LEADING ARTICLE

Drugs 2001; 61 (7): 897-907
0012-6667/01/0007-0897/$27.50/0



# Acute Respiratory Distress Syndrome
## Pharmacological Treatment Options In Development

*R. Duncan Hite* and *Peter E. Morris*

Section on Pulmonary and Critical Care Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.

## Abstract

The acute respiratory distress syndrome (ARDS) is a clinical syndrome with primarily supportive management options. Despite extensive basic and clinical investigations, multiple pharmacological and nonpharmacological modalities have been unsuccessful in decreasing mortality. Nonetheless, these efforts have substantially heightened our understanding of ARDS pathophysiology. Investigators continue to create new and more complex therapeutic strategies that may have significant clinical impact.

Several pharmacological agents for ARDS are in development and have shown either great promise or are at most, under phase III evaluation. The order in which therapeutic options are presented in this review highlights therapeutic options other than the anti-inflammatory approach. In addition to the anti-inflammatory category, vasodilators, surfactant therapy, immunonutrition and partial liquid ventilation are all being evaluated.

Within the anti-inflammatory category, new mechanistic approaches include the 'anti-inflammatory nature' of interleukin-10, the inhibitory aspects of lysophosphatidic acid on endothelial cell permeability, and the use of recombinant human anti-coagulant proteins (activated protein C and tissue factor pathway inhibitor) to reduce the inflammatory cycle that contributes to microvascular thrombi.

Previous work with surfactant in ARDS had its limitations, however, these trials were of sufficient success to spawn 2 new synthetic compounds. These new synthetic surfactants incorporate mixtures of phosphatidylcholine and phosphatidylglycerol (the key phospholipids within endogenous surfactant) and either recombinant surfactant protein C or an analogue of surfactant protein B.

Recently, the ARDS Network's low tidal volume study has broken the cycle of decades of negative ARDS trials and demonstrated an improvement in mortality.

Through better mechanistic approach and study design, investigator compliance with exclusion criteria, and better understanding of the complexities of patient management, the next pharmacological ARDS trials will hopefully be successful and lead to further reductions in patient mortality.

Since its initial description by Ashbaugh et al.[1] in 1967, the acute respiratory distress syndrome (ARDS) has been a clinical syndrome with primarily supportive management options. Despite extensive basic and clinical research investigations and numerous large-scale clinical trials, multiple pharmacological and nonpharmacological therapeutic modalities have generally proven unsuccessful. Nonetheless, these efforts have substantially heightened our understanding of the critical mechanisms in the

pathophysiology of ARDS. Investigators continue to create new and more complex therapeutic strategies that may have significant clinical impact in the not too distant future. In this article we highlight current strategies and drugs in development for this critical disorder.

A search was performed through MEDLINE using search terms of ARDS, critical care, intensive care, acute lung injury, inflammation to identify literature for this review.

## 1. Acute Respiratory Distress Syndrome

Although descriptions of ARDS can be traced to the medical literature long before the 1960s, Ashbaugh's[1] report in 1967 describing severe respiratory failure consistent with the respiratory distress syndrome (RDS) of neonates and children is typically cited as the founding description of respiratory distress syndrome in adults. That initial report included 12 patients with an average age of 27 years who developed rapidly progressive hypoxaemic respiratory failure requiring high levels of mechanical ventilatory support with 7 (60%) of those patients ultimately dying from the illness.

Over the subsequent 25 years, multiple clinical therapeutic trials were performed. Review of these trials reveals a lack of substantial therapeutic success. In addition, the earlier studies reveal large variability in entry criteria for patient enrolment, which stemmed from differing opinions on the diagnostic criteria for the syndrome. In 1992, a group of European and North American investigators at a consensus conference on ARDS, provided a working set of criteria for ARDS.[2] The majority of recent clinical trials have used these criteria.

These criteria are listed in table I and include: (i) hypoxemia as defined by the ratio of arterial oxygen pressure ($PaO_2$) to inspired oxygen fraction ($F_iO_2$) of less than 200; (ii) known associated risk factor (i.e., sepsis, trauma, pancreatitis); (iii) the presence of bilateral alveolar infiltrates on chest radiograph; (iv) no evidence of left atrial hypertension (pulmonary capillary wedge pressure < 18mm Hg or absence of consistent clinical findings). In addition, investigators defined a similar subset of patients with less severe impairment which they called acute lung injury (ALI) and which differs from ARDS only by the severity of hypoxemia ($PaO_2/FiO_2$ < 300mm Hg).

The pathophysiology of ARDS includes two generalisable and possibly overlapping phases.[3] The initial phase is characterised by acute inflammation that is predominantly driven by neutrophils and is at least chronologically associated with injury of the capillary endothelium and alveolar epithelium. The capillary leak of exudative oedema fluid into the alveoli results in significant inhibition and injury of the alveolar surfactant. During this phase hyaline membranes in the airways are typically seen. Hyaline membranes are probably the consequence of exudated proteins within the airway. In addition, this inflammatory response can lead to significant vascular injury and *vasoconstriction* which may result in pulmonary hypertension. Each of these abnormalities represents potential therapeutic targets, both as treatment and prevention of further injury.

