The pulmonary physician and critical care · 3

Pharmacotherapy in lung injury

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The term adult respiratory distress syndrome (ARDS) was first used in 1967 to define the condition of severe parenchymal lung injury leading to refractory hypoxaemia in the absence of left ventricular failure.[1] In 1972 it was suggested that there are around 150 000 cases of ARDS a year in the United States alone,[2] but European data are scarce and estimates of incidence vary widely. A recent retrospective study in a single region of the United Kingdom identified 2·5 cases a year per 100 000 population,[3] suggesting that 1000–1500 cases of established ARDS occur in Britain each year. The associated mortality is high,[4] approaching 70% in patients with sepsis complicated by ARDS and 90% when ARDS follows aspiration pneumonia.[5] The cause of death depends on the underlying insult, its site and severity, the response to treatment, and the incidence of complications affecting other organ systems: irreversible respiratory failure is responsible for only 16% of deaths,[6] and most deaths are due to multiple organ failure.

The clinical features that define ARDS can in part be attributed to an increase in permeability of the alveolar-capillary membrane. It is now apparent that increased vascular leakiness occurs in other organs, such as the kidney,[7] and all capillary beds seem likely to be influenced by the disease process to a greater or lesser extent. The endothelium is emerging as an important regulatory body in pulmonary[8] and systemic[9] vascular control and endothelial damage has important implications for the development of both ARDS and the syndrome of multiple organ failure.

Only a few of the patients with conditions associated with the development of ARDS, develop the full blown syndrome.[10] Consequently, there has been a growing awareness that ARDS represents the end of a spectrum of acute lung injury. The clinical criteria used to diagnose the condition at present are therefore too broad to allow comparisons of disease severity between different patients and clinical centres, which has important implications for the scientific evaluation of potential therapeutic interventions. Murray *et al*[11] have developed a score for patients with lung injury that takes account of the appearance of the chest radiograph, pulmonary compliance, the degree of hypoxaemia, and the degree of positive end expiratory pressure (PEEP) used in ventilatory support. These variables are graded for severity, permitting the calculation of an overall score of injury. Although this approach should change the perception of ARDS as a single disease entity and improve the way in which the efficacy of new treatments is assessed, limitations remain, including the omission of a loading factor for the underlying illness, which undoubtedly influences prognosis.

The treatment of lung injury up to and including ARDS remains supportive. Despite the use of sophisticated ventilatory techniques and extracorporeal membrane oxygenation, mortality is unaltered and no specific pharmacotherapy has been developed.

Aetiology and pathophysiology

Table 1 shows the most common causes of acute lung injury and ARDS. These can be divided into two groups: those that directly damage the lung and those in which a remote disease process is complicated by ARDS, presumably through the action of humoral inflammatory mediators. Probably identical mediators directly damage the alveocapillary membrane when released locally—for example, during pneumonia. Identifying these substances and their mechanisms of release, action, and interaction therefore holds the key to understanding the pathophysiology of ARDS and thus developing effective therapeutic interventions.

Sepsis is a systemic insult resulting in panendothelial damage, cardiovascular dysfunction,[12] and ultimately multiple organ failure, which includes ARDS in up to a quarter of cases.[13] Recent reports have described patients fulfilling the criteria for the sepsis syndrome with no demonstrable focus of infection, suggesting that uncontrolled activation of mediators of inflammation regardless of cause can reproduce clinical sepsis.[14] An identical phenomenon has been described in patients with ARDS in whom rigorous efforts were

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Table 1 Conditions associated with the adult respiratory distress syndrome

