REVIEW ARTICLE

New Therapies for Acute Respiratory Distress Syndrome (ARDS): - A Review

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Summary

Acute respiratory distress syndrome (ARDS) has been associated with high mortality. Improved understanding of the pathophysiology, recognition of precipitating events and improved management has decreased the mortality over the years. Mechanical ventilation is still the corner stone of the management of the disease. It is well recognised that high tidal volumes and airway pressures increase the morbidity, hence the need to use alternative modes of ventilation like pressure control with or without inverse ratio ventilation. Extracorporeal membrane oxygenation is still experimental and not easily available, whereas prone position to improve oxygenation is simple and inexpensive. The concept of pathological oxygen dependency and therapy aimed at supranormal values has failed to improve survival. Restricting the fluids to prevent further oedema formation in an already wet lung has improved the survival rate. Nitric oxide and surfactant have failed to produce desirable effect in large studies. Pharmacological support to inhibit inflammation with non steroidal anti-inflammatory drugs, antifungal agents, prostaglandin and corticosteroids have all failed. Interestingly corticosteroid rescue treatment in the late phase of ARDS has shown promise. Antiendotoxin and anticytokine studies which began with much enthusiasm is yet to produce desirable results.

Key Words: Acute respiratory distress syndrome, ARDS, Management

Definition

Acute Respiratory Distress Syndrome (ARDS) is defined as the clinical manifestations of severe acute lung injury; characterised by diffuse alveolar damage and by the development of non cardiogenic pulmonary oedema [1].

The American-European consensus conference on ARDS recommended the following criteria in the diagnosis of ARDS.

1. acute onset;
2. ratio of arterial oxygen tension to fraction of inspired oxygen ($Pa0_2/Fi0_2$) less than 200 mm Hg (≤ 26.6 kPa) regardless of positive end-expiratory pressure (PEEP) level;
3. pulmonary artery wedge pressure less than 18 mm Hg (≤ 2.4 kPa) or no clinical evidence of left atrial enlargement;
4. bilateral infiltrates seen on frontal chest x-ray.

Despite the fact that ARDS has been recognised as a distinct clinical entity for more than 25 years, many if not all aspects of ARDS management is still controversial. Remarkably, there is not a single, large randomised, prospective study which has shown any survival benefit for any therapy. The mortality continues to remain high. As a result, new approaches to treatment have been developed based on a rapidly evolving understanding of the events involved in the development of ARDS and the effects of conventional supportive therapy.

Table I
Management of ARDS[2]

A	**Supportive Therapy**
	1. Mechanical ventilation
	1.a Pressure controlled ventilation
	1.b Inverse ration ventilation
	1.c Permissive hypercapnia
	1.d extracorporeal carbon di-oxide removal ($ECCO_2R$)
	2. Prone position
	3. Fluid manggement
	4. Oxygen supply dependency
	5. Surfactant therapy
	6. Inhalation of nitric oxide
B	**Definitive Therapy**
	1. Prostaglandins
	2. Corticosteroids
	3. Eicosanoids and their inhibitors
	4. Antiendotoxin and anticytokine therapy
	5. Antioxidants

The management of ARDS is complex. Therapy can be divided into supportive and definitive (Table I).

1. Mechanical Ventilation

Patients with ARDS present great challenges for effective mechanical ventilation. They have decreased compliance, increased airway resistance and increased dead space[3]. In recent years the approach to mechanical ventilation of ARDS has been changed by the development of the concepts.

a. Lung injury secondary to barotrauma or volutrauma[4,5].
b. Heterogeneity of lung injury in ARDS [6,7].

Mechanical ventilation in ARDS should aim at protecting the lung and maximising gas exchange and oxygen delivery. The key elements to successful management include;

1. Limiting the peak airway pressure. Peak airway pressure of over 40 to 50 cm H_2O is associated with an increased risk of barotrauma during mechanical ventilation[4,8-10].
2. Maintaining sufficient total positive end expiratory pressure (PEEP), the sum of PEEP and auto PEEP during the initial phase of acute lung injury to prevent alveolar collapse and recruitment with each breath [6,11].
3. Increasing the mean transalveolar pressure (clinically measurable as mean airway pressure) sufficiently so as to achieve satisfactory gas exchange and oxygen delivery[12,13].

