Introduction

Multiple organ failure (MOF) is the commonest cause of death in the intensive care unit setting. There are numerous precipitating factors including sepsis, trauma and pancreatitis. The resulting tissue hypoxia, exaggerated inflammatory response and generation of free oxygen radicals leads to tissue damage and organ dysfunction. No definitive treatment exists despite considerable efforts to find a ‘magic bullet’. Management still revolves around support of organ function and prevention of iatrogenic complications until recovery occurs. An increasing emphasis is being placed on prevention of organ dysfunction, including maintenance of tissue oxygenation, nutrition and infection control.

Management of multiple organ failure: guidelines but no hard-and-fast rules

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Multiple organ failure is the commonest cause of death in the intensive care unit setting. There are numerous precipitating factors including sepsis, trauma and pancreatitis. The resulting tissue hypoxia, exaggerated inflammatory response and generation of free oxygen radicals leads to tissue damage and organ dysfunction. No definitive treatment exists despite considerable efforts to find a ‘magic bullet’. Management still revolves around support of organ function and prevention of iatrogenic complications until recovery occurs. An increasing emphasis is being placed on prevention of organ dysfunction, including maintenance of tissue oxygenation, nutrition and infection control.

Introduction

Multiple organ failure (MOF) is the commonest cause of death in the intensive care unit (ICU). A clinical assessment of a high likelihood of irreversible organ failure, particularly when multiple organs are involved, is the usual factor prompting a decision to withdraw treatment or not to add further therapy. Sepsis is one precipitating factor for MOF; numerous other causes of tissue damage are well recognized, e.g. trauma, burns and pancreatitis.

No definitive treatment exists and controversy surrounds many aspects of the management of MOF. Problems include (i) a shortage of major multi-centre, controlled studies in a well-defined patient population (other than immunotherapy trials which are often of flawed design), (ii) an inclination to use unproved interventions, (iii) over-extrapolation of data from laboratory studies, (iv) an often uncritical acceptance of simplified, schematic representations of inflammatory mechanisms, (v) variable disease syndrome definitions and (vi) diagnostic imprecision. The above contribute to the current lack of hard-and-fast rules regarding patient management; instead, there are a number of generally accepted guidelines which still provide considerable scope for treatment variability. Examples of current grey areas include selective gut decontamination, extracorporeal respiratory support, prophylaxis against stress-ulcer-related bleeding. There is also the widespread, though as yet unproven and unlicenced, use of nitric oxide inhalation in acute lung injury, and the quest for a single ‘magic bullet’ to ameliorate the generalized, exaggerated inflammatory response associated with severe sepsis. In the case of the strongly promoted concept of ‘supranormalizing’ haemodynamic parameters in the critically ill patient, whereby elevated values of cardiac output, oxygen delivery and oxygen consumption were striven for, it was several years before this approach was shown to be ineffective.

Nevertheless, and despite the above caveats, there has been progress in several areas. A better, though still incomplete, insight is being gained into the pathophysiological mechanisms underlying the exaggerated inflammatory response that frequently underlies MOF. There is a greater appreciation of the need to prevent organ dysfunction by optimizing the circulation and avoidance or rapid correction of tissue hypoxia in high-risk patients. There is a recognition of the importance of standard definitions, for example sepsis, the systemic inflammatory response syndrome (SIRS), the multiple organ dysfunction syndrome (MODS) (Table I), the acute respiratory distress syndrome (ARDS) and acute lung injury. There is also a recognized need to improve the description of organ dysfunction. In addition, general advances and the increasing availability of intensive care, superior ‘whole body’ organ support, appropriate infection control, nutrition and pressure area care, and avoidance of iatrogenic pulmonary barotrauma, have all contributed to improvements in outcome. This article will highlight the broadly accepted principles inherent in current ICU practice, allude to...
specific controversies and refer to current areas of research interest and novel approaches. Recommendations will also be given based on the author’s current practice.