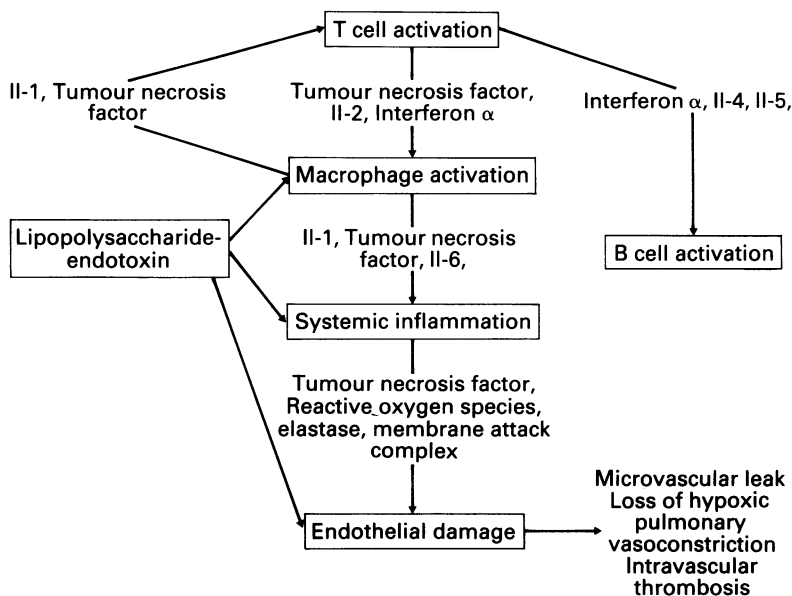| Pulmonary	Non-pulmonary
Aspiration	Sepsis
Near drowning	Fat embolism
Smoke inhalation	Hypovolaemia
Direct lung trauma	Head injury
Pneumonia	Disseminated intravascular coagulation
	Pancreatitis
	Eclampsia

Figure 1   Some interactions between inflammatory mediators in the adult respiratory distress syndrome initiated by endotoxaemia. Il—interleukin.

made to exclude infection.[15] A model of interactions between some mediators thought to contribute to acute lung injury associated with sepsis is shown in figure 1.

The role of mediators in ARDS

ENDOTOXIN

Infusion of endotoxin or lipopolysaccharide, a Gram negative bacterial cell wall component, produces clinical signs identical to the sepsis syndrome that include ARDS in experimental animal models.[16] The hydrophobic lipid A moiety of lipopolysaccharide, which interacts with host and bacterial cell membranes, is thought to be responsible for most of the toxicity of lipopolysaccharide and is highly conserved between Gram negative species. Assays of lipid A in intensive care units have shown predictably high concentrations in patients with recognised sepsis. Raised concentrations have also been found in patients with haemodynamic compromise secondary to variceal bleeding and major trauma, possibly as a result of translocation of bacteria or their cell wall constituents across gut mucosa whose barrier function has been impaired by ischaemia. All patients with ARDS in this study had detectable endotoxaemia.[17]

CYTOKINES

Many toxic effects of lipopolysaccharide are mediated by the local and systemic release of cytokines, which are low molecular weight glycoproteins. Technological advances of the last decade have facilitated the identification, cloning, recombinant synthesis, and functional study of many cytokines.[18] The large number of molecules, their complex interactions, and their often overlapping effects have complicated assessment of the role of individual agents. There is, however, now compelling evidence that the monokines (monocyte derived cytokines); interleukins (IL) Il–1, Il–6, Il–8; and especially tumour necrosis factor contribute to the uncontrolled inflammatory cascade that is manifest as the sepsis syndrome. Injection of tumour necrosis factor into rats produces pulmonary lesions indistinguishable from those of ARDS,[19] and raised concentrations of tumour necrosis factor and Il–1 have been found in blood samples and bronchoalveolar lavage fluid taken from patients with the clinical syndrome.[20 21] The relative contributions of direct toxic effects of monokines and those caused indirectly by products of activated cells and secondary mediators are not clear.