1.A Pressure Controlled Ventilation (PCV)

Pressure controlled ventilation seems to be superior to volume controlled ventilation [14]. During PCV, the peak airway pressure is maintained throughout inspiration, allowing inflation of all lung units depending upon the lung compliance. Thus lung units that are not inflated during conventional volume controlled ventilation may be inflated during PCV, so called alveolar recruitment[2]. Pressure-controlled ventilation is often used with inverse ratio ventilation or permissive hypercapnia.

1.B Iinverse Ratio Ventilation

Mean alveolar pressure is a major determinant of oxygenation. Hence ventilatory management which maintains mean alveolar pressure without exceeding peak airway pressure of 40-45 cm H_2O may be practical [12,13]. Inverse ratio ventilation prolongs the inspiratory time greater than expiratory time. Prolonging the inspiratory time can maintain mean alveolar pressure and tidal volume at lower levels of PEEP and peak alveolar pressure [8,13-15].

Inverse ratio ventilation (IRV) can be achieved by volume cycled (VC-IRV) or pressure control (PC-IRV) mode [8,13]. The lung is most recruitable in the early phase of injury [16]. The beneficial effects of inverse ratio ventilation may take several hours [15,17]. Hence if inverse ratio ventilation is to show an advantage, it would be in

the early phase of ARDS, not after all the methods have failed [8,13].

Both VC-IRV[18-20] and PC-IRV has been tested in patients with ARDS with encouraging results. Lain et al [14] using PC-IRV ventilated 19 patients with ARDS. The PC-IRV reduced peak airway pressure, PEEP, improved ventilation and oxygenation. Chan et al [21] evaluated PC-IRV in 10 patients with ARDS. The PC-IRV was associated with significant increases in PaO2, arterial pH, and mean airway pressure. Other reports confirm the same findings [13,15,17].

Mechanisms

The likely mechanisms of IRV improving oxygenation during inverse ratio ventilation are sustained inspiratory pressure may recruit unventilated alveoli effectively [8,14,15,17,18] and effect of auto PEEP[15,22-24].

Risk Associated With IRV

1. Increased risk of pneumothorax, interstitial emphysema, barotrauma[17,25].
2. Decrease in the venous return and cardiac output[18,21,22].
3. Requires deep sedation and paralysis with neuromuscular blocking drugs[15].

Many studies utilising IRV as a mode of ventilation in ARDS have suggested its usefulness when oxygenation cannot be maintained with conventional ventilation[13-15,17,26]. At present the role of pressure controlled inverse ratio ventilation is limited to patients in whom arterial oxygenation cannot be maintained with a PEEP of 15cm H_2O or less or when the PEEP is associated with excessive airway pressure[27].

1.C Permissive Hypercapnia

Ventilatory management of ARDS should include limiting the peak airway pressure to 30-35 cm H_2O and a PEEP level that prevents alveolar collapse. In many patients this will result in hypercapnia. The concept of permissive hypercapnia in ARDS was first tested by Hickling et al[28]. The authors subsequently confirmed these results in 53 patients with ARDS using low tidal volume (4-7 mL/Kg) and limiting the peak inspiratory pressure to 30 to 40 cm H_2O. The mean maximum $PaCO_2$ was 66.5 mm Hg (range 38 to 158 mm Hg) and the mean arterial pH at the same time was 7.23 (range 6.79 to 7.45). Bicarbonate was not used to buffer acidosis. The hospital mortality rate was significantly lower than that predicted by the APACHE II scores (26.4% vs. 53.3%)[29]. If the $PaCO_2$ is allowed to build up from 5.3 kPa to 10.6 kPa, the required alveolar ventilation could be reduced to 50% with no ill effect[30]. Acute hypercapnia results in increased cerebral blood flow, intracellular acidosis, pulmonary hypertension and activation of the adrenergic system[31]. Intracellular acidosis seems to be responsible for most of the effects of acute hypercapnia[32] and the intracellular pH returns to near normal within 3 hours[33].