**Definition of multiple organ failure and dysfunction**

There is no clear dividing line between organ function and failure and, as a consequence, no consensus as to when organ support should be instituted. For example, some argue for early institution of renal replacement therapy whereas others strive to maintain an adequate urine output and view the need for artificial support as a failure of therapy. The spectrum of organ dysfunction is broad and does not necessarily affect patient outcome; thrombocytopenia may be completely asymptomatic in some patients but, in others, the same platelet count may be associated with significant failure of haemostasis. Therapeutic intervention will also confuse interpretation, e.g. the ratio of arterial oxygen saturation to inspired oxygen saturation \((P_{a}O_2 / F_iO_2)\) will be influenced by ventilator settings such as inverse ratio ventilation and positive end-expiratory pressure. Organ dysfunction scores are becoming more sophisticated\(^{12,13}\) (Table II) yet do not always reflect the impact of therapeutic intervention. Nevertheless, these scores do provide a means of quantification and may have some value in assessing serial changes associated with either disease progression or specific therapy.

**Causes of multiple organ failure**

A combination of tissue hypoxia, an exaggerated systemic inflammatory response, and tissue damage arising from ischaemia, necrosis, free oxygen radical and protease attack all contribute to progressive organ dysfunction and, ultimately, failure. There also appears to be a degree of interaction between these different components; for example, endotoxaemic animals have a greater cytokine response and poorer survival in the presence of tissue hypoxia\(^{15}\) while hypoxia and/or reperfusion injury amplifies cytokine production by cultured macrophages.\(^{16}\) Priming of neutrophils, macrophages and other inflammatory cells after an initial insult may lead to an increased release of mediators if a second insult, e.g. secondary infection, occurs soon afterwards.\(^{17,18}\) It is poorly understood why patients receiving similar insults may either emerge relatively unscathed or suffer severe complications. Recent evidence suggests that genetic factor(s) may be important in that the ability to increase expression of tumour necrosis factor (TNF) in relation to the level of inflammatory response is correlated with ultimate outcome.\(^{19}\) Up-regulation of other cytokines has also been demonstrated in ARDS; this may result from either a genetic predisposition or to a long-lived phenotypic change induced by the ARDS process.\(^{20}\) Other environmental factors may play a part such as the degree of natural immunity to endotoxin; raised levels of endogenous anti-endotoxin antibody were found to be protective in severe sepsis.\(^{21}\)

**Tissue hypoxia**

Inadequate cellular oxygen supply may occur as a consequence of macro- and microvascular changes. Protracted hypovolaemia, anaemia, hypoxaemia or myocardial depression will result in a decrease in tissue oxygen delivery. The generalized inflammatory response leads to
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Increased endothelial permeability resulting in interstitial oedema, vessel obstruction by adherent neutrophils and platelets, and possible regional mismatching of perfusion by varying local concentrations of vasodilating agents (nitric oxide, prostaglandins) and vasoconstricting factors (endothelin, thromboxanes). Although diversion (‘shunting’) of oxygenated blood away from nutrient capillaries has been hypothesized, evidence remains scanty. On the other hand, cellular oxygen availability may be adequate but the oxygen cannot be used, possibly owing to abnormalities in the mitochondrial oxidative phosphorylation pathway with decreased ATP turnover though data relating to mitochondrial dysfunction are contradictory.

Inflammatory response

Macrophage/monocytes, endothelium, neutrophils, platelets and the coagulation, complement and fibrinolytic systems are all activated as part of the inflammatory response. This results in regional areas of dilatation and constriction, vessel blockade by aggregated neutrophils and platelets, endothelial disruption and interstitial oedema, all of which contribute to tissue hypoxia. Activated neutrophils release proteases and free oxygen radicals which can result in further tissue damage.

Free radical damage

Free oxygen radicals are generated by neutrophils as a mechanism for killing microorganisms and also as a consequence of ischaemia–reperfusion injury. ATP is broken down to ADP which is then broken down to AMP; this, in turn, is broken down to hypoxanthine, a substrate of xanthine oxidase which is a major source of free radicals. Natural anti-oxidant systems are overwhelmed, leading to uncontrolled oxidation of vital cellular constituents.