The subsequent phase of ARDS demonstrates evidence of fibrosis and repair. Pathological evidence of these two phases can be seen in the same biopsy sample from a patient with ARDS. Histologically, the later pathological aspects are characterised by interstitial fibrosis and marked engorgement and distortion of the distal pulmonary arterioles. Over a prolonged course, the fibrosis may resolve and the pulmonary capillary bed may

**Table I.** Diagnostic criteria for acute respiratory distress syndrome (ARDS)

| | |
|---|---|
| Appropriate clinical setting with one or more recognised risk factors | |
| New, bilateral, diffuse, patchy or homogeneous, pulmonary infiltrates on chest radiograph | |
| No clinical evidence of heart failure, fluid overload, or chronic lung disease (PAOP≤18mm Hg) | |
| ALI | $PaO_2$:$FiO_2$ ratio ≤300 |
| ARDS | $PaO_2$:$FiO_2$ ratio ≤200<br>Requirement for mechanical ventilation |

**ALI** = acute lung injury; **$FiO_2$** = inspired oxygen fraction; **$PaO_2$** = arterial oxygen pressure; **PAOP** = pulmonary artery occlusion pressure.

undergo extensive *neovascularisation*. In many survivors, this phase may take up to 2 years for completion.

ARDS can be triggered by a number of causes that are typically classified as direct and indirect. Sepsis syndrome is the single most common cause of ARDS but direct causes of ARDS including pneumonia are commonly seen. The severity of each aetiology typically dictates the likelihood of progression to ARDS. For example, bacteraemia tends to lead to ARDS in only 4% of patients, whereas ARDS develops in 40% of patients with sepsis syndrome. Similarly, in patients with pneumonia in the intensive care unit (ICU) only 12% will progress to ARDS, whereas 35% of patients with aspiration pneumonia will develop ARDS.[4-6] Additional risk factors such as alcoholism have been shown to be important co-factors in the risk of developing ARDS.[7] The more commonly associated clinical causes of ARDS are listed in table II.

**Table II.** Clinical disorders associated with acute respiratory distress syndrome (ARDS) [listed in rank of most-least frequent aetiology][6]

| |
|---|
| Sepsis |
| Aspiration |
| Shock from any aetiology |
| Trauma |
| Multiple transfusions |
| Severe acute pancreatitis |
| Drug overdose |
| Pneumonia |
| Near drowning |

The true incidence of ARDS is believed to be grossly under-reported. ARDS is not a reportable illness in and of itself. Currently, the incidence of ARDS, as estimated by leading investigators, is believed to be approximately 3 to 5 cases per 100 000 in the population.[2]

The list of inflammatory mediators that are involved in the process of this multifaceted lung injury is too long for sufficient review within this article. However, multiple therapeutic strategies target the following: (i) specific mediators released by neutrophils which can be toxic to both foreign pathogens as well as host; (ii) inhibitors of cytokines important in the recruitment of the inflammatory response to the lung; (iii) replacement of cytokines and natural anticoagulant proteins important in counterbalancing the proinflammatory response and which may be deficient in ARDS; (iv) specific pulmonary vasodilators to counterbalance the *vasoconstrictor* effects on the injured pulmonary endothelium; (v) replacement of the deficient and injured pulmonary surfactant. In the latter half of this article we summarise the previously performed trials manipulating the inflammatory responses as well as the current ongoing trials.

Early in the first 2 decades since the initial description of ARDS, mortality estimates remained extremely high, typically averaging 60 to 70%. However, over the past 10 to 15 years and particularly throughout the decade of the 1990s, overall mortality in ARDS was suspected to have trended downward. More recently, mortality has reached a plateau with reported mortality of approximately 40%.[8] Although many investigators have speculated on the explanation for this improvement, no conclusive evidence exists as yet. Most agree that changes in management of mechanical ventilation as well as overall improvement in the delivery of critical care are the likely major contributing factors. In addition, most agree that further improvement through specific therapeutics can be realised in the not so distant future. These novel agents are discussed within this article. These agents are the result of improved understanding of the delicate balance of the inflammatory response and how the inflammatory response may be manipulated to optimise patient benefit.

Within the spectrum of ARDS patients, there are differences in outcome based on specific factors. Patients who develop ARDS as the result of trauma have been suspected of having a better overall mortality than ARDS patients in general, based on reports with small numbers of patients.[9-10] A significant improvement has been seen in the outcome of ARDS patients in the subset with sepsis. Age has been shown in multiple studies to be

an important factor in predicting outcomes with mortality substantially higher in patients as they reach and exceed approximately 60 years of age.[6] It remains unclear as to whether age itself is an independent risk factor or simply is a marker of higher incidence of concurrent illnesses. It is important to note that the majority of deaths in patients with ARDS are not from respiratory failure. Strict respiratory insufficiency accounts for 10 to 15% of all ARDS deaths.[6] The majority of deaths in patients with ARDS are the result of the initial insult or aetiology that proves to be refractory to management. The second most common cause of death in ARDS patients is multisystem organ failure. The vast majority (>90%) of the deaths seen in ARDS occur within the first 2 to 3 weeks after the onset of the condition. Patients who survive the initial weeks of ARDS, have a greater than 90% likelihood of recovery.[6]