Application of Permissive Hypercapnia

a. **Positive End Expiratory Pressure**: The positive end expiratory pressure should be applied to the point of maximal alveolar recruitment as determined by lung mechanics and not by gas exchange. This point corresponds to maximal alveolar recruitment and compliance begins to decrease [34].

b. **Tidal Volume**: Tidal volume to be adjusted at 6-7 mL/kg and reduce if necessary to maintain the P plat $\leq$ 30 cm H_2O [28-31, 33,34]. The objective of this strategy is to maintain the total lung volume at the end of inspiration below predicted total lung capacity.

c. **Respiratory Rate**: The recommended rate is between 14-20 breaths/minute with or without intermittent mandatory ventilation [28,29,33].

d. **Acidosis**: The use of bicarbonate or other agents to correct pH during permissive hypercapnia has not been adequately evaluated. At present, a pH as low as 7 is regarded as acceptable provided the cardiac output and oxygenation are satisfactory[29,33,35].

Contraindications to permissive hypercapnia include raised intracranial pressure, ischaemic heart disease and

hypertension[35]. Even though permissive hypercapnia has been accepted as a strategy to minimise complications associated with high peak airway pressure, there is however lack of large prospective, controlled studies to support this strategy.

1.D Extracorporeal CO_2 Removal

Two forms of extracorporeal respiratory support have been evaluated in patients with ARDS, extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$).

Gattinoni in 1986[36] reported improved survival rate of 49% using low-frequency positive pressure ventilation with extracorporeal CO_2 removal (LFPPV-$ECCO_2R$). Subsequently Morris et al[37] in 1994 tried to reproduce the results of Gattinoni et al[36] in a prospective randomised study of 40 patients. They compared LFPPV-$ECCO_2$-R with controlled positive pressure ventilation. The survival was not different, 42% with conventional versus 33% with new therapy. Use of LFPPV-$ECCO_2$-R was associated with a high complication rate. In 7 out of 21 bleeding was a major problem which required termination of ECMO. At present LFPPV-$ECCO_2$ is not recommended for routine management of ARDS.

2. Prone Position

Because lung infiltrates in ARDS are nonuniformly distributed [6], positional changes can improve oxygenation by improving the distribution of perfusion. Interestingly 20 years ago Douglas et al[38] demonstrated that turning patients to the prone position in ARDS improved oxygenation. Subsequent studies in small number of patients have confirmed the benefits of the prone position[39-42].

Several mechanisms may be involved in the improvement of oxygenation during the prone position including reduction in shunt[43], improved ventilation to dorsal lung units while both ventilation in ventral lung units and perfusion to all lung regions are maintained[41]. Other mechanisms include increase in functional residual capacity and correction of venous stasis[40,41].

Mutoh et al [44] measured pleural pressure (PPL) in the dependent and non dependent lung regions when animals were supine and prone, before and after creating pulmonary oedema with volume infusion. It was noted the gravitational PPL gradient was less when the animals were prone compared to when they were supine. In the presence of pulmonary oedema PPL in the dependent lung region became positive, but was much less positive when they were turned prone.

The prone position is a simple and safe way to improve oxygenation. Its beneficial effect allows reduction in FIO_2 and PEEP. Decrease in the shunt may result in better elimination of CO_2. Despite the lack of large studies prone position seems to have been accepted as a modality to increase oxygenation.

3. Fluid Management

The pulmonary oedema in ARDS is caused by increased vascular permeability and intravascular hydrostatic pressures may still be a contributing factor. One of the priorities in the management of ARDS is to minimise oedema formation. Several clinical studies indicate that pulmonary function and outcome are better in patients who lose weight or in whom the pulmonary artery wedge pressure falls as a result of fluid restriction or diuresis[45-48].

Early fluid restriction with or without diuresis does not appear to be associated with higher incidence of complications[48]. At present fluid restriction is recommended in patients with ARDS, to maintain PAW at less than 12 mm Hg, with or without diuretics[49]. The benefit of continuing fluid restrictions or diuresis for more than three or four days is unclear[48].

4. Oxygen Supply Dependency

Under normal circumstances, oxygen consumption (VO_2) is relatively independent of oxygen delivery (DO_2) over a wide range. This portion of the DO_2-VO_2 graph is called oxygen supply independent region. As DO_2 decreases the slope becomes steeper until a point is reached where consistent VO_2 cannot be maintained and it falls with further decreases in DO_2. Oxygen consumption then becomes supply dependent. The level at which VO_2 becomes a function of DO_2 is known as critical DO_2 [50].

Pathological oxygen supply dependency is an abnormal situation, in which oxygen uptake varies directly with oxygen delivery. Measurement of VO_2 and DO_2 in patients with ARDS did not display a biphasic curve with a clearly defined critical DO_2. Instead a linear DO_2-VO_2 relationship was observed [51-54].

