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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 lungs[2] (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 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.

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

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 complement[18] 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

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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 infection[28] (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 lungs' 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 between patient hygiene by medical and nursing staff and the adoption of measures to reduce bacterial carriage by intensive care staff.[33] Selective decon-

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 failure[39] 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 lower-most 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 E_1 inhibited the formation of platelet microaggregates during experimental surgical shock[51] and favourably altered pulmonary haemodynamics in patients with ARDS in one study.[52] A multicentre controlled trial of PGE_1 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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References

1 Ashbaugh DG, Biglow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;ii:319–23.
2 Petty TL, Fowler AA. Another look at ARDS. *Chest* 1982;**82**:98–103.
3 Petty TL, Ashbaugh DG. The adult respiratory distress syndrome—clinical features, factors influencing prognosis and principles of management. *Chest* 1971;**70**:233–9.
4 Fein AM, Lippman M, Holzman H, Eliraz A, Goldberg SK. The risk factors, incidence and prognosis of the adult respiratory distress syndrome following septicaemia. *Chest* 1983;**83**:40–2.
5 Fowler AA, Hamman RF, Good JT, *et al.* Adult respiratory distress syndrome: risk with common predispositions. *Ann Intern Med* 1983;**98**:593–7.
6 Fowler AA, Hamman RF, Zerbe GO, Benson KN, Hyers TM. Adult respiratory distress syndrome. Prognosis after onset. *Am Rev Respir Dis* 1985;**132**:472–8.
7 Andreadis N, Petty TL. Adult respiratory distress syndrome: problems and progress. *Am Rev Respir Dis* 1985;**132**:1344–6.
8 Montgomery AB, Stager MA, Carrico J, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985;**132**:485–9.
9 Baumann WR, Jung RC, Koss M, Boylen CT, Navarro L, Sharma OP. Incidence and mortality of adult respiratory distress syndrome: a prospective analysis from a large metropolitan hospital. *Crit Care Med* 1986;**14**:1–4.
10 Rinaldo JE. The prognosis of the adult respiratory distress syndrome. Inappropriate pessimism? *Chest* 1986;**90**:470–1.
11 National Heart and Lung Institute. *Respiratory diseases. Task force report on problems, research approaches, needs.* Washington DC: US Government Printing office, 1972:167–80. (DHEW Publication No (NIH)73–432.)
12 Wardle EN. Shock lungs: The post-traumatic respiratory distress syndrome. *Q J Med* 1983;**211**:317–29.
13 Gelb AF, Klein E. Hemodynamic and alveolar protein studies in noncardiac edema. *Am Rev Respir Dis* 1976;**114**:831–5.
14 Shale DJ, Chapel H, Hussain A, Fisher A, Lee G. Preservation of selective permeability at the capillary-alveolar barrier in the adult respiratory distress syndrome [abstract]. *Thorax* 1985;**40**:239–40.
15 Brigham KL, Woolverton WC, Blake LH, Staub NC. Increased sheep lung vascular permeability caused by *Pseudomonas* bacteraemia. *J Clin Invest* 1974;**54**:792–804.
16 Kirton OC, Jones R, Zapol WM, Reid L. The development of a model of subacute lung injury after intra-abdominal infection. *Surgery* 1984;**96**:384–93.
17 Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ. Clinical predictors of the adult respiratory distress syndrome. *Am J Surg* 1982;**144**:124—30.
18 Weinberg PF, Matthay MA, Webster RO, Rokos KV, Goldstein IM, Murray JF. Biologically active products of complement and acute lung injury in patients with the sepsis syndrome. *Am Rev Respir Dis* 1984;**130**:791–6.
19 Bone RC, Francis PB, Pierce AK. Intravascular coagulation associated with the adult respiratory distress syndrome. *Am J Med* 1976;**61**:585–9.
20 McCollum CN, Campbell IT. The value of measuring intravascular platelet aggregates in the prediction of postoperative pulmonary dysfunction. *Br J Surg* 1979;**66**:703–7.
21 Scovill WA, Saba TM, Kaplan JE, Bernard H, Powers SR. Deficits in reticuloendothelial humoral control mechanisms in patients after trauma. *J Trauma* 1976;**16**:898–904.
22 Wilson RF, Mammen EF, Robson MC, Heggers JP, Soullier G, DePoli PA. Antithrombin, prekallikrein and fibronectin levels in surgical patients. *Arch Surg* 1986;**121**:635–40.
23 Weiland JE, Davis WB, Holter JF, Mohammed JR, Dorinsky PM, Gadek JE. Lung neutrophils in the adult respiratory distress syndrome. Clinical and pathophysiologic significance. *Am Rev Respir Dis* 1986;**133**:218–25.
24 Ward PA, Till GO, Hatherill JR, Annesley TM, Kunkel RG. Systemic complement activation, lung injury and products of lipid peroxidation. *J Clin Invest* 1985;**76**:517–27.
25 Baldwin RR, Simon RH, Grum CM, Ketai LH, Boxer LA, Devall LJ. Oxidant activity in expired breath of patients with adult respiratory distress syndrome. *Lancet* 1986;i:11–3.
26 Seidenfeld JJ, Pohl DF, Bell RC, Harris GD, Johanson WG. Incidence, site and outcome of infections in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1986;**134**:12–6.
27 Bell RC, Coalson JJ, Smith JD, Johanson WG. Multiple organ system failure and infection in adult respiratory distress syndrome. *Am Intern Med* 1983;**99**:293–7.
28 Wiles JB, Cerra FB, Siegel JR, Border JR. The systemic septic response: does the organism matter? *Crit Care Med* 1980;**8**:55–60.
29 Kaplan RL, Sahn SA, Petty TL. Incidence and outcome of the respiratory distress syndrome in gram negative sepsis. *Arch Intern Med* 1979;**139**:867–9.
30 Ashbaugh DG, Petty TL. Sepsis complicating the acute respiratory distress syndrome. *Surg Gynecol Obstet* 1972;**135**:865–9.
31 Daschner FD. Nosocomial infections in intensive care units. *Intens Care Med* 1985;**11**:284–87.
32 Salata RA, Lederman MM, Shlaes DM, *et al.* Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. *Am Rev Respir Dis* 1987;**135**:426–32.