Although mortality remains high in this condition, chronic limiting pulmonary morbidity in survivors is uncommon.[8] Pulmonary function studies performed on survivors typically demonstrate significant recovery to approximately 80 to 90% of baseline at or beyond 1 year after the onset of the illness. More recent data has suggested that there may be some neurocognitive deficits as a consequence of the prolonged ICU stay and exposure to centrally acting sedative agents.[11]

The length of time frequently required for mechanical ventilation in patients with ARDS is 2 to 3 weeks but it can be as long as several months. The duration of mechanical ventilation has become an important factor in the design of new ARDS studies. Previously, clinical trials in ARDS were required by the US Food and Drug Administration (FDA) to demonstrate a mortality benefit before drug approval. However, more recent trials have been allowed to use surrogate markers of health benefit outcomes, such as reduced time on mechanical ventilation and time in ICU. A reduction in ventilator use or ICU stay is believed to represent a significant benefit not only to patients but to society in general. Therefore, the design of future ARDS trials will very likely include length of recovery and long term outcome of ARDS patients.

## 2. Standard Treatment

The principal goal of treatment of ARDS is to identify and correct the underlying aetiology. Bone and colleagues[12] demonstrated that patients who begin to improve over the first week of their therapeutic course have a much greater likelihood of successful outcome. This trend corresponds to successful treatment of the underlying trigger. An aggressive diagnostic approach in the setting of uncertainty is a very important aspect of ultimate therapeutic success.

The manner in which mechanical ventilation is applied to patients with ARDS has been the subject of significant debate. This debate intensified significantly over the last decade. The centre of the debate focused on the potential harm that mechanical ventilation could induce, such as barotrauma (high pressures which result in microbarotrauma, alveolar rupture and subsequent pneumothorax, pneumomediastinum, subcutaneous emphysema) and volutrauma.[13] Volutrauma is a newer concept that implies the overdistension of alveoli leading to capillary and epithelial injury. Slutsky[14] has also defined the concept of biotrauma, which is the biological response triggered by volutrauma. Biotrauma, therefore, is very comparable to the systemic inflammatory response syndrome seen as a consequence to sepsis, pancreatitis, or other systemic injuries. Recent trials have suggested that maintaining lower tidal volumes and lower airway pressures improves overall patient outcome. The recently published ARDS Network (ARDSnet) trial demonstrated an overwhelming difference in survival in patients with ARDS when a low tidal volume (and therefore low plateau pressure) strategy was in place.[15] Lower tidal volumes have become an increasing standard within the management of ARDS patients.

## 3. Specific Investigational Strategies

### 3.1 Anti-Inflammatory Therapy

#### 3.1.1 Corticosteroids

The use of systemic corticosteroids remains a controversial topic in the management of patients with ARDS. Despite large trials in the mid 1980s, which were unable to demonstrate benefits, many authors continue to believe that further refinement and adjustment in the dose, administration and duration of corticosteroids may provide therapeutic benefits. Meduri et al.[16] have investigated the potential benefits of systemic corticosteroids in the fibrotic and recovery phase of ARDS with preliminary data suggesting a favourable outcome. This study is limited by the lack of true randomisation in the patient cohorts and is therefore premature to advocate widespread late-ARDS corticosteroid therapy. The National Institutes of Health (NIH)-sponsored ARDS Network (ARDSnet) is currently pursuing this hypothesis with an active, large-scale clinical trial.

#### 3.1.2 Lysophosphatidic Acid

Lysophosphatidic acid (LPA) is a molecule that decreases endothelial monolayer permeability. Interestingly, LPA is also the smallest noncytokine growth factor and seems to prevent apoptosis in a number of cell lines.[17] Platelets release a soluble factor that decreases the solute permeability of cultured bovine aortic endothelial monolayers. This factor was characterised as heat stable, trypsin sensitive, and was not chemically similar to serotonin, adenosine, adenosine diphosphate or adenosine triphosphate. It was later reported as LPA.

Endothelial permeability decreases rapidly, reversibly and repeatedly when exposed to platelet supernatants (shown to contain LPA). Continuous exposure to LPA-containing platelet supernatants produces a sustained decrease in permeability. LPA is currently undergoing study in animal lung injury models.

#### 3.1.3 Interleukin-10

Interleukin (IL)-10 is believed to be an anti-inflammatory cytokine. IL-10 levels are elevated in the bronchoalveolar lavage (BAL) fluid of patients with ARDS.[18] The absolute IL-10 level trended higher in a small series of patients who survived ARDS compared with the IL-10 in the BAL of nonsurvivors. IL-10 has been administered to humans in a number of chronic inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease.