Many investigators examined the concepts of supranormal values as an extension to pathological oxygen supply dependency in patients with ARDS with varying results. Some studies clearly showed benefit [54-58]. Others suggested no effect[59,60] or even worsening[61].

It may be worth while to ask the question. "Should we use supranormal values in critically ill septic patients to improve the outcome?". The answer to this question comes from the 3rd consensus conference in intensive care medicine held in 1995 on tissue hypoxia. It was concluded that at present supranormal values in the critically ill patients are unwarranted[62].

5. Surfactant Therapy

Patients with ARDS may have normal or low amount of surfactant and it is usually dysfunctional[61,62]. The most likely mechanism of the surfactant abnormality include inactivation of the surfactant by the protein-rich pulmonary oedema fluid and reduction in surfactant production due to failure of its secretion by damaged or inactivated pneumocytes [63].

Benefits of surfactant replacement could include reduced airway pressures, improved ventilation, and a reduced incidence of nosocomial pneumonia. Surfactant is a viscous substance and to be effective it must reach the terminal bronchioles and/or alveolar spaces. The role of exogenous surfactant in the treatment of ARDS has been studied.

Anzueto et al[64] reported one of the largest trials in ARDS using exogenous surfactant. They conducted a prospective, multi-center, double-blind, randomized, placebo controlled trial involving 725 patients. Exogenous surfactant administration did not improve oxygenation, peak airway pressure, or overall survival at 30 days, nor did it reduce the amount of time patients required mechanical ventilation.

Gregory et al[65], in a controlled clinical trial, treated 59 patients with bovine derived surfactant (Survanta ®, Ross Laboratories, Columbus, OH, USA) containing both lipid and protein moieties in a dose 50-100mg/kg. The surfactant was instilled into the lungs via the endotracheal tube. There was a dramatic decrease in mortality from 44 to 17%. Several possible explanations for the failure of the surfactant may be due to insufficient dose, lack of a protein component and lastly surfactant replacement may not be enough in acute lung injury in view of endothelial and epithelial permeability.

Several questions regarding administration of surfactant in ARDS like dose, frequency and mode of administration are yet to be clarified. At present the high costs of therapy and inconsistency of the results of large studies prohibits the use of the surfactant in ARDS.

6. Nitric Oxide

Pulmonary hypertension in ARDS is a result of vasoconstriction, vascular obstruction and obliteration. Pulmonary vasoconstriction is due to a direct effect of hypoxia and circulating mediators like thromboxane A_2 and platelet activating factor. Attenuation of hypoxic pulmonary vasoconstriction may result in maldistribution of ventilation relative to perfusion, an increase in shunt, and deterioration in oxygenation. Intravenous administration of vasodilator drugs like nitroglycerin, nitroprusside, prostaglandin E_1 aiming to reduce pulmonary vascular resistance is associated with a large decrease in systemic blood pressure and arterial oxygenation[66,67]. The rationale for the use of nitric oxide (NO) is based on the fact that nitric oxide causes pulmonary vasodilation and this vasodilation occurs only in the ventilated areas. Blood is diverted from non ventilated or poorly ventilated alveoli to better ventilated alveoli. This results in better V/Q match and reduction in the shunt[67].

Inhaled NO has no effect on the normal-non-constricted, pulmonary circulation[68]. Following diffusion into the blood it is rapidly inactivated by binding to haemoglobin and thus generalised vascular effects are spared. This is the basis for selective vasodilatation observed with nitric oxide in pulmonary vasoconstric-

tion and pulmonary hypertension[68]. In concentrations above 200 PPm, NO is cytotoxic. Nitric oxide should be diluted in the respiratory circuits before reaching the tracheobronchial tree.

Rossaint et al[67] reported the beneficial effects of NO in patients with ARDS. When used in a concentration of 18 PPm, a statistically significant reduction in pulmonary artery pressures and intrapulmonary shunt occurred while the $Pa0_2/Fi0_2$ ratio increased. Subsequent studies in a small group of patients confirmed the beneficial effect of nitric oxide[69, 70].

Krafts et al prospectively studied in 25 patients with ARDS associated with septic shock. Nitric oxide was administered at 18 or 36 PPm. Only 40% of patients responded by increasing $Pa0_2$ and decreasing mean pulmonary artery pressure. They concluded that inhaled NO is effective in only a subgroup of septic ARDS patients[71].

