

Editorial

The adult respiratory distress syndrome—20 years on

It is 20 years since Ashbaugh and colleagues formulated a definition of the adult respiratory distress syndrome (ARDS)¹ and therefore timely to review the current state of research and management. The original description, based on 12 patients, identified characteristics that now constitute major criteria for the diagnosis of the syndrome: an appropriate risk factor, pulmonary oedema, and refractory hypoxaemia associated with previously normal lungs² (table 1). The effects of corticosteroids, positive pressure ventilation and positive end expiratory pressure, and a high mortality rate (seven out of 12) were also recorded. The criteria for diagnosis, treatment options, and outcome appear to have changed remarkably little. The mortality rate has remained at 60–70% despite greater awareness of the disorder, ready access to intensive care, and an enormous amount of research.^{3–9}

At diagnosis the derangement of gas exchange and pulmonary haemodynamics probably indicate a common end point in the response of the lung to injury of various causes. Thus the criteria currently used for diagnosis of ARDS effectively define a state of great severity that carries a high mortality. There has been a tendency to adhere rigidly to these criteria because studies that have not done so may not be considered acceptable for publication. Unfortunately it is almost exclusively in such patients that the pathophysiology of ARDS has been studied and therapeutic trials carried out. Thus patients are studied at the worst end of the range of the syndrome, where benefit should not be expected, and this may explain the so far disappointing results of therapeutic trials. The criteria might reasonably be extended to cover a range of severity of pulmonary dysfunction that includes patients with the currently recognised state of established ARDS as a subgroup. If left unchanged the criteria seem likely to inhibit clinical research and the development of effective management. Undoubtedly some patients develop a transient "mild ARDS" with hypoxaemia and lung infiltrates but fail to meet the current criteria. Study of such patients is likely to be more informative regarding pathophysiological mechanisms and effective management options.¹⁰

The exact incidence of ARDS is unknown. In the United States the National Heart and Lung Institute

Table 1 *Criteria for diagnosis of the adult respiratory distress syndrome*

1	An appropriate risk factor—for example, sepsis, aspiration, or trauma
2	Severe hypoxaemia while breathing increased oxygen concentrations
3	Increased pulmonary shunt fraction
4	Reduced lung compliance
5	Radiographic evidence of pulmonary oedema
6	Previously normal lungs
7	No evidence of heart failure

has estimated that up to 150 000 cases occur annually,¹¹ making ARDS more common than lung cancer. Extrapolation to the United Kingdom would suggest about 15 000–30 000 cases a year,¹² though there are no data to support this figure and intensive care units do not appear to admit such a large number of patients. The lack of information on incidence is surprising in a disorder that remains a major management problem in intensive care medicine.

Mechanism of lung injury

The hallmark of ARDS is the accumulation of protein rich fluid in the alveoli as a result of an increase in pulmonary microvascular permeability to plasma proteins.^{13 14} This has been shown in various animal models^{15 16} and because pulmonary permeability to protein can be increased with certainty in these models they have been used to study possible mechanisms. Extrapolation of these findings to ARDS is easy but its validity is questionable. In man a specific insult does not initiate ARDS in all individuals, and there is often more than one risk factor in a given case.

There is evidence in man that insults, particularly sepsis, multiple trauma, and aspiration,^{5 17} activate the complement¹⁸ and coagulant cascades.¹⁹ This causes the formation of platelet and protein microaggregates in the circulation and probably explains the consumption of other plasma proteins such as fibronectin and antithrombin III.^{20–22} This particulate material is thought to lodge in the pulmonary capillaries, initiating further protein consumption and the release of chemotactic factors, causing the recruitment of eosinophils and polymorphonuclear neutrophils into the pulmonary circulation. These cells are activated during adhesion and generate or release various noxious products.²³ Superoxide anion, hydrogen peroxide, hypochlorous acid, and

hydroxyl ions may be generated and their products can be detected in the serum and breath of patients with ARDS.^{24 25} Intermediate metabolites of oxygen have been implicated in endothelial and epithelial cell injury by neutrophils, degranulation and the release of lysosomal enzymes adding further to the damage.²³ Injury leads to increased protein permeability at the capillary-alveolar barrier, pulmonary oedema, and the clinical state of ARDS.

