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Future Drugs for Treatment of Acute Respiratory Distress Syndrome

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Abstract: The acute respiratory distress syndrome (ARDS) is a common clinical disorder characterized by injury to the alveolar epithelial and endothelial barriers of the lung, acute inflammation and pro rich pulmonary edema leading to acute respiratory failure. Knowledge of the pathophysiology and management of ARDS has been improved immensely since its original description. But pharmacotherapies have not been hopeful in treatment of ARDS in clinical trials. Mortality from ARDS has decreased in certain centers over the last 10 years due to advances in supporting critically ill patients. This trend may open the window of opportunity for pharmacological manipulation of ARDS. This study reviews conventional and new treatment challenges like use of nitric oxide nebulizer, prostacycline, surfactants, anti-inflammatory agents, antioxidants, phosphodiesterase inhibitors, immunonutrients, prostaglandin E₁, anti-interleukins and inhibitors of thromboxanes and leucotriens.

Key words: Acute respiratory distress syndrome, nitric oxide, prostacycline, surfactant, N-acetyl cystein, procystein, prostaglandin E₁, corticosteroids

Definitions of disease: Before 1992, the acronym ARDS represented the adult respiratory distress syndrome. In 1994 the American-European Consensus Committee on ARDS standardized the definition and renamed it acute rather than adult respiratory distress syndrome because it occurs at all ages. The term acute lung injury (ALI) was also introduced at that time. The committee defined ALI as "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension. The distinction between ALI and ARDS is the degree of hypoxemia. ALI is defined by a PaO₂/FiO₂ ratio less than 300 and 200 mm Hg or less is required for ARDS^[1].

Epidemiology: The true incidence of ALI and ARDS is currently unknown; in 1972 an incidence of 75 cases of ARDS per 100000 population per year was estimated. Several subsequent studies have estimated a much lower annual incidence of 1.5-13.5 cases per 100000 population. However, the true incidence of ALI/ARDS may not be as high as the 1972 NIH estimate nor as low as subsequent studies^[2].

Pathophysiology: In ARDS, the injured lung is believed to go through three phases: exudative, proliferative and fibrotic, but the course of each phase and the overall disease progression is variable. In the exudative phase, damage to the alveolar epithelium and vascular endothelium produces leakage of water, protein and inflammatory and red blood cells into the interstitium and alveolar lumen. Neutrophils and multiple mediator cascades induce these changes. Both TNF- α and IL-8 are keys to this response. Type I alveolar cells are irreversibly damaged and the denuded space is replaced by the deposition of proteins, fibrin and cellular debris, producing hyaline membranes, while injury to the surfactant-producing type II cells contributes to alveolar collapse. In the proliferative phase, type II cells proliferate with some epithelial cell regeneration, fibroblastic reaction and remodeling. In some patients, this progresses to an irreversible fibrotic phase involving collagen deposition in alveolar, vascular and interstitial beds with development of microcysts^[3].

Causes of ARDS: ARDS can develop after direct lung injuries such as pneumonia, aspiration, inhalation injury, near drowning, pulmonary contusion, reperfusion

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pulmonary edema (post lung transplantation or pulmonary embolectomy) and fat embolism. It can also happen in course of indirect lung injuries including sepsis, severe trauma, acute pancreatitis, cardiopulmonary bypass, massive transfusions and drug overdose^[4].

Clinical presentation and diagnosis: ARDS usually develops within 24 to 48 h after the initial lung injury. Tachypnea and dyspnea occur initially with normal auscultatory findings in the chest. Patients then become tachycardic with mild cyanosis and later develop coarse rales. They progress to respiratory distress with diffuse rhonchi and signs of consolidation. A presumptive diagnosis can be made with arterial blood gas analysis and chest x-rays. This analysis initially shows a very low PaO₂, a normal or low PaCO₂ and an elevated pH (acute respiratory alkalosis). Chest x-rays usually show diffuse bilateral alveolar infiltrates similar to cardiac acute pulmonary edema, but the cardiac silhouette is usually normal. After immediate treatment of hypoxemia, further diagnostic steps such as using a Swan-Ganz catheter (when heart failure is suspected) may help. Characteristically, pulmonary arterial wedge pressure (PAWP) is less than 18 mm Hg in ARDS and higher than 20 mm Hg in heart failure. If pulmonary embolism is suspected pulmonary angiography should be performed when possible. In immunocompromised patients *Pneumocystis carinii* pneumonia and other primary lung infections may mimic ARDS and should be ruled out by lung biopsy or bronchoalveolar lavage^[5]. A CT scan shows diffuse consolidation with air bronchograms and can detect complications of ARDS and those related to catheter and tube placement such as bullae, pleural effusions, pneumomediastinum, pneumothoraces, lung cysts and catheter malposition^[6].