There is only 1 clinical trial to date that administered IL-10 to patients with acute lung injury.[19] In this pilot study of 60 patients, IL-10 was associated with a good safety profile, with no direct IL-10–associated toxicity observed. The treatment group received either 8 or 20 μg/kg of parenteral IL-10 daily for the first 6 days post-injury. In this small study, the baseline characteristics of the study groups were similar except for the presence of shock. Shock was not a study exclusion. Shock was present at the time of enrolment in 9%, 39% and 55% of the patients in the placebo, 8 μg/kg and 20 μg/kg groups, respectively. The overall $PaO_2$/$FiO_2$ ratio on entry was 122 +/-64. Plasma tumour necrosis factor (TNF) and IL-6 levels tended to increase in the placebo group but declined in the groups receiving IL-10. BAL TNF levels rose over time in the placebo group but declined in the IL-10 groups. Mortality was 6/22 (27%), 2/18 (11%), and 5/20 (25%) and ventilator free days were 9, 15 and 6 for the placebo, 8 μg/kg and 20 μg/kg groups, respectively.

Further study using IL-10 in patients with ARDS is currently in the design phase.

#### 3.1.4 Pentoxifylline

Pentoxifylline, a xanthine derivative, has been used for more than 20 years in patients with peripheral vascular disease. *In vitro* and *in vivo* studies have shown that pentoxifylline suppresses or reduces the production of TNFα.[20] Beneficial effects have been reported in disorders such as cerebral malaria, graft-versus-host disease, rheumatoid arthritis, autoimmune disorders, vasculitis, and heart failure. These are disorders in which TNFα has been suspected of playing an important role.

Because of the prominence of pro-inflammatory cytokines such as TNF detected in the early

phases of acute lung injury, pentoxifylline has become a potential therapy. The NIH-sponsored investigative group, the ARDSnet, has planned an investigation with the administration of lisofylline in patients with ARDS.

#### 3.1.5 Metalloproteinase Inhibitors

ALI results in part from activation of neutrophils. Activated neutrophils release neutral serine, elastase, and matrix metalloproteinases (MMPs) and oxygen radical species, which damage alveolar-capillary basement membranes and the extracellular matrix, resulting in an ALI. Activation of sequestered neutrophils leads to the release of proteases and oxygen radical species. Elevated plasma levels of neutrophil elastase and MMPs are present in patients after cardiac bypass and in both plasma and BAL fluid of patients with ARDS.[21-23] MMPs released from activated neutrophils degrade type IV collagen, which provides the framework for the basement membrane of pulmonary capillaries, and interstitial collagen and proteoglycan.[24-25] Aside from direct collagenolysis, MMPs inactivate endogenous antiproteases, allowing unrestricted protease activity.[26] Studies by Golub et al.[27] have confirmed that, by non-antimicrobial mechanisms, chemically modified tetracyclines can directly inhibit MMPs and prevent activation of pro-MMPs to MMPs by scavenging reactive oxygen species. This inhibits direct collagenolysis and protects against inactivation of endogenous antiproteases.

The use of MMP inhibitors in patients with ARDS has not yet been reported in the medical literature.

#### 3.1.6 Neutrophil Elastase Inhibitors

Neutrophils secrete a proteolytic enzyme, neutrophil elastase, which has emerged as a significant mediator in the pathogenesis of inflammatory airway disease. This enzyme has been found to strip the bronchial epithelium, reduce ciliary beating and stimulate excess mucus secretion, leading to mucus retention, bacterial proliferation and recurrent infections. Neutrophil elastase also stimulates epithelial cell IL-8 secretion and produces other chemoattractant cleavage products which lead to further neutrophil recruitment. Neutrophil elastase has also been shown to adversely alter antithrombin and C1 inhibitor. It also impairs host defences by damaging the major opsonophagocytic receptor on the neutrophil and by weakening the efficacy of immunoglobulins. For this reason, an important goal in the treatment of ARDS should be to prevent or shorten the duration of neutrophil elastase release.

Several approaches have been proposed in an effort to modulate the proteinase burden. These include direct inhibition of elastase and interference with the recruitment, adherence and degranulation of neutrophils. An even more fundamental approach would start in the bone marrow, where attempts might be made to modulate or modify neutrophil precursors so as to limit the destructive potential of the mature neutrophils.[28-31]

#### 3.1.7 Platelet Activating Factor Acetylhydrolase

*In vitro* and *in vivo* studies have now examined the anti-inflammatory activities of recombinant human platelet activating factor (PAF) acetylhydrolase. Recombinant human PAF acetylhydrolase (rhPAF acetylhydrolase), converts PAF to biologically inactive lyso-PAF.

A Phase II trial of rhPAF acetylhydrolase has recently been concluded. ICOS Corporation stated in a press release that rhPAF acetylhydrolase was administered in a placebo-controlled multicentre study in 240 patients with severe sepsis or severe traumatic injuries at risk for the development of ARDS. 28-day all cause mortality was reported to be 28.4% the placebo group, whereas it was 14.5% in the treated-group. Although not yet published in peer review form, the company's press release states that there were statistically significant findings in mortality and in the reduction of the incidence of ARDS, as well as length of stay in the ICU.

A Phase III study with rhPAF acetylhydrolase is in the last stages of planning.

#### 3.1.8 Natural Anticoagulant Protein Replacement

There is evidence in many patients with sepsis-induced ARDS of profound activation of the clotting cascade. These patients typically do not demonstrate overt bleeding and in general are not

considered to have clotting defects prior to their abrupt illness.