Most patients at risk who develop ARDS do so within 72 hours of exposure to the risk factor,⁵ a period in which inflammatory mechanisms are initiated and cascade to the point of increasing permeability to plasma proteins. Interruption of these processes at an early stage would appear to be the best way to reduce the incidence and high mortality rate of ARDS. Unfortunately none of the work on mechanisms so far has yielded a marker or method for detecting early changes, or a simple means of monitoring progress. Studying patients with established ARDS may be the reason for the difficulty of translating research on inflammatory mechanisms into practical measures, such as early detection, monitoring, and more effective management. In future research aimed at defining the initiation of the inflammatory response in at risk groups rather than the isolated study of one mediator or one cell in established ARDS may answer some of these criticisms.

Sepsis and ARDS

The infection-sepsis syndrome is both the main risk factor for ARDS and the most important complication of ARDS.^{4 5 17 26 27} The sepsis syndrome consists of clinical and laboratory findings indicative of a systemic response to infection but does not require microbiological proof of infection²⁸ (table 2).

In retrospective and prospective surveys of ARDS sepsis has been present in 4–50% of cases.^{4 5 17 26 29}

Table 2 *Criteria for diagnosis of the sepsis syndrome*^{8 28}

Two of the following findings indicating possible infection:	
Temperature	>39°C or <36°C
White blood count	<3000 or >12000 cells/mm ³ or with 10% immature granulocytes
Blood culture	positive for a commonly accepted pathogen
Known or strongly suspected source for systemic infection that has yielded a culture of a known pathogen	
Gross pus in a closed space	
Plus one of the following, indicating a deleterious systemic effect:	
Unexplained metabolic acidosis with a base excess of	>5 mmol (mEq)/l
Systemic vascular resistance	<800 dynes/s/cm
Unexplained hypotension with systolic BP	<90 mm Hg for more than 2 h

The wide range depends on whether sepsis is defined as bacteraemia or as the sepsis syndrome, the higher incidence figures being associated with the sepsis syndrome.^{4 17 29} Mortality rates for patients with ARDS and associated sepsis in these studies was 80–90% compared with 35–55% in bacteraemic patients not developing ARDS.^{4 29} There is overlap between the sepsis syndrome and ARDS. In one prospective study of ARDS in various at risk groups there was an overall mortality rate of 68% and the figure was similar in those with sepsis. Patients with the sepsis syndrome who did not develop ARDS, however, had a mortality of 76%.⁸ Both the patients with ARDS and those with the sepsis syndrome had a high incidence of multiple organ failure, and infection rather than respiratory failure could be invoked as the main factor in the high mortality rate.

The importance of secondary sepsis in ARDS was recognised in early studies, in which intensive respiratory treatment was found to reduce deaths due to respiratory failure but not to reduce the overall mortality rate.³⁰ Secondary sepsis was present in 68–90% of non-survivors, compared with 10–59% of survivors.^{8 30} Respiratory failure may not therefore be the major determinant of outcome in patients with established ARDS. In a prospective study of patients developing ARDS only 16% of deaths were due to respiratory failure, whereas the sepsis syndrome was a major factor in 60%. In late fatalities, occurring after three days of intensive respiratory support, development of the sepsis syndrome was considered to be a factor in 73% of deaths.⁸ In most patients secondary infection arose from the respiratory tract (75%) whereas intra-abdominal infection was the main source of sepsis preceding ARDS. The predominance of pulmonary infection would be expected from the high incidence of colonisation and infection of the respiratory tract with hospital acquired pathogens in mechanically ventilated patients in intensive care units.^{31–32}

In ARDS pulmonary clearance mechanisms may also be reduced by oedema. This breach of the lung defences leads to secondary sepsis and irreversible multiple organ failure. Secondary infection coupled with consumption or reduced production (or both) of circulating acute phase proteins and opsonising proteins may be factors in the sustained high mortality rate in established ARDS.^{21 22}

There are two approaches to the problem of sepsis and ARDS—firstly, control of the development of secondary infection and, secondly, maintenance of host defences.

Nosocomial infection can be reduced by good hygiene between patient and nursing staff and the adoption of measures to reduce bacterial carriage by intensive care staff.³³ Selective decolonisation

tamination of the gastrointestinal tract, including the oropharynx, a major source of pathogens in ventilated patients,³⁴ has been tried. A mixture of non-absorbed antibiotics (polymixin E, tobramycin, and amphotericin B) has been reported to reduce mortality due to secondary respiratory infection.^{35 36} In a trial in patients with trauma requiring ventilation for more than five days infection rates were reduced fivefold, from 81% to 16%, in selectively decontaminated patients and infection from the respiratory tract with oropharyngeal derived organisms from 59% to 8%.³⁶ This approach may be the way to reduce mortality in established ARDS but further studies are needed.