Conventional therapy:

1. Oxygen should be administered via cannula or mask. Endotracheal intubation and assisted ventilation should be considered if the respiratory rate is higher than 30 breaths/min or if an FiO₂ higher than 60% by face mask is required to maintain arterial PaO₂ at 70 mm Hg. To avoid pathologic changes associated with high FiO₂ (edema, alveolar thickening and fibrinous exudate), FiO₂ should be titrated toward 0.60 as long as oxygen saturation can be maintained at 90% or higher^[5].

PEEP should be increased rapidly to keep FiO₂ levels less than 0.60. The use of PEEP higher than 12 mm Hg may decrease cardiac output and require monitoring of oxygen transport and cardiac parameters.

To avoid barotrauma and volutrauma associated with increasing minute ventilation permissive hypercapnia (PaCO₂ of 50-77 mm Hg and a pH of 7.20-7.30) is allowed. Tidal volume less than 6 mL kg⁻¹ and low plateau pressure ventilator strategy has been associated with less mortality. It is recommended that limiting the airway pressure take priority over limiting the FiO₂^[6].

2. Intravascular volume is often depleted with the onset of ARDS (sepsis, diuretic therapy, initiation of PPV decreases venous return). Despite the presence of alveolar edema, IV fluids should be given about <2400 mL/24 h of daily maintenances. If urinary output is less than 0.5 mL kg h⁻¹ or patient is critically ill a Swan-Ganz catheter is generally used to guide volume infusions, particularly if PEEP is needed. As a rule, patients with ARDS do better if kept on the "dry" side by restricting fluids and judiciously using diuretics as long as cardiac output and tissue perfusion are not impaired^[5].
3. Use of vasopressors like dopamine (2-20 µg kg min⁻¹ IV; titrate to BP) after correction of hypovolemia.
4. Use of diuretics like Furosemide (20-80 mg IV).

Advanced strategies: Liquid ventilation is performed by filling the lung with a perfluorocarbon, a low surface tension liquid with a high affinity for oxygen and carbon dioxide. Suggested mechanisms of action are prevention of alveolar collapse in the filled lung, efficient removal of mucus and debris and possible clearance of injury-producing cytokines. Clinical trials in adults with partial and full liquid ventilation are ongoing.

Extracorporeal membrane oxygenation oxygenates blood through an artificial lung using a venovenous or arteriovenous circuit while resting the lung. In prospective studies, the use of extracorporeal membrane oxygenation alone has shown no advantage, but it may have a role in combination with other modes in patients who are refractory to other interventions^[6].

Pharmacologic and supportive treatment

Vasodilators: Nitric oxide (NO) is a free radical gas produced constitutively in the lung by nitric oxide synthase from L-arginine, NADPH and oxygen and cause pulmonary vasodilation^[7]. Since NO is rapidly inactivated, its vasodilatory effects are restricted to the blood vessels at the site of generation or administration. When inspired at concentrations of 5-80 ppm, NO dilates pulmonary vessels perfusing aerated lung units, diverting blood from poorly ventilated or shunt regions. Thus gaseous NO is potentially an ideal agent to treat pulmonary hypertension and severe hypoxemia in ALI/ARDS patients. Encouraging results in some animal models have led to

the evaluation of the therapeutic potential of NO in ALI/ARDS patients^[8,9]. Approximately 60% of patients with ARDS or ALI of all causes respond to inhaled NO, increasing their paO_2 by more than 20%^[10]. The effect can frequently be seen in less than 10 min or may take several hours^[11]. However in several trials the oxygenation shows considerable inter-individual variations^[12]. Randomized controlled trials in patients with ARDS have shown that, inhaled NO temporarily improves oxygenation and reduce pulmonary artery pressure but its use is not associated with an improved outcome. However patients with severe refractory hypoxemia and inadequate right ventricular function secondary to pulmonary hypertension may benefit from inhaled NO^[12]. NONOates are a group of novel compounds that in time may prove to be superior to gaseous NO as selective pulmonary vasodilators because their long NO-release half-lives allow intermittent therapy. In addition, because of stability of NONOates in solid form and highly water solubility they can be delivered into the lung using a small volume nebulizer without the need for elaborate monitoring system. Diethylenetriamine nitric oxide adduct (DETA/NO), is a NONOates which was first used in a patient with severe ARDS and produced selective pulmonary vasodilation, with an improvement in pulmonary hemodynamics and oxygenation without measurable effect on systemic circulation^[13].