Side effects of nitric oxide should not be overlooked, which include methaemoglobinaemia, rebound hypoxaemia, and pulmonary hypertension after sudden NO withdrawal. Too high concentrations may result in pulmonary oedema and metabolic acidosis[72].

Experience with inhaled nitric oxide is too limited to allow recommendation of its routine use in ARDS.

Nitric Oxide with Almitrine

Intravenous administration of almitrine enhances hypoxic pulmonary vasoconstriction. In ARDS patients, almitrine administered at a concentration of 16 µg/kg/min. increases pulmonary artery pressure and pulmonary vascular resistance[73]. Wysocki et al reported the additive effects of nitric oxide and intravenous almitrine in 17 ARDS patients. The rationale for this combination was to reinforce hypoxic pulmonary vasoconstriction in non-ventilated lung units with almitrine, and at the same time to reverse the constriction of pulmonary vessels perfusing ventilated regions with NO[74]. However controlled clinical studies are lacking.

Definitive Therapy

1. **Prostaglandin E_1 :** Prostaglandin (PGE1) a powerful vasodilator, inhibits platelet aggregation and has immunomodulatory effects. The effect of PGE1 is dose-dependent and lasts only minutes after discontinuation of the infusion. The vasodilating effect of PGE1 is not restricted to pulmonary vasculature, its effect on the systemic vasculature results in systemic hypotension[66].

   Bone et al[75] in a randomized placebo-controlled trial demonstrated that infusion of PGE1 significantly improved cardiac index, oxygen delivery ($D0_2$) and oxygen consumption ($V0_2$) in patients with ARDS. However this did not improve the survival rate.

Inhaled Prostacyclin

The disadvantages of intravenous prostaglandins are well known[66]. Recently, aerosolized prostacyclin (PGI_2) in doses as low as 2 mg/kg/min has been shown to induce selective pulmonary vasodilation, improve oxygenation and reduce shunt [76,77]. The reason for these beneficial effects is the selective distribution of inhaled prostacyclin (PGI2) to ventilated lung units thereby dilating only vessels of aerated alveoli similar to nitric oxide.

Abraham et al studied the effect of liposomal prostaglandin E_1 (PGE1) in a randomized prospective, double blind, placebo controlled study in patients with ARDS. They demonstrated increased oxygenation, increased lung compliance and decreased ventilator dependence. The mortality rate was 6% in the PGE1 compared to 25% in the placebo group[78]. Despite these encouraging results several questions concerning long-term prostacyclin nebulization needs to be addressed before advocating its use for ARDS such as the optimum mode of administration and dose?

2. Corticosteroids

Adrenocorticosteroids (methyl prednisolone) have been used in the treatment of sepsis and ARDS. Subsequently two prospective, multicenter, placebo-controlled trials in 304 and 99 ARDS patients, failed to

demonstrate any beneficial effect of steroids. Mortality was higher in patients who received steroids[79,80]. Because of the results of these randomized, placebo controlled studies, corticosteroid therapy have been abandoned in the management of sepsis and ARDS.

Recently corticosteroids have been proposed for the prevention or treatment of pulmonary fibrosis in late ARDS, the so called fibro-proliferative phase (7 to 10 days after onset)[81]. During this phase the lung attempts to repair the initial or persistent injury to the endothelial and epithelial lining of the respiratory units. Unhalted this leads to fibrosis. Clinically this can be recognised between days 3 to 7 of mechanical ventilation by their inability to improve gas exchange, worsening static compliance, increased minute ventilation and pulmonary hypertension[82].

Hooper et al[83] evaluated the role of methylprednisolone in 10 patients with late ARDS. After 4-7 days of therapy, significant clinical improvement in ventilatory requirements, oxygenation and chest roentgenograms were apparent in all patients. Meduri et al[84] administered methylprednisolone intravenously 2-3 mg/kg/day to 25 patients with late ARDS. A significant physiologic improvement in terms of acute lung injury score and PaO_2/FIO_2 ratio of >100 was seen in 21 patients. Survival was 86% in responders and 25% in nonresponders. The dosage requirement of methylprednisolone is 2 to 3 mg/kg/day intravenously every 6th hourly until extubation. After extubation the dose is gradually tapered over a period of 6 weeks[84].

