Multi-organ dysfunction in the critically ill: epidemiology, pathophysiology and management

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The syndrome of multiple organ failure has been recognised as a distinct entity since the 1970s, and is the leading cause of mortality in intensive care1. It was subsequently appreciated that patients develop a spectrum of organ dysfunction which may or may not require pharmacological (eg inotropic) or mechanical (eg ventilation) support. This led to the coining of a new syndrome, multi-organ dysfunction syndrome (MODS), defined as altered organ function in an acutely ill patient.

Aetiology and outcome

Multiple organ dysfunction arises from many possible insults, including sepsis, trauma, burns, pancreatitis, inhalation injury, haemorrhage, drug overdose, drowning and myocardial infarction. In a US study, MODS occurred in 14% of intensive care unit (ICU) patients.

Mortality is high, and correlates with the number of failed organs (Table 1). It has been decreasing due to better overall supportive care. A 16% survival rate was found in patients with three or more organ system failures on ICU day 4 (or later) admitted over the period 1988–90 compared with a 2% rate over 1979–82. A systematic review of septic shock also showed mortality reduction, from 61.6% in 1988–91 to 53.1% in 1994–97. Likewise, outcome has improved for patients with acute respiratory distress syndrome (ARDS), the pulmonary component of MODS, for which mortality fell from 65% to 35% between the early and mid-1990s.

Table 2 demonstrates the frequency of organ dysfunction in the ICU population. Initial neurological dysfunction (mean time from ICU admission, 1.6 days) was followed by respiratory, cardiovascular, renal, coagulation and, finally, hepatic (mean 4.9 days) dysfunction. Cardiovascular and renal failure had the highest impact on mortality (odds ratio, 1.68 and 1.46, respectively).

Pathophysiology

Inflammation

MODS is considered to be the final result of severe, persistent and generalised inflammation. The insult leads to excessive and inappropriate stimulation of pro-inflammatory pathways, including activation of macrophages, neutrophils, platelets, endothelium, complement, coagulation and fibrinolytic pathways. Many inflammatory mediators are produced in excess, including cytokines, arachidonic acid metabolites, nitric oxide (NO) and endothelins, with consumption of endogenous defence mechanisms such as antithrombin III and activated protein C. Expression, affinity and activity of numerous receptors (eg soluble tumour necrosis factor receptors, adrenoreceptors) are also affected. However, despite the pro-inflammatory phase dissipating within days, organ failure may persist for weeks or even months. Precise mechanisms through which organ damage occurs have yet to be determined.

Numerous multicentre patient studies attempting to modulate the inflammatory response have all signally failed to show either significant survival benefit or a consistent reduction in the number or duration of organ system failures. The use of these immunomodulatory agents may be inappropriate in either dose or timing, or be unable to affect the larger picture of systemic inflammation and subsequent organ failure.

Tissue hypoxia

Tissue oxygen delivery (DO	extsubscript{2}), the product of cardiac output, haemoglobin and arterial oxygen saturation, is approximately 1,000 ml/min in normal, resting adults. The amount of oxygen delivered is generally in excess of the body’s needs as only a quarter is usually consumed. This reservoir is utilised in conditions of increased consumption (VO	extsubscript{2}) (eg exercise) or decreased delivery (eg haemorrhage, cardiac failure or hypoxaemia). At a critical level of DO	extsubscript{2} (DO	extsubscript{2,crit}), where demand outstrips supply, an oxygen debt develops and anaerobic respiration ensues (Fig 1). Tissue hypoxia, in itself, is a powerful trigger of
the inflammatory response, as is the reoxygenation/reperfusion injury that occurs following resuscitation.

The size and duration of the tissue oxygen debt have been related to postoperative organ dysfunction and death after major surgery (Fig 2). Patients who maintained higher values of DO₂ and VO₂ (and thus lower oxygen debt) showed a consistent 4–5 fold reduction in mortality and morbidity. This can be achieved therapeutically with controlled fluid loading and vasoactive drug support.

However, in critically ill patients this approach of DO₂ and VO₂ ‘supranormalisation’ failed to improve outcome. Although spontaneous achievers of high values fared better, attempts to drive non-achievers to these levels with high-dose dobutamine resulted in a significant increase in deaths. This disparity emphasises major differences between relatively healthy elective surgical patients and those with established critical illness. These differences are poorly understood, though they may be related to more profound derangements in microcirculation and cellular metabolism. Indeed, the DO₂/VO₂ relationship is altered in critical illness, with the DO₂/VO₂ shifted to the right — that is, anaerobic respiration ensues at higher levels of DO₂.

**Microcirculation**

The increase in DO₂-ret in sepsis is traditionally ascribed to blood shunting away from nutrient capillary beds. This is because of loss of microvascular control mechanisms, including increased levels of NO, thromboxane, changes in adrenoreceptor density, and occlusion of capillaries by adherent platelets, white cells and fibrin clots. Interstitial oedema increases the diffusion distance that oxygen has to travel from vessel to cell.