Prostacycline: Prostacycline (PGI_2) an endothelium-derived prostaglandin synthesized in endothelial cells from arachidonic acid is a potent vasodilator that inhibits platelet aggregation and neutrophil adhesion. In intravenous administration it reduces pulmonary artery pressure but increases intrapulmonary shunt and reduces $\text{PaO}_2/\text{FiO}_2$ ratio and systemic arterial pressure^[12]. However afterload reduction may improve systemic oxygen delivery and mixed venous oxygen content^[14,15]. Similar to NO, nebulized PGI_2 ($0\text{-}50 \text{ ng kg min}^{-1}$)^[16,17], or alprostadil (PGE_1 , $20\text{-}80 \text{ mg h}^{-1}$)^[17] may lead to vasodilation in well-ventilated areas of the lung, with minimal systemic side effects and without measurable dysfunction, but to date no large, prospective, randomized trials have been done to define the role of inhaled prostacycline in ARDS. Nevertheless, the relatively simple delivery system, harmless metabolites and no requirement for special monitoring make nebulized PGI_2 an attractive alternative to inhaled NO, despite its expense^[7].

Surfactant replacement therapy: Surfactant, which is normally produced by type II pneumocytes, decreases surface tension at the airfluid interface of small airways and alveoli. Without the beneficial effect of surfactant, alveoli may collapse and resist opening, even with high

airway pressures^[6]. The same effect reduces the hydrostatic pressure gradient favoring fluid movement into the alveolar space. It has also antiinflammatory and antimicrobial properties^[7]. Surfactant also inhibits superoxide production by human neutrophils by translocation of cytosolic components of the respiratory burst oxidase to the plasma membrane^[18,19]. Surfactant deficiency in animal models and human ARDS have been reported^[20,21]. The deficiency of surfactant is not a primary causal event in ARDS, rather the inflammatory processes lead to surfactant dysfunction as a secondary factor^[22]. Moreover, a change, in the lipid composition of surfactant contributes to poor surfactant function^[21]. Non-randomized trials of surfactant therapy show significant benefit in selected patients^[23,24]. Various preparations, doses, administration regimens and delivery techniques have been proposed. An early, prospective double blind, placebo controlled multicenter trial in 51 patients found that a synthetic surfactant failed to improve any physiologic variable^[25]. Some newer surfactant preparations with recombinant surfactant proteins are in current clinical trials in ALI/ARDS patients. Bovine surfactant administered intratechally in a small trial has shown that high doses are required to alter alveolar surfactant composition^[26]. Based on successful use of surfactant in animal models of lung injury and in neonatal respiratory distress syndrome and some trials, surfactant could be beneficial in ARDS. Moreover, several questions need to be answered before its clinical role. These include the optimal dosage, delivery system, timing and the actual preparations^[27].

Therapeutic strategies to reduce sepsis-induced ARDS: Patients with ALI/ARDS from sepsis have higher mortality than patients with ALI/ARDS from most other causes^[28]. Treatment of sepsis before or in the early phase of ALI/ARDS could improve outcomes in these patients. Unfortunately large clinical trials of anti-inflammatory agents for sepsis such as high doses of glucocorticoids, antiendotoxin monoclonal antibody, ibuprofen, anti-INF-antibodies and anti-interleukin (IL)-1 therapy had no impact on the mortality associated with ARDS so far^[29,30]. However, recently, activated protein C has been shown to reduce mortality in sepsis patients by novel antiinflammatory and anticoagulant mechanisms^[41]. A 96 h infusion of protein C resulted in 20% relative reduction in mortality in a large international multicenter trial^[31,32]. Efficacy of administration of a recombinant E_1 , E_3 -deleted adenovirus expressing heat shock protein (HSP-70) directly into the trachea of rats at the time of Cecal ligation and perforation, a standard model for sepsis and a subsequent ARDS-like syndrome were examined.

The two major isoforms of this family are the constitutively expressed HSP-73 and the stress inducible HSP-72. The latter has been widely studied and is thought to play a major role in the cytoprotection induced by stress response with decrease in dramatic edema and neutrophil accumulations^[33]. The HSP appear to represent a broad-spectrum defense mechanism, effective in protection against injury by maintaining and repairing intracellular proteins as a molecular chaperone^[34].

