressures and the consequences of high inspired oxygen). The two commonest alternatives to traditional intermittent positive pressure ventilation (IPPV) are high-frequency ventilation and pressure controlled-inverse ratio ventilation (PC-IRV). A recent review of these alternatives¹⁷⁰ could find no evidence of improved survival as compared with standard treatment, though this is mainly because of the paucity of controlled randomized clinical data. However, clinical interest remains and so the basic principles will be reviewed.

High-frequency ventilation

Since the 1960s when HFV was first developed,¹⁷¹ clinical application has evolved around three techniques as defined by the use of different ventilatory frequencies (Table II). These represent tidal volumes that are less than the anatomical dead space. High-frequency positive pressure ventilation (HFPPV) may be employed via normal endotracheal tubes using a modified ventilator and is rarely employed in the ICU. High-frequency oscillatory ventilation (HFOV) has not been evaluated beyond limited animal studies. It requires an electromagnetic device to produce high-frequency oscillations in a constant stream of oxygen and is thought to possibly have a role in the management of neonates.¹⁷² High-frequency jet ventilation (HFJV) has been used quite extensively in ICU and though it requires a special 'jet ventilator', it may be instituted by a modified endotracheal tube through a mintracheostomy, or via cricothyroid puncture with a cannula.

Physiology of gas transfer during HFJV is still not fully understood. Diffusive processes are thought to be responsible for the movement of gas between alveoli but the mass transfer of gas from trachea to alveoli may be due to convection, turbulent dispersion, acoustic resonance, or Pendelluft (exchange of gas between lung units with different time constants). However, it has been shown that alveolar ventilation is a function of

minute ventilation in HFJV as well as during conventional IPPV.¹⁷³ HFJV still poses multiple practical problems, most notably with humidification of the inspired gases. Still, it remains an attractive proposition as it has the potential to increase patient comfort thus reducing sedation requirements. It may also offer greater haemodynamic stability, reduce barotrauma by lowering the peak airway pressure, and possibly improve oxygenation. No randomized controlled clinical trial to date has found any improvement in survival or in reduction of ICU stay. Therefore, it still remains to be seen whether the advantages will outweigh the not inconsiderable difficulties of employing this relatively novel ventilatory mode.

Inverse ratio ventilation

Standard IPPV employs an inspiratory:expiratory ratio of 1:2 to 1:4, thus traditionally the expiratory phase is considerably longer than the inspiratory. Reversing this ratio and controlling the inspiratory gas flow through limitation of airway pressure as opposed to limitation of tidal volume (PC-IRV) is thought to recruit closed alveolar units in a more homogeneous manner. The pressure control prevents the increases in airway pressures often needed in standard volume controlled IPPV. Significant improvements in oxygenation with lower minute volumes, peak airway pressures and positive end expiratory pressure requirements were seen in one study group not being adequately oxygenated by conventional means.¹⁷⁴ The individual response was variable and this has also been reported for HFJV¹⁷⁵ and seems to relate to abrupt changes in cardiac filling pressures. If the intravascular pressures suddenly decline, the afterload experienced by the right ventricle reduces and as its performance improves the right heart output increases. This in turn may then deliver an unwelcome load upon the left ventricle, the pulmonary artery wedge pressure rises and the ventricle may 'fail'. Thus instead of seeing an improvement, the oxygen delivery to the tissues may fall. This underlines the importance of careful monitoring of the cardiorespiratory systems when instituting changes in man-

agement, as an increase in arterial oxygen tension does not necessarily imply an increase in oxygen delivery.

Developments in the pharmacological management of severe respiratory failure

The use of corticosteroids, non-steroidal anti-inflammatory and other agents in the treatment of the acute inflammatory response syndrome was discussed earlier. Evaluation of the role of surfactant replacement is still in its early stages^{176,177} in adult intensive care. The practicalities of introducing it in a uniform fashion, ensuring dispersion to diseased pulmonary units is even more difficult in the adult than the neonate. The accumulation of protein-rich fluid in the alveoli that is thought to be the major reason for defective surfactant function is in itself the reason why any introduced surfactant may also be inhibited and so repetitive dosing is required. If repeated doses of surfactant are shown to have a beneficial role in the treatment of severe respiratory failure it is estimated that in order to treat the 150,000 adults who develop ARDS in the USA each year, a ton of surfactant will be needed. This will have huge financial and logistic implications.¹⁷⁷