Prophylaxis of multiple organ failure

Maintaining tissue oxygenation

The importance of maintaining adequate tissue perfusion in the high-risk patient, particularly in the per-operative period, is increasingly recognized. The level of per-operative tissue oxygen debt has been related to post-operative morbidity and mortality. Whether prevention or reduction of this debt can be achieved by intravenous fluids alone, or by the addition of vasoactive agents such as dobutamine or dopexamine, remains to be clarified. Controversy also surrounds the treatment endpoints which should be sought. In reported studies ‘supranormal’ goals of oxygen delivery and consumption were only achieved in half the patients in whom this was attempted. There are potential risks associated with this approach, as demonstrated in a careful controlled study by Hayes et al. who showed that supranormalization of oxygen delivery and

### Table II. Sepsis-related organ failure assessment (SOFA) score (after Vincent et al.)

<table>
<thead>
<tr>
<th>System</th>
<th>Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>$P_{A}O_2/FIO_2$ (mmHg)</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Platelets ($\times 10^{11}$/L)</td>
<td>20-32</td>
<td>30-101</td>
<td>100-208</td>
<td>100-308</td>
</tr>
<tr>
<td>Liver</td>
<td>Bilirubin (µmol/L)</td>
<td>&lt;10</td>
<td>&lt;20</td>
<td>&lt;30</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Mean blood pressure (mmHg)</td>
<td>&lt;70</td>
<td>&lt;80</td>
<td>&lt;90</td>
<td>&lt;100</td>
</tr>
<tr>
<td>CNS</td>
<td>Glasgow coma score</td>
<td>13-14</td>
<td>10-12</td>
<td>7-10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Renal</td>
<td>Serum creatinine (µmol/L)</td>
<td>110-170</td>
<td>171-299</td>
<td>300-440</td>
<td>&gt;441</td>
</tr>
</tbody>
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With respiratory support.
consumption failed to influence mortality in a critically ill population admitted to intensive care; indeed, patients receiving high doses of inotropes fared significantly worse than conventionally managed patients. Continuing controlled, multi-centre trials may clarify the situation.

Suggested management: Expedient intravascular volume repletion with artificial colloids, aiming to correct tissue hypoperfusion as signified by an arterial base deficit (or, in the presence of renal failure, a lactataemia) in excess of 2 mmol/L. Failure to do so, or to achieve an adequate urine output, would prompt early institution of more sophisticated haemodynamic monitoring, including cardiac output measurement and, possibly, administration of vasoactive drugs including inotropes or vasodilators.

Early fixation (internal or external) of long bone or pelvic fractures, debridement of necrotic tissue (e.g. patients with burns), decompression of any tissues affected by compartment syndrome and surgical or percutaneous drainage of abscesses have all been associated with prevention of subsequent organ failure and a good outcome.

Infection control

Strict attention to infection control is mandatory. This includes handwashing before and after handling patients, removing watches and bracelets, and appropriate protective isolation for infectious or immunosuppressed patients. In recent years routine changes of intravenous and intra-arterial cannulae and catheters have been supplanted by a wait-and-see policy with suitable transparent dressings covering the entry sites. Many, including ourselves, now consider line changes only when the entry site looks infected, when a positive culture is obtained from blood drawn through the catheter or from a line tip changed over a guide wire, or when there is unexplained pyrexia or circulatory decompensation. Short courses of prophylactic antibiotics may be needed before certain invasive procedures, for example, in patients undergoing bowel surgery or with prosthetic or abnormal heart valves.

Diagnosis

Considerable problems exist in diagnosing bacterial infection. In particular, differentiating colonizing bacteria from pathogenic bacteria is vexatious and clinical signs of supposed ‘infection’ are often associated with no bacterial growth despite the absence of previous antibiotic therapy. Microbiological confirmation of pneumonia was made in only 34 (23%) of 147 mechanically ventilated patients suspected of having nosocomial pneumonia on the basis of a new pulmonary infiltrate and purulent tracheal secretions. No combination of 16 clinical variables evaluated by stepwise logistic regression analysis was useful in distinguishing patients with bacterial pneumonia. The same group of authors demonstrated that only 33% of proposed antibiotic treatments represented effective therapy and that it was unnecessary in a further 16%.

