Clinical management of ARDS

Intense frustration and disappointment exist among clinicians that multiple avenues of research into the pathophysiology of the adult respiratory distress syndrome (ARDS) have not translated into improved outcome for the majority of patients with this condition in the intensive therapy unit (ITU). Despite the continuous discovery of new inflammatory mediators and their antagonists, there is still no drug therapy of proven value.

Much of the original disease was a consequence of inadequate or late resuscitation [1]. Improved understanding and management of trauma and haemorrhagic shock has now almost eliminated this actiology as a cause of death in the ITU. Modern ARDS is frequently the pulmonary component of a systemic inflammatory process, resulting from sepsis [2]. Death is rarely caused by lung failure alone, but rather by multiple organ failure. Failure to appreciate that ARDS is not a single disease entity, but a spectrum of disease states, has undoubtedly hampered clinically useful research and highlights the need for a more holistic approach. ARDS is typical of many of the heterogeneous states found in the ITU and for which, presently, there is no satisfactory system of disease classification or stratification. This seriously undermines measures of outcome. Future clinical research into ARDS requires a method of defining the disease that must include actiology, severity and chronicity [3].

It seems unlikely therefore that new therapies directed solely at treatment of the lung in ARDS will reduce mortality significantly from what is essentially a systemic disease. Currently, all approaches to the treatment of ARDS are supportive, aiming to minimize secondary lung damage until natural healing processes occur. Thus ventilatory support remains the cornerstone of clinical management. Although it is generally agreed that it is important to maintain peak inspiratory pressure at less than 40 cm H₂O and mean airway pressures less than 30 cm H₂O to prevent secondary lung damage resulting from barotrauma and volutrauma [4], the best way to achieve this is still uncertain. There are currently several approaches, including high frequency jet ventilation [5], inverse ratio ventilation and pressure controlled ventilation [6], permissive hypercapnia [7] and ventilation in the prone position [8]. However, there is no evidence that any of these techniques, alone or in combination, improve mortality. Similarly, the pursuit and attainment of supranormal therapeutic goals of oxygen delivery and consumption, clearly of value in the post-surgical and trauma patient [9], have failed to produce a benefit in septic ARDS. So where can progress be made?

Gut-derived endotoxin probably plays a central role in the initiation and maintenance of the systemic inflammatory response associated with ARDS [10]. The use of gut-directed therapy, including the establishment and maintenance of early enteral feeding, particularly with glutamine-rich substrates, may offer a valuable tool in the prevention of gut failure [11, 12]. Prevention of failure of this organ is believed to be so important that a feeding jejunostomy should be considered. This is particularly pertinent as monoclonal antibody to endotoxin, HA1A, after initially promising results, has not proved to be clinically effective.

The injured lung in ARDS is prone to secondary infection. The prevention of nosocomial pneumonia by the use of selective decontamination of the digestive tract (SDD) is an area of intense debate, but a recent meta-analysis suggested that it may be valuable [13].

Inevitably there is keen interest in the development and use of inflammatory mediator antagonists in the prevention and treatment of ARDS associated with the systemic inflammatory response syndrome (SIRS) [14]. Those agents undergoing clinical investigation at present are platelet activating factor (PAF) antagonists, interleukin-1 (IL-1) receptor antagonists and antagonists to tumour necrosis factor (TNF). Ibuprofen and oxpentifylline (a xanthine derivative which inhibits both the production of oxygen-free radicals and TNF-α) are also being studied.

It may be that appropriate therapy will eventually be guided by sophisticated assessment of concentrations of mediators and of disease markers such as manganese superoxide dismutase [15]. However, it is unreasonable to expect that any single inflammatory mediator antagonist will be able to control the enormously complex multiplicity of biochemical processes characteristic of SIRS, which have beneficial as well as damaging effects.

Techniques such as extracorporeal membrane oxygenation [16] (ECMO) and intravascular oxygenation (IVOX) [17] are fraught with difficulties and have not been successful universally. They are unlikely to be available outside highly specialized units. A new approach which, if successful, may eliminate the need for such invasive procedures, is the use of the inhalation route for agents such as nitric oxide (NO) [18], prostacyclin [19] or even.
perfluorocarbons [20]. The first two agents not only produce pulmonary vasodilatation but, more importantly, dilate only those vessels in contact with ventilated areas of lung. Intrapulmonary shunting is thus reduced, as is the need for potentially damaging high inflation pressures and high inspired concentrations of oxygen.

Naturally occurring nitric oxide appears to play a role in systemic vasodilatation [21]. Nitric oxide synthetase, the enzyme which allows the production of nitric oxide from arginine, occurs in two forms. A constitutive form is vital for normal vascular tone and an inducible form is responsible for the pathological vasodilatation characteristic of SIRS. Preliminary work with inhibitors of nitric oxide synthetase, for example N-(omega)-nitro-L-arginine [22], which acts as a false substrate for this enzyme, suggests that these inhibitors may be useful in refractory shock. Thus it may be that in the near future we shall be administering small concentrations (10–20 ppm) of nitric oxide gas by inhalation to patients with septic ARDS, while also giving an inhibitor of nitric oxide synthetase parenterally.

Deficiency of lung surfactant is present in ARDS [23] and experience with a nebulized surfactant (Exosurf) suggests that the use of drugs by the inhalation route is practical in any ITU, even if a sophisticated nebulization technique is required to deliver the drug. Unfortunately, the Exosurf study failed to demonstrate any reduction in mortality from ARDS; 41% of patients died within 30 days in both the treated and placebo groups [24]. This is in contrast with the proven value of Exosurf in infant respiratory distress syndrome (IRDS) and highlights the need for caution before extrapolating results of animal and human neonatal research to ARDS. IRDS and ARDS are fundamentally different diseases. It was, however, a very good example of a randomized, double-blind study of the value of a therapy in ARDS associated with sepsis in which aetiology, pathophysiology and chronicity were defined. Such studies are difficult and expensive, but are essential if progress is to be made in answering some of the fundamental questions facing intensive therapy today. We still do not know, for example, the largest inspired oxygen concentration that may be administered safely for any particular patient and therefore when PEEP should be introduced to ensure adequate oxygen delivery.

Finally, there is a small group of ARDS patients with irreversible lung damage but only single organ failure. Our experience when faced with such patients has been that there is no clear consensus among transplant surgeons within the U.K. on the value of lung transplantation in such circumstances. We hope that clearer criteria will emerge that will assist intensive therapists in the management of these difficult patients.

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REFERENCES
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