In the fibroproliferative phase of ARDS locally produced cytokines are thought to regulate the growth, chemotaxis, and metabolic activity of lung fibroblasts, influencing the ultimate balance between fibrosis and remodelling of normal lung tissues.[22]

NEUTROPHILS

The important role played by neutrophils in mediating acute lung injury has been established in both clinical studies and animal models.[23] Depletion of neutrophils prevents acute lung injury in sheep following the injection of neutrophil activators. Although ARDS occurs in neutropenic patients, the extent of lung injury is increased by neutrophil supplementation. The importance of endothelial cell and neutrophil adhesion molecules in orchestrating interactions between the two cells is now established.[24] Expression of adherence molecules is controlled by activators of neutrophils, such as lipopolysaccharide, tumour necrosis factor, Il–1, and the products of complement activation.[25] Dissection of the individual stages of neutrophil activation and adhesion is likely to provide targets for future immunopharmacological interventions. The mechanisms governing neutrophil responses in ARDS are reviewed in a recent editorial in this journal by Donnelly and Haslett.[26]

Neutrophils damage endothelial cells directly by the release of proteolytic enzymes (for example, elastase), reactive oxygen species, and other inflammatory mediators (for example, platelet activating factor). Intravenous administration of elastase increases pulmonary vascular resistance, induces pulmonary leucostasis and microembolisation, and increases the venous admixture of oxygen.[27] Experimental administration of agents that generate reactive oxygen species causes pathological changes resembling those of ARDS.[28] Apart from damaging endothelial cells directly, elastase and reactive oxygen species inactivate protease inhibitors and detoxifying agents (such as glutathione) in their microenvironment, facilitating their own actions and those of unrelated inflammatory mediators. Studies of bronchoalveolar lavage fluid in patients with ARDS have produced evidence of increased oxidant and elastolytic activity.[29 30]

LIPID MEDIATORS

Lipid mediators are formed after the activation of membrane phospholipase A_2 and probably mediate many of the inflammatory effects of the
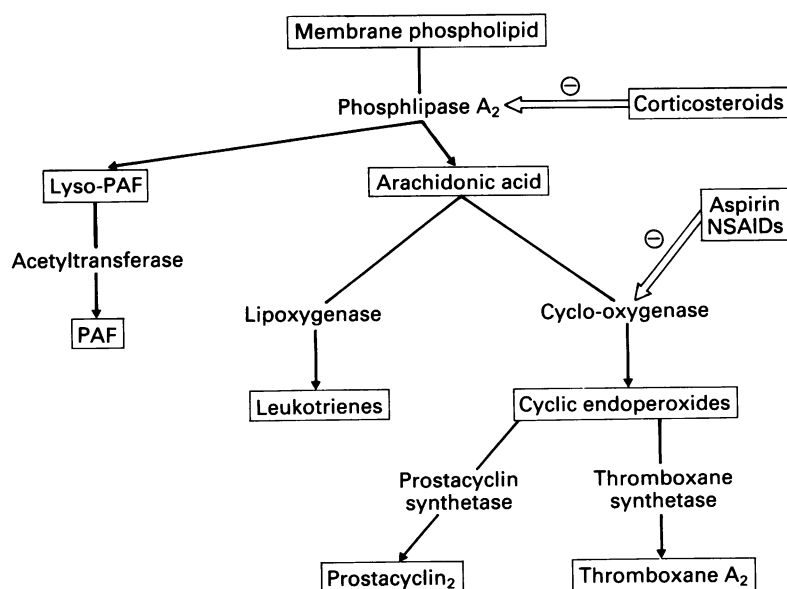
Figure 2 The synthetic pathway of lipid mediators in the adult respiratory distress syndrome and sites of possible pharmacological manipulation.
PAF—platelet activating factor; NSAIDs—non-steroidal anti-inflammatory drugs.

agents described above. The synthetic pathways of these chemically related compounds and means of their pharmacological manipulation are shown in figure 2. Platelet activating factor is released by white blood cells, endothelial cells and alveolar macrophages. Administration of platelet activating factor causes activation of platelets and neutrophils and reproduces many features of endotoxic shock in vivo,[31] including pulmonary hypertension and oedema, decreased compliance, and bronchoconstriction.[32]

The most extensively studied arachidonic acid metabolites in acute lung injury are thromboxane and the leukotrienes, whose actions closely resemble those of platelet activating factor.[33 34]