Corticosteroids: Corticosteroids reduce the production of a great number of inflammatory and profibrotic mediators by many mechanisms. Several prospective, multicenter, placebo-controlled studies have shown that patients with ARDS do not benefit from high doses of corticosteroids, administered early in the disease^[31,35]. However recent studies have suggested a potential benefit for use of corticosteroids in refractory, or the late (7-14 days from diagnosis) fibroproliferative stage of ARDS^[6,36].

Antioxidant therapy: In ARDS patients, oxidant stress increased and plasma antioxidant levels are reduced^[40]. Endogenous antioxidant system includes superoxide dismutase, catalase, glutathione, α -tocopherol, ascorbic acid and sulfhydryls^[27]. Prevention of oxidant-mediated tissue injury was beneficial in both *in vitro* and *in vivo* experiments^[37-39]. There is evidence that concentration and reduced activity of glutathione in bronchoalveolar lavage fluid of patient with ARDS is recovered by administration of N-acetylcysteine (NAC) and procysteine (L-2-oxothiazolidine-carboxylate). However, complete effect on plasma, erythrocyte, neutrophil and bronchoalveolar lavage (BAL), concentrations of glutathione in patients of ARDS may require about 10 days treatment^[40]. Early results of NAC therapy were promising, but several trials have found no difference in mortality, length of ventilatory support, or improvement in oxygenation in patients with established ARDS^[41,42].

Lisofylline and pentoxifylline: Pentoxifylline is a phosphodiesterase inhibitor that inhibits neutrophil chemotaxis and activation in animal models of ARDS^[43,44]. Limited clinical experience in humans suggests some beneficial effects^[45] but there is not enough information to allow definite recommendations for clinical use yet^[6]. Lisofylline, the more potent than pentoxifylline inhibits the release of free-fatty acids from cell membranes under oxidative stress and lower cytokine production, neutrophil activation, pulmonary neutrophil sequestration and attenuate lung injury in animal models. Unfortunately a recently completed phase III trial^[46] in ALI/ARDS patients showed no beneficial effect of lisofylline^[43].

Immunonutrition: The provision of adequate nutrition via the enteral or parenteral routes has become the standard of care for critically ill patients including those with ALI/ARDS^[6]. Parenteral nutrition has been used frequently in ALI/ARDS patients, but experimental and clinical trials suggest that enteral nutrition may be superior^[45]. The composition of nutritional supplementation in patients with ALI/ARDS is an area of ongoing research. Avoiding nutritional depletion while delivering a high fat, low carbohydrate diet to reduce carbon dioxide production and ventilatory demand seems appropriate for patients with ARDS. Another approach has been to supplement feeding with immunomodulatory nutrients such as arginine, glutamine, ribonucleotides and omega-3 fatty acids. Immunonutrition aims to influence inflammation positively and to protect gastrointestinal integrity. The aminoacids glutamine and arginine may be useful dietary additives for patients at risk of or with established ARDS^[47]. In patients with ARDS, enteral immunonutrition supplemented with antioxidants for at least 4 days was associated with reduced pulmonary neutrophil recruitment, improved oxygenation, a shortened duration of mechanical ventilation and reduced morbidity in terms of new organ failure^[48]. However, there was no difference in mortality between the control and treatment groups. A meta-analysis of 12 randomized controlled trials comparing critically ill medical, surgical and trauma patients given standard enteral nutrition with patients receiving immunonutrition suggested reduced rates of infection including nosocomial pneumonia, but again no effect on mortality^[49]. Generally real benefits of immunonutrition in surgical and trauma patients seem, but a long double blind, multicenter, randomized controlled trial is required^[7].

Prostaglandine E₁: Intravenous PGE₁ causes both pulmonary and systemic vasodilation and, in some critically ill patients, increase cardiac output and oxygen delivery^[50]. Although the effect on the pulmonary circulation is usually small, vasodilation is more marked under hypoxic conditions and the nebulized drug improves ventilation perfusion matching^[17]. PGE as a vasodilator also blocks platelet aggregation and decreases neutrophil activation. This agent showed promise in experimental and preliminary clinical studies of lung injury^[51]. However a multicenter study of 100 ALI/ARDS patients showed no evidence of reduced mortality in those treated with IV prostaglandin E₁^[52]. The dose of PGE, is limited by side effects, particularly systemic hypotension. More recent trials have used liposome technology to increase drug delivery while mitigating side effects^[53]. The use of a liposome itself is

associated with immune modulating effects including down regulation of neutrophil adhesion molecules. Liposomal preparation in a rodent model of ALI reduced pulmonary neutrophil infiltration and capillary leak. However, the results of phase II and III trials of liposomal PGE₂, showed that patients with ARDS receiving the drug has more rapid improvements in the PaO₂/FiO₂ ratio, but neither a survival benefit nor a reduced requirement for ventilatory support was found in the treatment group. Retrospective subgroup analysis suggested that high dose therapy might reduce the time to extubation^[54].