Abdominal sepsis is also often difficult to diagnose. Suspicion should be aroused by culture of gut-derived bacteria or unexplained circulatory decompensation, since clinical signs of abdominal infection are often absent in the mechanically ventilated, sedated and, sometimes, paralysed patient. Ultrasound examination may reveal collections of pus, cholecystitis, pancreatitis, or gynaecological or renal sepsis. However, false negatives are relatively commonplace; if doubt persists, either CT scanning or diagnostic laparotomy should be undertaken. These procedures may have to be performed in critically ill, unstable patients but, provided transfer facilities are adequate, can usually be undertaken safely. The benefits accruing from making a diagnosis which subsequently leads to directed treatment often outweigh the risks involved in transportation or surgery.

Antibiotic therapy

While appropriate antibiotics should be commenced at an early stage, often empirically, it is equally important to discontinue them either when the infection has been clinically cleared or no benefit has resulted. In the latter instance, and if the patient’s clinical condition allows, withdrawal of antibiotics may maximize the chances of obtaining a positive culture. The duration of antibiotic treatment, the need for monotherapy versus combination therapy, and the choice of antibiotic are often contentious. Other than for specific pathogens or conditions, e.g. endocarditis, tuberculosis, atypical pneumonia and meningitis, short courses (e.g. 3–5 days) are often sufficient. These can usually be discontinued on clinical resolution or 24 h after the pyrexia has settled. A pyrexia persisting for 3–5 days may prompt the cessation of all antibiotic therapy with a renewed search for causative organisms. Often no organisms can be implicated so other causes should be considered, e.g. inflammatory conditions, adverse drug reactions. Short antibiotic courses may reduce the risk of developing antibiotic resistance though some authorities argue that incomplete courses resulting in failure to eradicate the bacteria may promote a similar problem. The incidence of secondary fungal infection may be reduced by a policy of short, intensive antimicrobial therapy. Retrospective analysis of one year’s data from our ICU revealed a positive yeast culture from any site in only 34 (11%) of 297 patients resident on the unit for more than 72 h. Only eight patients had a positive blood culture and systemic fungal therapy was only given to 13 patients in total. It is noteworthy that 15% of the 297 patients were immunosuppressed. With this regimen multi-resistant bacterial strains are uncommon.
Physiological support

General

A sound maxim to adopt is to prevent the preventable. Cardiorespiratory perturbations (e.g. hypotension and hypoxaemia) should be avoided during manoeuvres such as manual hyperinflation, postural changes, endotracheal suction and syringe changes. The use of poor aseptic techniques during invasive procedures, and the development of pressure sores, malnutrition and biochemical abnormalities are all potentially avoidable complications.

Early diagnosis and prompt treatment of organ hypoperfusion and possible sources of infection are also indicated. Regular physiotherapy and good nursing care are also likely to contribute to patient survival. Pressure areas should be protected, if necessary by the use of specialized mattresses or beds. Clinically obvious deep venous thrombosis is unusual in ICU patients, probably because many patients have underlying coagulopathies. The need for routine heparinization or use of elasticated support stockings is, therefore, questionable. There is an appreciable incidence of myopathy and/or neuropathy in ICU patients although these often become apparent only during recovery from the acute phase of the illness. They are probably related to the underlying inflammatory process of the acute illness, although drugs such as neuromuscular blocking agents or corticosteroids have also been implicated. There is no evidence of a difference in outcome between colloid and crystalloid for volume replacement. Smaller volumes of colloid are needed to achieve a comparable haemodynamic effect to crystalloid though the cost is far higher. Similarly, no single colloid offers any particular clinical advantage; human albumin solution is expensive, carries potential risks, is inferior to artificial colloids in terms of intravascular half-life and produces no better outcome than an artificial colloid.