PEPTIDE MEDIATORS
Figure 3 shows how activation of the proteolytic cascades of the complement, coagulation, and contact systems by endotoxin may contribute to the pathogenesis of ARDS. Intravenous C5a causes hypotension and leucopenia in animals. This is associated with

activation and aggregation of neutrophils, which can be seen in the lung and are associated with increased permeability of the pulmonary endothelium.[35] Activation products of complement are increased in human sepsis and a positive correlation has been shown between their plasma concentrations and the development of ARDS.[36] This finding has not, however, been confirmed in subsequent studies.[37]

Pharmacotherapy

CORTICOSTEROIDS
Corticosteroid treatment has been advocated for patients at risk from ARDS and those whose disease is detected early in its course on the basis of favourable reports from non-randomised trials. A prospective study by Schumer also suggested that corticosteroids reduced the mortality in septic shock from 38·4% to 10·5%.[38] Nevertheless, two large randomised controlled prospective studies failed to show any benefit from corticosteroid treatment and suggested that mortality in patients with sepsis may even be increased.[39 40] Steroids have been used recently in patients recovering from ARDS who then developed the signs of sepsis with no identifiable source.[15] Results from this study and isolated case reports on similar patients[41] suggest that further trials of steroids in the late phase of ARDS are warranted.

NEUTRALISATION OF THE EFFECTS OF ENDOTOXIN
Two large trials have been published recently describing the effects of monoclonal antibodies to endotoxin core glycoprotein in the human sepsis syndrome.[42 43] Both showed advantages in terms of survival and resolution of system failures only in subgroups of patients. E5, a murine IgM antibody, significantly decreased mortality in patients with Gram negative sepsis with no evidence of circulatory shock. In this group, 28% of the total, ARDS resolved in four of 10 patients who received E5 compared with two of nine patients given placebo. By contrast, HA-1A, a human monoclonal IgM antibody, was found to be effective regardless of shock, but only in patients with proved Gram negative bacteraemia. Data specific to ARDS were not given, but in the group that responded all major morbidities (including ARDS) resolved within seven days in 38 of 61 patients given HA-1A compared with 26 of 62 given placebo. There were no significant side effects attributable to either antibody. Problems that may preclude the more widespread application of these novel treatments include their high cost and difficulties in identifying those patients with Gram negative bacteraemia (about 30%) rapidly enough to maximise the therapeutic potential.

MODULATION OF THE CYTOKINE RESPONSE
It is theoretically possible to block the damaging effects of cytokines at several levels (see table 2), though most of these potential treatments are as yet untried in vivo. Animal studies have shown that when administered prophylactically neutralising antibodies for tumour
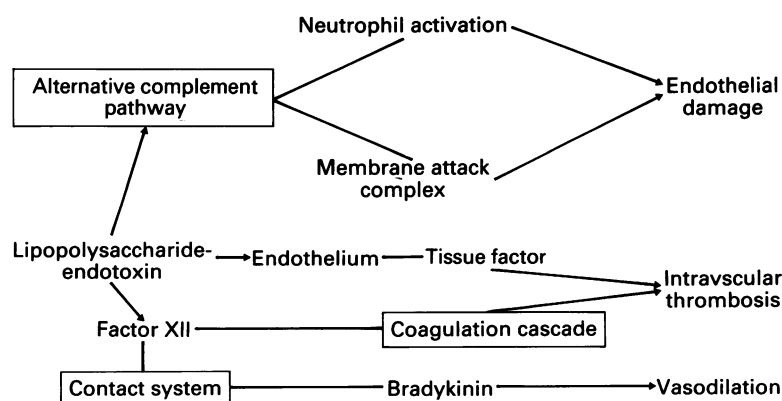

Figure 3 Schematic representation of the possible role of peptide mediators in the pathogenesis of the adult respiratory distress syndrome initiated by endotoxaemia.