Audit in the ICU

The changes in NHS management require that health care provision becomes more business-like. This has major implications for both clinicians and patients in the ICU. On first inspection, intensive care could be seen as luxury that we may not be able to afford. Certainly, the £1,000–2,000 daily cost per patient (Singer *et al.*, submitted for publication) admitted to the ICU is greater than for any other department, but the real question to be answered is whether appropriate admission to an intensive care unit will be cost effective in the long term.¹⁷⁸ The answer to this will be difficult to establish as, in purely fiscal terms, dying is often a cheaper option than the prolongation of a life whose quality, though precious to its owner, may need further support from health care resources in the future. This then could be an argument against trying to produce a financial justification for intensive care services at all. However, the reality is that we are being increasingly required to make decisions based in part upon these financial considerations, and in order to do this with any hope of fairness and rationality, we need an information base. This is one of the functions of clinical audit.

The aim of conducting clinical audit is to close the so-called 'audit circle'. This means that practice is initially observed, data collected, outcome assessed and any shortcomings identified. Changes

in practice are then implemented and this new practice is observed with any improvement in outcome then identified, thus closing the audit circle. Auditing is not new on the ICU, many systems comparing patient data and outcome have been developed, including the simplified acute physiology score (SAPS),¹⁷⁹ therapeutic intervention scoring system¹⁸⁰ and the most widely used, the APACHE (acute physiology and chronic health evaluation) series.¹⁸¹ The APACHE score now commonly features in the literature as a means of comparing patient data in multiple disciplines, both between different centres and over time, although it has not found universal acceptance.¹⁸² More controversial is the use of scoring systems to prognosticate. The recently developed APACHE III system¹⁸³ refines further the scoring system's ability to predict hospital mortality for critically ill adults. There is increasing pressure to rationalize the use of intensive care beds, and if this is to be achieved then accurate prognostic indices will become even more necessary to aid sensible decision making. The immediate obligation is to the patient and the intensivist must be reasonably confident that these crucial decisions are made in the light of patient imposition, benefit and anticipated quality of life. Clinicians often use less formalized collections of clinical data in order to prognosticate or decide whether admission to an ICU for instance is appropriate.

Using a formalized collection of data such as the APACHE system is morally no different. However, no one piece of clinical information, APACHE score, patient's past history, nor any particular physiological parameter can be held as an absolute in this decision-making process. The potential capacity of these scoring systems should not be completely ignored in favour of our firmly held faith in the power of clinical judgement. An interesting result¹⁸⁴ was obtained when medical and nursing staff were asked to predict 'likely to die' or 'outcome unknown' while blinded to the APACHE II prediction in a heterogeneous group of ICU patients. Neither set of predictions were acted upon during the course of the study, which was probably fortunate as the medical and nursing staff had falsely predicted death in 7–16% of patients. However, the computer model did not predict death incorrectly in any patient.

The two patient populations in particular whose appearance upon the ICU is often considered inappropriate for both humanitarian and financial reasons are the elderly and those suffering from haematological malignancies. The elderly population certainly suffer a higher mortality and possibly poorer long-term outcome with equivalent disease than the younger patients.^{185,186} However, it is equally clear that individual elderly patients do benefit from intensive monitoring and nursing care.

Rather than taking the negative view of simply inspecting the higher mortality figures of the elderly it is perhaps worth pondering the possibility that of patients 'destined' to survive, those managed intensively may ultimately suffer less long-term morbidity because of successful preservation of organ function. This is entirely consistent with the emerging philosophy that the ICU is not so much a place where patients are sent when all else fails but should be the area where aggressive preventive medicine is practised. Patients at risk of life-threatening disease should be maintained in optimal condition, rather than attempting to salvage a hopeless situation.

When considering the management of patients with malignancy, it is also a commonly held belief

that providing intensive care for patients with active malignant disease is both inhumane and a waste of resources. Long-term survival is, however, more related to progress of the underlying disease¹⁸⁷ than the acute condition. Therefore it is reasonable to offer intensive supportive therapy to patients while there is a prospect that the malignancy can be successfully treated. Determining whether this is the case or not is the really difficult question to be answered. In terms of the humanity of submitting these often young, possibly dying patients to intensive care it is worth noting that, when followed-up, all long-term survivors in this study said that they would go through intensive care again.

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