**Cellular derangements**

In severe sepsis, lactic acidosis is commonplace, the magnitude correlating with poor outcome. Though traditionally ascribed to anaerobic phosphorylation. Changes seen in critical illness suggest failure of bioenergetic pathways as a possible mechanism of organ dysfunction. Disruption to key enzymes within the pathway has been demonstrated in vitro. NO and its metabolites (eg peroxynitrite) have been implicated. There is anecdotal evidence of decreased ATP levels and altered mitochondrial enzyme activities in human sepsis.

**Clinical management of organ failure**

In the absence of a ‘magic bullet’ cure, the emphasis is firmly based upon organ support, attempting to minimise iatrogenic trauma and complications such as nosocomial infection.

**Supportive care**

Recent improvements in outcome are more likely due to better supportive care, with increased attention paid to adequate and early nutrition (including replenishment of vitamins and trace elements), skin care, physiotherapy (mobilisation of chest secretions,
prevention of joint contractures, etc) and infection control. Efforts to identify infection and more rational use of antibiotics are reducing secondary problems such as multiresistance and fungal overgrowth. Accepting physiological and biochemical values compatible with survival and organ function, though not necessarily ‘normal’ — for example, permissive hypercapnia and maintenance of mean blood pressures sometimes as low as 55–60 mmHg — is likely to reduce iatrogenic complications.

**Cardiovascular**

The general philosophy of cardiovascular care is to maintain an adequate circulation (both blood pressure and flow), with intravascular fluid loading as the first and most important step. Epinephrine and dobutamine are predominantly used for low output circulations, while norepinephrine is currently favoured for high output states. Steroid therapy has previously been discredited, but recent reports have demonstrated enhanced reversal of septic shock and outcome benefit. For septic shock resistant to catecholamine therapy, other approaches include low dose vasopressin, plasmapheresis and high volume haemofiltration. The ideal level of haemoglobin is still unknown. A recent Canadian study suggested 7–8 g/dl was better in younger, less sick patients, though caution is required in interpretation of the results as many patients were excluded from randomisation. The role of invasive monitoring (pulmonary artery catheterisation) is also being questioned, and randomised trials will soon begin in Britain and the US.

**Respiratory**

Respiratory support has traditionally relied on mechanical ventilation. Ventilation with lower tidal volumes (6 ml/kg vs 12 ml/kg) demonstrated clear outcome benefit in a recent multicentre study. The impact of lung recruitment through use of high levels of positive end expiratory pressure, surfactant therapy or other modalities is being investigated, as is the possible benefit of extracorporeal oxygenation and partial liquid ventilation. Recent trials of inhaled NO revealed no outcome benefit in ARDS. There has been renewed interest in the use of steroids in late ARDS, sometimes with dramatic improvement in gas exchange. The last decade has seen a reduction in the use of neuromuscular blockers and sedatives, with the emphasis on patients being awake yet comfortable. This, plus the introduction of more sophisticated, ‘patient-friendly’ ventilators, reduces the duration of mechanical ventilation.

**Renal**

Apart from avoiding hypoperfusion, no therapy has been shown to prevent or reverse renal failure. Dopamine at ‘renal’ dose appears to be little more than a diuretic. Renal replacement therapies are becoming more sophisticated with continuous haemofiltration and/or dialysis techniques using highly biocompatible membranes. As these membranes can adsorb or remove inflammatory mediators from the circulation, studies investigating high volume filtration or different membranes have been prompted. The optimal timing for renal replacement therapy remains unknown.

**Gastrointestinal**

Adequate nutrition, particularly from an enteral approach, is being emphasised. Direct protective benefits are conferred on the gut, and there are strong suggestions of a reduced incidence of nosocomial infection and improved patient outcome. A recent multicentre study revealed significant outcome benefit using a protocol of early enteral nutrition with a standard feed (W Sibbald; personal communication). Studies of immunonutrition suggest additional benefit: that is, nutrition supplemented with additives with immunomodulating effects (eg glutamine, polynsaturated fatty acids, arginine and RNA). The role of selective gut decontamination is hotly debated. Although meta-analyses suggest that administration of topical and systemic antibiotics reduces rates of infection and improves outcome, this approach has not been generally adopted. Stress ulcer prophylaxis includes maintaining adequate perfusion, enteral nutrition and, if necessary, the use of either an H2-blocker or sucralfate.

**Haematological**

Haematological support consists of maintaining an adequate haemoglobin level and replacing clotting factors and platelets as cover for clinically obvious bleeding or invasive procedures. Studies are continuing in critically ill septic patients on supplementation with antithrombin III, activated protein C and tissue factor pathway inhibitor. Haemoglobin substitutes are being developed from bovine sources, recombinant technology or intravenous perfluorocarbons. Regular injection of erythropoietin to reduce the need for blood transfusion is under investigation.

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**Key Points**

- Multi-organ dysfunction results from severe generalised inflammation and can be triggered by a number of factors
- Mortality remains high, but is improving
- Microcirculatory derangements and alterations in cellular bioenergetic pathways are important in the pathogenesis
- Management is through support of failing organs
- There is no ‘magic bullet’
Conclusion
In summary, a better understanding of the pathophysiology of multi-organ failure has undoubtedly assisted patient management, with the recognition that some therapies may give short-term gain but cause long-term harm. The failure of anticytokine and other immunomodulatory therapies underlines the fact that much remains to be learnt.

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