Table 2 Modulation of the cytokine response in the adult respiratory distress syndrome and sepsis

Inhibition of cytokine production	Corticosteroids,[44] pentoxifylline,[45] dietary n-3 fatty acids,[46] interleukin-4,[47]
Binding of cytokines	Monoclonal antibodies, CB0006 anti-TNFα,[48] haemofilters (eg polyacrylnitrite[49])
Binding of cytokine receptors	Monoclonal antibody against the murine Il-1 receptor.[50]
Modulation of cytokine receptors	Down regulation of murine TNF and Il-1 by Il-1.[51]
Interference with postreceptor events	Cyclooxygenase inhibitors ibuprofen,[52] prostacyclin and PGE$_1$,[53] antioxidants (eg vitamin E,[54])
Induction of cell protection	Induction of production of antioxidant enzymes and heat shock proteins by Il-1.[55]
Enhanced cytokine clearance	High volume haemofiltration.[56]

TNF—tumour necrosis factor; Il-1—interleukin 1; PGE$_1$—prostaglandin E$_1$.

necrosis factor protect against lethal endotox-aemia and bacteraemia,[57 58] though only one study has shown benefit when such antibodies were given after injury.[59] A phase 1 study of a murine IgG monoclonal antibody to recombinant human tumour necrosis factor in patients with septic shock revealed no serious side effects,[48] and results of a larger study examining therapeutic efficacy are awaited.

Haemofiltration is a mainstay of the supportive treatment of multiorgan failure and ARDS, facilitating the correction of biochemical abnormalities and fluid balance; but recent studies have also suggested that high volume pumped veno-venous haemofiltration may be useful in removing mediators of sepsis.[56] No trials have assessed the possible benefit of introducing haemofiltration in sepsis or ARDS earlier than is indicated by traditional criteria. Future developments in this area may involve incorporation of antibodies or other materials known to bind cytokines into filtration membranes.

Non-steroidal anti-inflammatory drugs

Clinical data on the use of non-steroidal anti-inflammatory drugs in ARDS are scarce, though theoretically they should be of benefit in the late and established phases of ARDS. In animal models ibuprofen and indomethacin have been shown to alter the course of acute lung injury. In the early phases pulmonary hypertension was reduced, arterial hypoxaemia diminished, and neutrophil adherence and activation decreased. The incidence of pulmonary oedema was also less in treated subjects.[60–62] So far, however, there is no evidence from any large clinical trial to support the use of non-steroidal anti-inflammatory drugs despite encouraging experimental data (reviewed in ref 63).

PROSTAGLANDIN

Prostaglandins (PG) E$_1$ and E$_2$, by preventing platelet adherence, reducing pulmonary hypertension, causing a decrease in lymphokine production and the generation of reactive

oxygen species by macrophages, and inducing T lymphocyte suppressor function, have been thought to be of potential therapeutic benefit.[63] Patients with ARDS had an increased 30 day survival rate, though most were from a surgical intensive care unit with inadequate documentation of pulmonary artery occlusion pressures,[64] and a subsequent multicentre trial of PGE$_1$ treatment failed to show a reduction in mortality.[65]

Inhibition of thromboxane by dazoxiben, a specific thromboxane inhibitor, was not beneficial in established ARDS,[66] but a randomised prospective study in patients at risk showed a reduced incidence in the group given ketoconazole, which reduces plasma thromboxane concentrations in vivo.[67]

ANTIOXIDANTS

In patients with early ARDS and in those at high risk protection against reactive oxygen species mediated injury by the use of N acetyl cysteine has been shown to reduce injury. The liver frees cysteine, itself a free radical scavenger, for incorporation into glutathione, a powerful scavenger of reactive oxygen species. Preliminary studies have been completed and a multicentre trial is now under way.[68] The use of specific antioxidants in ARDS is complicated by the pro-oxidant effect of many of these compounds. Lower concentrations of the antioxidant vitamin E have been found in patients who develop ARDS than in those who do not,[69] but high concentrations of both vitamin E and vitamin C have been shown to promote lipid peroxidation, suggesting they produce damage mediated by free radicals.[70] In the isolated perfused rat lung model reactive oxygen scavenging with dimethylthiourea prevents damage caused by activated neutrophils.[71]