Through many years of laboratory and patient-specific study, it has become clear that component proteins of the coagulation system have many properties beyond those of clot formation. The coagulation proteins interact with cytokines, complement, prostaglandins, platelets, and endothelial cell surface proteins. Through these patients' illnesses, the natural anticoagulant proteins fall out of balance with the pro-clotting proteins. It is believed that activation of the clotting cascade occurs primarily through activation of the extrinsic pathway. There is rapid consumption and depletion of various clotting elements and natural coagulation inhibitors. Fibrinolysis may be initiated but is more often unsuccessful secondary to the inhibition by the action of plasminogen activator inhibitor (PAI)-1.

The end product is a very wide spread deposition of fibrin throughout vital microvasculature beds. By administration of the natural anticoagulant proteins during this systemic 'microvasculature' clotting state, it is believed that end-organ injury will be decreased.

There are 3 natural anticoagulant proteins that are currently at the phase III level of FDA investigation.[32-38] Centeon has concluded a phase III study on antithrombin III therapy. The findings were presented in the US fall (autumn) of 2000. The data did not demonstrate a statistically significant reduction in mortality. Eli Lilly has recently announced that their trial of human recombinant activated Protein C (drotrecogin alfa) in patients with sepsis, met early efficacy criteria. Eli Lilly has stopped their trial following their Data and Safety Monitoring Board's recommendation that drotrecogin alfa therapy in patients with sepsis was associated with an overwhelming reduction in mortality compared to the placebo group. The primary endpoint of the Activated Protein C in Sepsis study was 28-day all cause mortality between study drug and placebo groups. The data have not yet been published in abstract or manuscript form. Chiron has recently initiated a Phase III study of tissue factor pathway inhibitor. The trial is being conducted in many sites across Europe and North America.

### 3.2 Vasodilators

Two therapeutic agents have been extensively studied over the past 5 to 10 years, epoprostenol (prostacycline) and nitric oxide (NO). Both of these agents have shown the ability to vasodilate the pulmonary vascular bed in patients with pulmonary hypertension from conditions other than ARDS. The particular interest for pulmonary vasodilation in ARDS, stems from the desire to vasodilate areas which have optimal ventilation. These agents are administered to maximise perfusion to these ventilated regions and in so doing lower overall shunt fraction. To achieve these goals, both agents must be delivered via the airways. Systemic administration of either type of agent would lead to significant systemic hypotension. Additionally, vasodilation of poorly ventilated areas, with subsequent worsening of shunt fraction could occur.

#### *3.2.1 Nitric Oxide*

In the original 1993 report on inhaled NO (iNO) in patients with ARDS, Rossaint and colleagues[39] demonstrated that shunt fractions did decrease in patients who responded to iNO therapy. Unfortunately, their initial report suggested that NO might have significant mortality benefits, but this study was based on patients with longstanding ARDS which was compared to a retrospective control group.

Subsequent studies of the benefits of iNO have not demonstrated significant overall mortality benefits in either adults or neonates with RDS.[40] Consistently these studies have demonstrated that approximately 30 to 40% of patients will have some improvement in oxygenation which may help limit exposure to high concentrations of oxygen. The recent FDA approval for NO is based on its benefits in persistent pulmonary hypertension of the newborn and remains the only indication that has received FDA approval.

#### 3.2.2 Epoprostenol (Prostacyclin)

Inhaled epoprostenol has been studied in patients with ARDS. Similar to NO, inhaled epoprostenol reveals benefits with a small fraction of patients with ARDS. Patients who received inhaled epoprostenol showed an improvement in oxygenation.[41] However, there was no clinical evidence of any improvement in mortality, length of mechanical ventilation, time in ICU or total hospital days.

For now, NO and epoprostenol continue to be used in the setting of ARDS only under investigational protocols.

### 3.3 Surfactant Replacement Therapy

Replacement of surfactant in neonatal RDS has now been well established as a standard of care. Surfactant administration is a lifesaving manoeuver where surfactant deficiency is the principal abnormality. In neonatal RDS there is a limited degree of inflammatory response. Since Konishi's and Fujiwara's report in 1988,[42] substantial clinical investigations have been conducted. These studies have further defined surfactant therapy, identifying key issues related to the importance of specific compositional factors within the surfactant preparation, route of delivery, frequency and timing of administration, and cost analyses.

Multiple compounds now exist for the therapy of neonates with RDS including: (i) colfosceril palmitate, a synthetic surfactant containing a mixture of tyloxapol, hexadecanol, and phosphatidylcholine (DPPPC); (ii) beractant, an extract of bovine surfactant which includes a more natural mixture of the phospholipids contained within endogenous surfactant but a relative paucity of the surfactant apoproteins; (iii) poractant alfa, an extract of porcine surfactant that is not approved in the US but is commonly used throughout Europe; (iv) calfactant, a newly approved bovine surfactant which retains almost a completely normal distribution of surfactant phospholipids and the hydrophobic apoproteins, SPB and SPC.