The incidence of clinically significant stress-ulcer-related bleeding has declined significantly over the last two decades to the point where reports of major morbidity are now unusual. This is ascribed to better general care and organ perfusion, and the earlier institution of enteral feeding, though there is a suggestion from a recent meta-analysis that prophylactic agents may be beneficial. The current low complication rate has called into question the need for routine administration of gastric protectants such as H2-antagonists, antacids or sucralfate which may carry their own hazards, e.g. nosocomial pneumonia.

Nutrition

Increasing awareness of the detrimental effects of starvation and the positive effects of nutrition on protein synthesis, immunological enhancement and gut protection has led to a greater emphasis on instituting adequate and prompt nutrition for ill patients. Though still to be confirmed in a general intensive care population, studies have shown an advantage of enteral over parenteral nutrition and early over delayed nutrition. Immunological manipulation by glutamine supplementation or with Impact (Sandoz Pharma, Basel, Switzerland), a proprietary feed containing arginine, nucleotides and fish oil, has been claimed to demonstrate an improvement in mortality and morbidity, respectively.

Suggested management. Early enteral nutrition should be instituted aggressively within the first 24 h, aiming to reach assessed optimal requirements within 12–16 h of commencing feeding. Exceptions (and failures) are few and are usually related to concerns surrounding bowel integrity or specific surgical management which contra-indicates its use, e.g. following pancreatitis or faecal peritonitis. At present I do not use immunoenhancing feeds or supplements but await the results of large, multi-centre controlled trials with interest.

Sedation and paralysis

A combination of increasingly sophisticated mechanical ventilators and concerns regarding possible adverse effects have led to considerable reductions in both the duration and dosages of sedating and paralysing agents. This evolution in drug usage permits patient comfort and awareness, enhances cough and is likely to shorten the period of mechanical ventilation.

Early cessation or dosage reduction should be attempted when the patient’s analgesic requirements, respiratory compliance, need for paralysis or inspired oxygen concentration permit. Opiates and benzodiazepines at the lowest possible dosages are recommended for long-term sedation. Similarly, paralysis should be reserved for patients with endotracheal intubation, severe respiratory disturbances or other specific indications.

Haematinics

The optimal level of haemoglobin in the patient receiving intensive care has yet to be ascertained. It is likely to vary between patients and to depend on any underlying conditions. Traditional target levels of 8–11 g/dL are a compromise between increased viscosity and reduced oxygen-carrying capacity though effects on microvascular blood flow remain to be elucidated. Other factors including cardiac output and arterial oxygen saturation must also be considered in terms of maintaining adequate oxygen delivery to tissues. A recent multi-centre pilot study found no difference in outcome between a restricted and a liberal transfusion policy. Some evidence exists to suggest that fresh red cell transfusions are more advantageous though logistic difficulties often preclude their use.

Platelet transfusions are generally not needed unless: (i) thrombocytopenia is severe (e.g. <20 × 109/L); (ii) platelet levels are low (e.g. <50 × 109/L) with clinical evidence of bleeding or before surgical or other invasive procedures; or
(iii) existing platelets are dysfunctional, for example if aspirin has been recently ingested.

Likewise, fresh frozen plasma (and, rarely, cryoprecipitate) should be reserved for severe coagulopathies (e.g. International Normalized Ratio (INR) > 3), or for milder coagulopathies with evidence of bleeding or before surgical or other invasive procedures.

**Surgery and other invasive procedures**

If the patient is thought to have intra-abdominal pathology, in particular abscesses, prompt investigation is indicated with either operative or percutaneous treatment as indicated. Radiological procedures such as CT or ultrasound frequently produce false-negative results, but a negative laparotomy should not be considered a failure. Other investigations such as magnetic resonance imaging and radionuclide studies (e.g. gallium-labelled white cell scanning) are occasionally merited. Regular CT, ultrasound or echocardiographic examinations may also be required to follow disease progression.