PENTOXIFYLLINE

Pentoxifylline is a methylxanthine derivative that reduces the production of tumour necrosis factor and Il-1 and decreases the response of neutrophils[72 73] and the pulmonary endothelium to these cytokines. It also improves red cell deformability and decreases red cell and platelet aggregation. The haemodynamic changes associated with sepsis are ameliorated, as are indices of lung injury, when pentoxifylline is used either before or soon after a pulmonary insult.[74] Oxygen delivery is maintained in models of haemodynamic shock, possibly by preventing white cell adherence in the pulmonary and systemic microcirculations.[75] This suggests a potential role for pentoxifylline in ARDS, although this has yet to be defined.

SURFACTANT

The increased activity mediated by reactive oxygen species that is associated with ARDS reduces the concentration of alveolar surfactant. Surfactant production by type II pneumocytes is further influenced by hypoxia, hyperoxia, and infection. Bronchoalveolar lavage fluid from patients with ARDS contains low concentrations of surfactant.[76] In the infan-

tile respiratory distress syndrome instillation of surfactant has a profoundly beneficial effect on outcome.[77] Similarly, in animal studies exogenous surfactant replacement has been shown to reduce shear forces in damaged lung and reduce injury.[78] Trials are under way to assess the value of surfactant in ARDS.

MANIPULATION OF THE L-ARGININE PATHWAY
There is now good evidence that induction of nitric oxide synthase by inflammatory mediators contributes to the resistant hypotension of septic shock.[79] Reports of two such patients being successfully treated with an inhibitor of nitric oxide synthesis have been published recently.[80] The characteristic pulmonary circulatory changes of sepsis and ARDS, however, are loss of hypoxic pulmonary vasoconstriction and hypertension. Studies in rats have implicated nitric oxide in the modulation of hypoxic pulmonary vasoconstriction and have suggested that low dose tumour necrosis factor inhibits the action of nitric oxide before disrupting the endothelium.[81 82] Hence inhaled nitric oxide has been used in certain centres to decrease pulmonary vascular resistance and to improve oxygenation by decreasing intravascular shunt. Results have yet to be published. Concern about the toxicity of inhaled nitric oxide has been allayed by recent experience in animals[83] and patients.[84] Furthermore, in many respects inhaled nitric oxide is an ideal pulmonary vasodilator as it is inactivated by haemoglobin in the circulation rapidly enough to prevent systemic actions and dilates only vessels supplying ventilated alveoli.

Conclusions
Recent advances suggest that similar inflammatory processes may generate the sepsis syndrome and ARDS by their uncontrolled systemic and pulmonary actions. Discovery of an ever increasing number of inflammatory mediators has provided new targets for immune therapy, but has also revealed a complex system with enormous redundancy, implying that a single agent is unlikely to be able to arrest the process once initiated. In this respect targeting initiators or early mediators, such as endotoxin, is an attractive option but it depends on instituting treatment immediately after the insult, which is not always feasible in the clinical setting.

Monoclonal antibody technology has developed to such a level that binding of individual mediators or receptors is now being used in clinical practice.[85] Such treatments will be expensive and should be introduced only after their efficacy has been proved in large, well designed trials. Costs can also be offset against the benefits of decreased mortality in patients who are often young and expected to recover fully, and of a shorter time spent within the intensive care unit.

Optimism about anti-inflammatory treatments has been dampened by their consistent failure in trials. Corticosteroids cannot be recommended for routine use in patients with

ARDS, though certain subgroups—for example, those with fat embolism—may benefit. Given the high incidence of infection complicating ARDS, immunosuppressant treatment must be used with caution. Of the new agents outlined above, inhaled nitric oxide is particularly exciting, though its emerging role as an immunomodulator and its interaction with reactive oxygen species remain to be characterised.

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