33 Daschner FD. Useful and useless hygenic techniques in intensive care units. *Intens Care Med* 1985;**11**:280–3.
34 van Uffelen R, van Saene HKF, Fidler V, Lowenberg A. Oropharyngeal flora as a source of bacteria colonizing the lower airways in patients on artificial ventilation. *Intens Care Med* 1984;**10**:233–7.
35 Stoutenbeek CP, van Saene HKF, Miranda DR, Zandstra DF. A new technique of infection prevention in the intensive care unit by selective decontamination of the digestive tract. *Acta Anaesthesiol Belg* 1983;**34**:209–21.
36 Stoutenbeek CP, van Saene HKF, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intens Care Med* 1984;**10**:185–92.
37 Hynes RO, Yamada KM. Fibronectins: multifunctional modular glycoproteins. *J Cell Biol* 1982;**95**:369–77.
38 Fourrier F, Chopin C, Wallaert B, Mazurier C, Mangalaboyi J, Durocher A. Compared evolution of plasma fibronectin and angiotensin converting enzyme levels in septic ARDS. *Chest* 1985;**87**:191–5.
39 Richards WO, Scovill WA, Shin B. Opsonic fibronectin deficiency in patients with intra-abdominal infection. *Surgery* 1983;**94**:210–7.
40 Stevens LE, Clemmer TP, Laub RM, Miya F, Robbins L. Fibronectin in severe sepsis. *Surg Gynecol Obstet* 1986;**162**:222–8.
41 Saba TM, Blumenstock FA, Shah DM, *et al.* Reversal of opsonic deficiency in surgical, trauma and burn patients by infusion of purified human plasma fibronectin. *Am J Med* 1986;**80**:229–40.
42 Lundsgaard-Hansen P, Doran JE, Rubli E, Papp E, Morgenthaler JJ, Spath P. Purified fibronectin administration to patients with severe abdominal infections. A controlled trial. *Ann Surg* 1985;**202**:745–59.
43 Wattwill LM, Sjostrand UM, Borg UR. Comparative studies of IPPV and HFPPV and PEEP in critical care patients. 1: A clinical evaluation. *Crit Care Med* 1983;**11**:30–7.
44 Holzapfel L, Perrin RF, Gaussorgues P, Giudicelli DP. Comparison of high frequency jet ventilation to conventional ventilation in adults with respiratory distress syndrome. *Intens Care Med* 1987;**13**:100–5.
45 Hedenstierna G, Baehrendtz S, Frostell C, Mebius C. Differential ventilation in acute respiratory failure. Indications and outcome. *Bull Eur Physiopathol Respir* 1985;**21**:281–5.
46 Coggeshall JW, Marini JJ, Jewman JH. Improved oxygenation after muscle relaxation in the adult respiratory distress syndrome. *Arch Intern Med* 1985;**145**:1718–20.
47 Weigelt JA, Norcross JF, Borman KR, Sayder WH. Early steroid therapy for respiratory failure. *Arch Surg* 1985;**120**:536–40.
48 Mizus I, Summer W, Farrukh I, Michael JR, Gurtner GH. Isoproterenol or aminophylline attenuate pulmonary oedema after acid lung injury. *Am Rev Respir Dis* 1985;**131**:266–9.
49 Braude S, Royston D. Infused salbutamol accentuates acid-induced lung injury in the rat. *Clin Sci* 1986;**71**:205–9.
50 Basran GS, Hardy JG, Woo SP, Byrne AJ, Ramasubramanian R. Beta 2 adrenoceptor agonists as inhibitors of lung vascular permeability to radiolabelled transferrin in the adult respiratory distress syndrome in man. *Eur J Nucl Med* 1986;**12**:381–4.
51 Poskett KR, Irwin JTC, Karacagil S, McCollum CN. The influence of prostaglandin E_1 on pulmonary microembolisation during major surgery. *Br J Surg* 1986;**73**:507.
52 Tokioka H, Kobayashi O, Ohta Y, Wakabayashi T, Kosaka F. The acute effects of prostaglandin E1 on the pulmonary circulation and oxygen delivery in patients with the adult respiratory distress syndrome. *Intens Care Med* 1985;**11**:61–4.