Although many of the early studies on surfactant replacement therapy in neonatal RDS were conducted using colfosceril palmitate and beractant, the use of colfosceril palmitate has significantly decreased over the past several years because of its compositional limitations. Recent studies have begun to suggest that the retention of key apoproteins, which permit retention of surfactant surface tension activity, by calfactant may offer therapeutic advantage over beractant.

In contrast, for adults with ARDS, surfactant replacement therapy has made slower progress. An important difference for the adults with ARDS, is the lack of available surfactants in sufficient quantities to treat adults. Adults would require a substantially larger volume of drug than neonates. As mentioned earlier, all of the available surfactants with the exception of colfosceril palmitate, are animal extracts which are purified by a complex, low yield method which leads to high expense. The end result of this process is that the cost of care for an adult with ARDS could increase substantially. The cost is not only the result of a much larger dose, but that far more doses are necessary as a consequence of the ongoing inflammation which injures the administered surfactant.

One trial using colfosceril palmitate was conducted on adults with no overall therapeutic advantage identified.[43] However, this trial was flawed because of the relatively low dose of surfactant that was delivered, and the use of a nebulised delivery system which delivered surfactant to predominantly well-ventilated regions of lung. Therefore, the nebulised surfactant did not reach the poorly ventilated areas, where it may have better served to recruit alveoli and help reverse the alveolar collapse. Two trials using poractant alfa and beractant have been conducted revealing improvement in oxygenation and possibly mortality in a small subset of the patients. Neither trial was of sufficient scale to warrant recommendation for large scale use.[44-45]

However, these trials were of sufficient success to spawn 2 new synthetic compounds which incorporate mixtures of phosphatidylcholine and phosphatidylglycerol (the key phospholipids within endogenous surfactant) and either recombinant SP-C (lusupultide) or an analogue of SP-B (sinapultide). A small phase I study using sinapultide in adults

has been published with improvement in oxygenation noted and with no significant safety issues detected.[46] Each compound is currently undergoing large phase II/III trials, which should be completed within the next 1 to 2 years.

It is important to note that a recent trial of calfactant in children with RDS, which is a more comparable problem to that seen in adults than neonatal RDS, has been completed. The use of calfactant in paediatric RDS revealed significant improvements in oxygenation, time on mechanical ventilation, length of time in ICU and oxygen requirements upon discharge. This study provides substantial hope for the future of surfactant replacement therapy in adults.

### 3.4 Enteral Feeding With Eicosapentaenoic Acid, Gamma-Linolenic Acid

Studies in animal models of sepsis-induced ARDS have shown that a low-carbohydrate, high-fat diet combining the anti-inflammatory and vasodilatory properties of eicosapentaenoic acid (EPA; fish oil), gamma-linolenic acid (GLA; borage oil) and antioxidants improved lung microvascular permeability, oxygenation and cardiopulmonary function, and reduced proinflammatory eicosanoid synthesis and lung inflammation.

A prospective, multicentre, double-blind, randomised controlled trial was carried out to determine whether ARDS patients could benefit from such a regimen.[47] This trial studied 146 patients with ARDS caused by sepsis/pneumonia, trauma or aspiration injury. Patients who met entry criteria were randomised and continuously tube-fed either EPA+GLA or an isonitrogenous, isocaloric standard diet at a minimum caloric delivery of 75% of basal energy expenditure x 1.3 for at least 4 to 7 days.

Baseline characteristics of 98 evaluable patients revealed significant decreases (approximately 2.5-fold) in the number of total cells and neutrophils per ml of recovered BAL fluid from multiple lavages during the study with EPA+GLA compared with patients fed the control diet. Significant improvements in oxygenation ($PaO_2/FiO_2$) from baseline to study days 4 and 7 with lower ventilation variables ($FiO_2$, positive end-expiratory pressure and minute ventilation) occurred in patients fed EPA+GLA compared with controls. Patients fed EPA+GLA required significantly fewer days of ventilatory support (11 *vs* 16.3 days; $p = 0.011$), and had a decreased length of stay in the ICU (12.8 *vs* 17.5 days; $p = 0.016$) compared with controls. Only 4 of 51 (8%) patients fed EPA+GLA versus 13 of 47 (28%) control patients developed a new organ failure during the study ($p = 0.015$).

Although there were no statistically significant differences in mortality between these 2 groups, the overall approach and reduction in ventilator time are very promising results. The beneficial effects of the EPA+GLA diet on pulmonary neutrophil recruitment, gas exchange, requirement for mechanical ventilation, length of intensive care unit stay, and the reduction of new organ failures suggest that this enteral nutrition formula should be further studied.

### 3.5 Partial Liquid Ventilation

The development of inert perfluorocarbon (PFC) liquids with high oxygen and carbon dioxide solubility, has made gas exchange with liquid ventilation possible. In 1991, the technique of partial liquid ventilation was introduced where PFC liquids are instilled into the lungs while continuing with conventional mechanical ventilation. Partial liquid ventilation has been shown to improve gas exchange and lung function with decreased secondary lung injury in animal models of acute lung injury and surfactant deficiency. The theoretical advantages of partial liquid ventilation include lower airway pressures, decreased alveolar surface tension and increased alveolar recruitment. It has been used in trials in preterm neonates, and preliminary results are available from a trial of partial liquid ventilation in patients with ARDS.[48]

Perfluorocarbons can also be used to deliver drugs to the lungs, to lavage inflammatory exudate and debris from the lungs, and as an intrapulmonary radiography contrast medium.