The complementary approach is to maintain or augment host defences against infection. The serum protein fibronectin, a glycoprotein of molecular weight 400 kD synthesised by vascular endothelial cells, hepatocytes, and macrophages, has attracted attention as a possible therapeutic agent because of its role as an opsonising protein in inflammation and tissue repair. Fibronectin molecules have specific binding sites for a wide range of biological agents—fibrin, actin, DNA, collagen, gelatin, heparin, *Staphylococcus aureus*, and various cells, including fibroblasts, macrophages, and endothelial cells.³⁷ Serum fibronectin concentrations are reduced in man after surgery, trauma, and burns and in sepsis.^{21 22 38 39} In surgical patients with intra-abdominal infection low fibronectin levels fell even further postoperatively in those developing multiple organ failure³⁹ but showed a slow and delayed rise in survivors. In patients with ARDS a progressive increase in fibronectin concentration was associated with survival.³⁸ Initial trials of infused cryoprecipitate, a concentrated source of fibronectin, and purified human fibronectin were very successful in sepsis and established ARDS^{40–41}; but recent reports suggest that the effect on mortality is smaller, though survival time was increased in the treated subjects.⁴² These trials were small, and in those using cryoprecipitate as a source of fibronectin it is impossible to know whether benefit was due to fibronectin or other plasma factors present in cryoprecipitate, such as fibrinogen, von Willebrand factor, α_2 macroglobulin, and factor VIII. A major problem with fibronectin purified from either source is knowing how functionally active the molecule is and whether specific binding sites relevant to sepsis and injured lung are available. The use of immunological assays and current functional assays (for example, gelatin binding and phagocytic assays) cannot completely answer this question. Large scale, well designed trials are needed to ascertain the role of fibronectin, and they will require a source of active fibronectin and assays capable of determining the presence of appropriate binding site activity.

Developments in current management

Despite these exciting and potentially valuable approaches current management, after treatment of the underlying cause, remains supportive, depending primarily on improving ventilation and maintaining satisfactory systemic arterial oxygenation. This is achieved by mechanical ventilation with positive end expiratory pressure and high inspired oxygen concentrations. Variations in ventilatory technique have been tried to minimise lung damage from both positive end expiratory pressure and high inspired oxygen concentrations, but neither high frequency positive pressure ventilation nor high frequency jet ventilation has shown any advantage over the traditional ventilatory techniques.^{43 44} Differential ventilation with selective positive end expiratory pressure to the lowermost lung in patients nursed on their sides has been reported to improve gas exchange,⁴⁵ and muscle paralysis is one means of reducing oxygen requirements.⁴⁶ Most alternative forms of ventilation have not been studied adequately and cannot currently be recommended. Pharmacological intervention has been attempted with corticosteroids, β_2 agonists, and prostaglandins, all of which have shown benefit in animal models. The use of corticosteroids in ARDS has long been controversial owing to inadequate clinical trials. Their use has been further questioned as a result of a recent study in patients at risk of developing ARDS, where mortality rates in those treated were higher as a result of sepsis.⁴⁷ Isoprenaline has been reported to reduce pulmonary microvascular permeability in rabbits,⁴⁸ whereas salbutamol has been shown to increase pulmonary oedema in a rat acid aspiration model.⁴⁹ In an open study the accumulation of transferrin (molecular weight 75 kD) in the lungs of patients with ARDS was reduced with terbutaline,⁵⁰ but controlled trials are needed to clarify the role of such agents. Prostaglandin E₁ inhibited the formation of platelet microaggregates during experimental surgical shock⁵¹ and favourably altered pulmonary haemodynamics in patients with ARDS in one study.⁵² A multicentre controlled trial of PGE₁ in established ARDS is under way and a prevention study is planned in the United States.

The often quoted failure to improve the mortality rate in ARDS is very depressing, but we should not concentrate on this at the expense of the enormous increase in knowledge gained in the last 20 years. An appraisal of this period suggests that clinicians and research workers have been blinkered by the over rigid use of diagnostic criteria and concentration on individual components of the inflammatory response. In the future ARDS of a wider range of severity needs to be studied and the early pathophysiological mechanisms defined. There are potentially effective treat-

ments available which should reduce the mortality rate. Trials of such treatments need to be large scale and rigorously controlled and to encompass patients at risk of developing established ARDS at an earlier stage of the disease process.

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