The beneficial effects of steroids in the fibro-proliferative phase of ARDS may be related to modulation of macrophage and fibroblast activity resulting in the halting of progression to fibrosis[84]. Corticosteroid are not recommended during the early exudative phase of ARDS or in patients with uncontrolled infection. To date there is no randomized, controlled clinical trial in the late fibro-proliferative stage of ARDS has been undertaken.

3. Eicosanoids and their inhibitors

In ARDS, neutrophils, macrophages and platelets as well as pulmonary endothelial and epithelial cells can release arachidonic acid metabolites as shown in Figure 1.

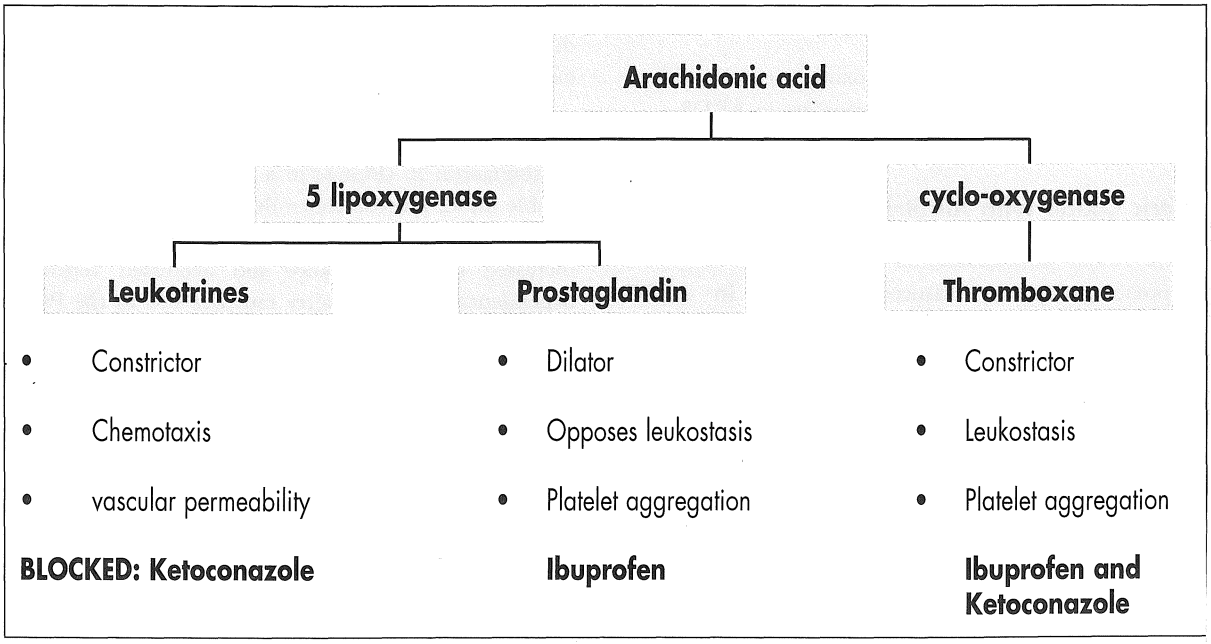

Fig. 1: Arachidonic acid metabolites and drugs blocking their effects

The eicosanoids are metabolites of arachidonic acid and include cyclo-oxygenase metabolites (prostaglandins and thromboxane A_2) and lipoxygenase metabolites (leukotrines). Eicosanoids regulate vascular tone, vascular permeability and inflammation.

3.a Non Steroidal Anti Inflammatory Drugs

Bernard et al[85] studied the effect of a cyclo-oxygenase inhibitor in 30 patients with sepsis. They found that the production of prostaglandin and thromboxane was increased. Ibuprofen 800 mg administered 4 hourly rectally increased urinary concentration of thromboxane B2 and 6-Keto-Prostaglandin FI alpha and decreased temperature, heart rate, and peak airway pressure.

Haupt et al[86] evaluated the safety of ibuprofen in 29 patients with clinical evidence of sepsis. They administered 600mg or 800mg IV over 20 minutes, followed by three 800mg doses rectally every 6 hrs. There was no significant difference in haemodynamic and respiratory parameters.

No major randomized, placebo-controlled studies on the efficacy of non steroidal anti-inflammatory drugs in human ARDS have been published. At present these substances are, therefore, not recommended[2].