However, many questions about partial liquid ventilation remain unanswered, particularly with regard to the dose of PFC required, its ideal method of administration and the long term effects. The use of partial liquid ventilation as a standard modality has not yet been established by large, multicentre trials.

## 4. Conclusion

Recently, the improvement in mortality with the ARDSnet low tidal volume study has broken the cycle of decades of negative ARDS trials. Through better study design, investigator compliance with exclusion criteria, and better understanding of the complexities of patient management, the next series of ARDS trials will hopefully be successful and lead to further reductions in patient mortality.

## Acknowledgements

The authors wish to thank Ms. Kim Slattery for her patience and support in the preparation of this manuscript. This work was funded in part by NIH award M01 RR02602, and the American Lung Association of Kentucky (Dr. Morris), and NIH-HR-01-01 (Drs Hite and Morris). Drs Hite and Morris are investigators for Apex Bioscience, Altana, Byk Gulden, Chiron, Discovery Laboratories, Edwards, Eli Lilly, Glaxo, and ICOS Corporation. Drs Hite and Morris have served as consultants for Discovery Laboratories, Eli Lilly and Xoma Corporation.

## References

1. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. Lancet 1967; II (7511): 319-23
2. Bernard G, Artigas A, Brigham K, et al. The American-European consensus conference on ARDS. Am J Respir Crit Care Med 1994; 149: 818-24
3. Tomashefski Jr JF. Pulmonary pathology of the adult respiratory distress syndrome. Clin Chest Med 1990; 11 (4): 593-619
4. Fowler AA, Hamman RF, Good JT, et al. Adult respiratory distress syndrome: risk with common predispositions. Ann Intern Med 1983; 98: 593-7
5. Pepe PE, Potkin RT, Reus DH, et al. Clinical predictors of the adult respiratory distress syndrome. Am J Surg 1982; 144: 124-30
6. Hudson LD, Steinberg KP. Epidemiology of acute lung injury and ARDS. Chest 1999; 116 Suppl. 1: 74S-82S
7. Moss M, Bucher B, Moore FA, et al. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 1996; 275 (1): 50-4
8. Milberg JA, Davis DR, Steinberg KP, et al. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. JAMA 1995; 273: 306-9
9. Sloane PJ, Gee MH, Gottlieb JE, et al. A multicenter registry of patients with acute respiratory distress syndrome: physiology and outcome. Am Rev Respir Dis 1992; 146: 419
10. Donnelly SC, Strieter RM, Kunkel SL, et al. Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. Lancet 1993; 341: 643-7
11. Davidson TA, Caldwell ES, Curtis JR, et al. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA 1999; 281 (4): 354-60
12. Bone RC, Maunder R, Slotman G, et al. An early test of survival in patients with the adult respiratory distress syndrome: the PaO2/FIO2 ratio and its differential response to conventional therapy. Chest 1989; 96: 849-51
13. Marini JJ. New options for the ventilatory management of acute lung injury. New Horiz 1993; 1: 489-502
14. Slutsky AS. Lung injury caused by mechanical ventilation. Chest 1999; 116: 9S-15S
15. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342: 1301-8
16. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998; 280 (2): 159-65
17. Alexander JS, Patton WF, Christman BW, et al. Platelet-derived lysophosphatidic acid decreases endothelial permeability in vitro. Am J Physiol 1998; 274: H115-22
18. Donnelly SC, Strieter RM, Reid PT, et al. The association between mortality rates and decreased concentrations of interleukin-10 and interleukin-1 receptor antagonist in the lung fluids of patients with the adult respiratory distress syndrome. Ann Intern Med 1996; 125 (3): 191-6
19. Bernard GR, Wheeler AP, Naum CC, et al. A placebo controlled, randomized trail of IL-10 in acute lung injury (ALI). Chest 1999; 116: 260S
20. Balibrea JL, Arias-Diaz J, Garcia C, et al. Effect of pentoxifylline and somatostatin on tumour necrosis factor production by human pulmonary macrophages. Circ Shock 1994; 43 (2): 51-6
21. Butler J, Pillai R, Rocker GM, et al. Effect of cardio-pulmonary bypass on systemic release of neutrophil elastase and tumor necrosis factor. J Thorac Cardiovasc Surg 1993; 105: 25-30
22. Faymonville ME, Pincemail J, Duchateau J, et al. Myeloperoxidase and elastase as markers of leukocyte activation during cardiopulmonary bypass in humans. J Thorac Cardiovasc Surg 1991; 102: 309-17
23. Torii K, Iida KI, Miyazaki Y, et al. Higher concentrations of matrix metalloproteinases in bronchoalveolar lavage fluid of patients with adult respiratory distress syndrome. Am J Respir Crit Care Med 1997; 155: 43-6
24. Kawamura M, Yamasawa F, Ishizaka A, et al. Serum concentration of 7S collagen and prognosis in patients with the adult respiratory distress syndrome. Thorax 1994; 49: 144-6
25. Suter PM, Suter S, Girardin E, et al. High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, and elastase, in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. Am Rev Respir Dis 1992; 145: 1016-22
26. McCroskery PA, Richards JF, Harris Jr ED. Purification and characterization of a collagenase extracted from rabbit tumors. Biochem J 1975; 182: 131-42