Anti IL-8 therapy and other potential anti-inflammatory strategies: Other anti-inflammatory strategies could be effective in attenuating lung injury or preventing its development in high-risk patients. One approach is to reduce the number of neutrophils that migrate into the extravascular space of the lung by interfering with neutrophil adhesion to the lung epithelium, or by reducing the release of chemotactic factors in the extravascular space^[6]. IL-8 levels are raised in the BAL fluid of patients at risk who ultimately develop ARDS. It is a powerful neutrophil chemo attractant derived from alveolar macrophages and other cells that are regulated by hypoxia/hyperoxia^[55]. Other potentially useful strategies for modulating inflammation in patients with ALI/ARDS include platelet-activating factor inhibitors, antiproteases, anticytokine therapies and agents designed to inhibit the coagulation cascade^[6]. Without any bleeding occurrence and remaining normal clotting parameters, ARDS can be safely treated with plasminogen activator^[56].

Thromboxane synthase and 5-lipoxygenase inhibitors: Thromboxane and leukotriens are in part responsible for the pulmonary hypertension and hypoxemia of ARDS. TXA₂ can initiate microvascular thromboses consisting of neutrophil and platelet aggregates that are responsible for perfusion abnormalities and recurrent ischemia-reperfusion injury to the lung. The vasoconstrictive effect of TXA₂ similarly contributes to impaired gas exchange^[57]. Leukotrienes (LT) are derived from arachidonic acid by 5-lipoxygenase. LTB₄ is a potent neutrophil chemokine while LTC₄ and LTD₄ cause pulmonary vasoconstriction, capillary leak and pulmonary edema. The role of leukotrienes in ARDS has been less well searched but bronchoalveolar lavage fluid from patients with ARDS contains increased concentration of LTB₄, LTC₄ and LTD₄, which may be markers for developing ARDS^[58]. Ketoconazole, a potent inhibitor of thromboxane synthase and 5 lipoxygenase reported to prevent the development of ALI/ARDS in high-risk surgical patients^[59].

Future of the ARDS treatment: Two gene therapeutics have been used to treat ARDS. In the first method plasmide cationic liposomal complexes containing the COX or cyclooxygenase gene are delivered intravenously. The gene is inserted into the endothelial cells (lipofection) and encodes enzymes to increase prostacycline and PG-E₂. This method has been successful in rabbits. In the second method plasmid cationic liposome complexes are used to place alpha1-antitrypsin into a variety of different cells. In cultured cells, alpha1-antitrypsin delivered cells had decreased IL-8 production and increased protection against RSV infection^[60].

The major mechanism in clearing lung edema fluid is the activity of sodium potassium ATPase pump located on the basolateral aspect of type II cells. Terbutaline and dopamine both increase the activity of this pump and enhance edema clearance. Gene therapy with a beta1 subunit of sodium potassium ATPase has also been shown to increase the activity of this pump^[61].

Treatment of ARDS using gene therapy is still not clinically viable. However, gene therapeutics, the transient expression of a gene using nonviral vectors to treat an acquired disease may have considerable utility in the management of ARDS in the future.

In another study use of a developed PAF (platelet activating factor) in activator in patients with primary sepsis reduced development of ARDS and mortality.

The second agent is IL-10, which is a natural anti-inflammatory substance. In a study in which patients with ALI have been randomized BAL fluid has shown a reduction in IL-8 and TNF in the treated population^[62].

CONCLUSION

Improved understanding of the pathogenesis of ALI/ARDS has led to important advances in the treatment of ALI/ARDS patients. Most pharmacological strategies used in ARDS have targeted the inflammatory response, although most anti-inflammatory strategies have been disappointing in clinical trials, further trials are underway to evaluate the effect of cytokine inhibitors, anti inflammatory cytokines, antiproteases and endotoxin agents and other approaches to modulate of inflammation in ALI/ARDS. Furthermore, because of wide overlap between sepsis and ARDS, the improvement in the treatment of sepsis may influence the incidence and outcome of ARDS. The recent success of activated protein C therapy for severe sepsis makes it likely that the severity of sepsis associated with ALI/ARDS will be attenuated by this new therapy. In the future of ARDS treatment lies in improvements in the management of multi-organ failure, then the pharmacological approach to

treating lung injury may change. An exciting new area of research is the modulation of alveolar epithelial function and healing that may provide an important new direction for treatment of ALI/ARDS.

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