3.b Ketoconazole

Ketoconazole is an imidazole-based compound used in clinical practice for its antifungal properties. It is a potent inhibitor of thromboxane and leukotrine synthesis[87]. Slotman et al[87] evaluated Ketoconazole in 71 patients who were at high risk for developing ARDS. This was a prospective randomized placebo-controlled trial. Ketoconazole decreased the incidence of ARDS from 31% to 6%. Yu and Tomasa in a similar study of 56 patients reported that treatment with Ketoconazole decreased the frequency of ARDS from 64% to 15% and reduced the mortality rate from 39% to 15%[88].

The major side effect is hepatotoxicity. Therapies that reduce gastric acidity should be avoided to ensure bio-availability. Since no studies have evaluated the use of Ketoconazole in the treatment of established ARDS, its usage cannot be recommended at the moment. More studies are needed to assess the role of ketoconazole as a prophylactic agent in the prevention of ARDS, before it can be accepted as a preventive drug.

4.a Antiendotoxin Therapy

Sepsis due to gram negative infection is the commonest aetiological factor for the development of ARDS. Administration of gram negative bacteria or endotoxin produces ARDS in animals. Two monoclonal antibodies against endotoxin; human monoclonal anti-lipid A antibody (HA-lA) and E5 have been tested. However none of the agents tested to date in prospective trials have shown any benefit in terms of overall mortality [89, 90].

Bone et al[91], evaluated the safety and efficacy of E5 in the treatment of patients with Gram-negative sepsis. Eight hundred and forty seven patients were enrolled in a double-blind, placebo controlled trial. Two doses of E5 (2 mg/kg/day by intravenous infusion 24 hrs apart) or placebo was administered. There was no significant improvement in survival over 30 days. However 48% of patients with gram-negative sepsis experienced resolution of major organ failure if they received E5 compared with 25% patients receiving placebo. E5 also provided some protection against the development of ARDS.

4.b Anticytokine Therapy

Tumor necrosis factor (TNF) is a polypeptide cytokine produced by macrophages in response to stimulation by endotoxin, interleukins and other cytokines. Administration of TNF causes ARDS in animals and its antibodies prevent *Escherichia coli* induced lung injury in baboons.

Studies utilising murine monoclonal anti-TNF-L antibody against Gram-negative sepsis with or without shock have failed to demonstrate any beneficial effect[92].

5. Antioxidants

Oxidant injury from toxic oxygen radicals is thought to play a role in the ARDS. N-acetylcystein acts as an oxygen free-radical scavenger and as a precursor for glutathione.

There are at least three prospective randomised, double blind placebo controlled studies looking at the effect of N-acetylcystein[93-95]. None of the studies demonstrated any beneficial effect in terms of survival rate. At present

Table II
Recommendation for the treatment of ARDS:

Recommendation	Intervention
YES	pressure controlled ventilation, inverse ratio ventilation, permissive hypercapnia prone position, fluid restriction
NO	supranormal O_2 delivery, ECMO, $ECCO_2$- R, surfactant, early corti costeroids, NSAIDS, prostaglandins, antifungal agent, N-acetylcystein, antiendotoxin, anticytokine
PENDING	NO, late corticosteroids

$ECMO_2$ = extracorporeal membrane oxygenation
$ECCO_2$ - R = extracorporeal C02 removal
NSAIDS= non steroidal anti-inflammatory drugs
NO = nitric oxide

N-acetylcystein cannot be recommended for routine clinical use in acute respiratory distress syndrome.

Conclusion

The mortality of ARDS continues to remain high, inspite of major progress in the understanding of ARDS. This does not mean mortality has remained unchanged from the past 30 years. With a better understanding of the pathophysiological events that occur in ARDS mortality can be decreased from 60% to 40%[96]. One should not pin too much hope on pharmacological support for the prophylaxis or treatment of ARDS since they are either unproven, useless or the benefit may be restricted to a subgroup. Corticosteroid therapy in the late fibro-proliferative phase of ARDS may be safe. The recommendations for the management of ARDS are summarised in Table II. The best way to treat ARDS is to "prevent" ARDS. As Rinaldo in 1982[97] correctly stated "... improved survival in ARDS would have to await a better understanding of the pathophysiology .... and probably would not be attained solely through the development of improved life support technology".

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