27. Golub LM, Evans RT, McNamara TF, et al. A non-antimicrobial tetracycline inhibits gingival matrix metalloproteinase and bone loss in Porphyromonas gingivalis-induced periodontitis in rats. Ann NY Acad Sci 1995; 732: 96-111
28. Kishi M, Richard LF, Webster RO, et al. Role of neutrophils in xanthine/xanthine oxidase-induced oxidant injury in isolated rabbit lungs. J Appl Phys 1999; 87 (6): 2319-25
29. Wang HG, Shibamoto T, Miyahara T, et al. Effect of ONO-5046, a specific neutrophil elastase inhibitor, on the phorbol myristate acetate-induced injury in isolated dog lung. Exp Lung Res 1999; 25 (1): 55-67
30. Yamazaki T, Ooshima H, Usui A, et al. Protective effects of ONO-5046*Na, a specific neutrophil elastase inhibitor, on post-perfusion lung injury. Ann Thor Surg 1999; 68 (6): 2141-6
31. Miyazaki Y, Inoue T, Kyi M, et al. Effects of a neutrophil elastase inhibitor (ONO-5046) on acute pulmonary injury induced by tumor necrosis factor alpha (TNFalpha) and activated neutrophils in isolated perfused rabbit lungs. Am J Respir Crit Care Med 1998; 157 (1): 89-94
32. Giudici D, Baudo F, Palareti G, et al. Antithrombin replacement in patients with sepsis and septic shock. Haematologica 1999; 84 (5): 452-60
33. Inthorn D, Hoffmann JN, Hartl WH, et al. Effect of antithrombin III supplementation on inflammatory response in patients with severe sepsis. Shock 1998; 10 (2): 90-6
34. Eisele B, Lamy M, Thijs LG, et al. Antithrombin III in patients with severe sepsis. A randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. Int Care Med 1998; 24 (7): 663-72
35. Baudo F, Caimi TM, de Cataldo F, et al. Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: a controlled double-blind, randomized, multicenter study. Int Care Med 1998; 24 (4): 336-42
36. Goldfarb RD, Glock D, Johnson K, et al. Randomized, blinded, placebo-controlled trial of tissue factor pathway inhibitor in porcine septic shock. Shock 1998; 10 (4): 258-64
37. Randolph MM, White GL, Kosanke SD, et al. Attenuation of tissue thrombosis and hemorrhage by ala-TFPI does not account for its protection against E. coli: a comparative study of treated and untreated non-surviving baboons challenged with LD100 E. coli. Thromb Haemostasis 1998; 79 (5): 1048-53
38. Carr C, Bild GS, Chang AC, et al. Recombinant E. coli-derived tissue factor pathway inhibitor reduces coagulopathic and lethal effects in the baboon gram-negative model of septic shock. Circ Shock 1994; 44 (3): 126-37
39. Rossaint R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993; 328 (6): 399-405
40. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998; 26 (1): 15-23
41. Zwissler B, Kemming G, Habler O, et al. Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med 1996; 154 (6 Pt 1): 1671-7
42. Konishi M, Fujiwara T, Naito T, et al. Surfactant replacement therapy in neonatal respiratory distress syndrome. A multicentre, randomized clinical trial: comparison of high- versus low-dose of surfactant. Eur J Ped 1988; 147 (1): 20-5
43. Anzueto A, Baughman RP, Guntupalli KK, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf acute respiratory distress syndrome sepsis study group. N Engl J Med 1996; 334 (22): 1417-21
44. Gregory TJ, Steinberg KP, Spragg R, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1997; 155 (4): 1309-15
45. Spragg RG, Gilliard N, Richman P, et al. Acute effects of a single dose of porcine surfactant on patients with the adult respiratory distress syndrome. Chest 1994; 105 (1): 195-202
46. Wiswell TE, Smith RM, Katz LB, et al. Bronchopulmonary segmental lavage with Surfaxin (KL(4)-surfactant) for acute respiratory distress syndrome. Am J Respir Crit Care Med 1999; 160 (4): 1188-95
47. Gadek JE, DeMichele SJ, Karlstad MD, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Crit Care Med 1999; 27 (8): 1409-20
48. Hirschl RB, Conrad S, Kaiser R, et al. Partial liquid ventilation in adult patients with ARDS: a multicenter phase I-II trial. Ann Surg 1998; 228 (5): 692-700

Correspondence and offprints: Dr *Peter E. Morris*, Section on Pulmonary and Critical Care Medicine, Wake Forest University School of Medicine, 3rd Floor Gray Building, Medical Center Boulevard, Winston-Salem, NC 27157, USA.
E-mail: pemorris@wfubmc.edu