**Haeodynamic management**

The vogue for ‘supranormalizing’ oxygen delivery as advocated by Shoemaker et al. appears to have been largely superseded by a less rigid approach wherein oxygen delivery is kept at adequate levels as judged by maintenance of organ perfusion. This is demonstrated by a good urine output, absence of metabolic (lactic) acidosis and lack of electrocardiographic ST-segment elevation. This change in approach has been prompted by the lack of demonstrable improvements (and possible harm) in patient outcome in carefully performed prospective controlled trials. The use of the relatively insensitive clinical markers described above highlights the current lack of reliable, simple and non-invasive monitors of the adequacy of regional (organ) perfusion. Tonometric measurement of gastric mucosal pH (pH$_{2}$) is the regional technique most heavily investigated to date though a paucity of studies demonstrating improved outcome by targeting normal pH$_{2}$ values has not encouraged widespread usage. Furthermore, this technique is user-dependent, prone to interference by enteral nutrition and requires the administration of an H$_{2}$-receptor antagonist which, in itself, may carry risks.

No consensus exists as to an optimal blood pressure; some authorities suggest a mean blood pressure of 60 mmHg or even lower is adequate provided existing organ function remains intact. Others aim for values commensurate with normal pre-illness figures. The majority of intensive care physicians opt for an intermediate level.

It is generally accepted that tissue oxygen delivery should, in the first instance, be increased by intravascular fluid loading. As described previously, within reason the choice of fluid is probably unimportant. The choice of inotrope and vasopressor rests largely with individual preference as numerous studies have shown both advantages and disadvantages for every drug and no agent clearly stands out as superior. Drugs purported to improve the splanchnic and renal circulations, e.g. dopexamine and epoprostenol, have yet to demonstrate definite effects such as improved survival or faster resolution of MOF.

A variety of other treatments are available for treating patients with borderline cardiovascular function. None has undergone any rigorous investigation, particularly of outcome benefit, though an ongoing multi-centre trial of a nitric oxide synthase inhibitor (L-NMMA) in severe sepsis is addressing this point. Options for the treatment of high output, low pressure states which fail to respond to conventional vasopressor therapy (noradrenaline or dopamine) include angiotensin, methylene blue which blocks the effect of nitric oxide on cGMP, and high dose corticosteroids which inhibit NO synthesis and restore a possibly reduced adrenocortical response. There are also advocates of the use of plasmapheresis for the removal of circulating mediators of the acute inflammatory response and replenishment of plasma factors by concurrent replacement with fresh frozen plasma.

**Respiratory management**

The respiratory component of MOF, A R D S, is probably the most comprehensively studied facet of this condition. Attention has been directed in recent years towards reducing iatrogenic lung trauma by ventilator settings designed to reduce airway pressures and shear stresses and by the acceptance of abnormal values of P$_{a}$CO$_{2}$ (permissive hypercapnia). There is no consensus as to acceptable levels of arterial oxygen saturation or tensions. Opinion is divided between Europe and North America over the danger of oxygen toxicity relative to other forms of iatrogenic trauma. Extracorporeal respiratory support remains a contentious area and is currently limited to a few specialized centres. Trials of surfactant administration have failed to show an outcome benefit. Regular postural changes (prone ventilation) and inhalation of either nitric oxide or epoprostenol have been shown to produce frequent improvements in gas exchange. However, as for the other manoeuvres and procedures described above, outcome benefit has yet to be demonstrated in large multi-centre controlled trials. Few would disagree that the ability to prolong life has been enhanced by the technological innovations described above. Two recent papers have suggested that survival from A R D S has actually improved over the last two decades. There is increasing evidence that high-dose corticosteroids administered in the fibroproliferative phase of A R D S (i.e. 7-10 days after onset) hastens resolution in a significant proportion of patients without obvious harmful effect.

**Suggested management.** Use of tidal volumes $\leq$10 mL/kg, permissive hypercapnia and inverse ratio ventilation to
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Renal management

Whether patients with acute renal failure die from renal failure itself or from the underlying predisposing condition is unresolved. A recent study suggested that renal failure appears to increase the risk of dying with an odds risk ratio of 5.6. However, patients in this study were generally treated by peritoneal dialysis or haemodialysis. There are data to suggest that continuous renal replacement therapy (such as haemofiltration or haemodiafiltration) results in better outcome than intermittent dialysis. The widespread availability of such therapies, which are being increasingly operated by ICU staff, has revolutionized the management of renal failure in the critically ill patient. Modern machines are pump-driven from venovenous access with in-built safety features and automated fluid delivery and removal. These technological advances have resulted in machines which are easy to use and have reduced iatrogenic complication rates considerably. Greater haemodynamic stability, improved fluid balance and temperature control, and possible benefits such as cytokine and inflammatory mediator removal have established this technology in the forefront of intensive care management. Questions still remain as to the best type of membrane, replacement solution, anticoagulation regimen, and rate of blood flow and ultrafiltrate removal.

The optimum timing for starting renal replacement also remains contentious. Unfortunately, pharmacological advances to prevent renal failure have not kept pace with the developments in equipment. A dequate intravenous volumes, flows and pressures are now recognized as being of paramount importance in managing the patient. The use of drugs such as dopamine, frusemide and mannitol is often empirical and not directed by reliable research.

Endocrine management

Studies have associated a poor or absent adrenocortical response to synacthen with a poor outcome in patients with MOF. In such patients, corticosteroid therapy may often dramatically improve circulatory status but whether outcome is affected remains open to question. Hyperglycaemia related to stress, parenteral nutrition, etc. should be corrected, usually with a continuous insulin infusion. Small-scale studies have also shown benefit from the administration of growth hormone in patients with burns. Multi-centre studies examining the use of growth hormone and insulin growth factor to expedite weaning from mechanical ventilation are in progress.

Prognosis of multiple organ failure

It is well recognized that persisting organ failure is associated with a poor prognosis for the patient, with mortality increasing stepwise as the number of organ systems involved increases. Has there been any improvement in recent years with the better technology, facilities and understanding of the disease processes? This is difficult to assess as many variables are continually changing. For example, the patient population has altered with many more elderly patients being admitted, particularly after major high-risk surgery. Nevertheless, multiple organ dysfunction still constitutes a major drain on available ICU resources. Improvements in techniques for both the prevention and treatment of MOF are needed. Several areas of investigation are being followed and some of the more significant are briefly described in the next section.

New treatments and approaches

Immunotherapy

The expectation that manipulation of the immune response and inhibition of the actions of factors such as endotoxin would result in improved outcomes has yet to be realized. Successive multi-centre trials have failed to deliver advantages over conventional regimens, e.g. methylprednisolone, anti-endotoxin monoclonal antibody, IL-1 receptor antagonist, anti-TNF antibody. Moreover, these treatments are invariably expensive. Enthusiasm has been further tempered by the recent demons-
A more wary and considered approach is required. A current anti-TNF antibody trial uses the presence of high plasma levels of IL-6 as a criterion for patient entry, thus ensuring that drug is given to patients in the acute septic state. Attention is being directed, via fundamental research programmes, at the neutrophil, the endothelium and free oxygen radicals and their role in MOF. Trials of antioxidants such as N-acetyl-cysteine are also being undertaken. Inhibition of the enzymes responsible for the synthesis of nitric oxide or of its actions on organs are progressing. Efforts to antagonize the inducible isoform of the synthesize enzyme selectively are also attracting considerable effort. Continuing trials of immunomodulation by supplementation or modification of enteral and parenteral feeds may reveal any therapeutic benefits from this approach.

Metabolic

Multi-centre trials of growth hormone and insulin growth factor therapy are assessing effects on outcome and duration of weaning from ventilator support.

Respiratory

On both sides of the Atlantic multi-centre trials of inhaled nitric oxide are currently being undertaken. ‘Liquid’ ventilation, using a perfluorocarbon liquid instilled into the lungs, also appears to improve gas exchange and has shown promising early results. Progression to phase III studies is expected soon. Various modes of action have been postulated such as enhancement of alveolar recruitment of atelectatic lung regions, alteration of pulmonary vascular resistance and lavage of exudate from the peripheral airways.

References


A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-α concentrations and outcome of patients with severe sepsis. Critical Care Medicine 24, 381–4.


