

## REVIEW

# Pharmacological therapies for acute respiratory distress syndrome

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Nothing to declare

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### Abstract

Acute respiratory distress syndrome (ARDS) has no specific treatment, the only effective therapy currently being limited to minimizing potentially harmful ventilation and avoiding a positive fluid balance. These treatments could not be completely effective in severe disease and several measures must be undertaken simultaneously, including pharmacological therapies aimed at correcting the etiology or targeting the pathogenesis. In this review article we provide update on pharmacological thera-

pies in ARDS, showing their effect on outcome in recent trials.

### Introduction

Acute respiratory distress syndrome (ARDS) is a severe form of acute hypoxemic respiratory failure due to various direct or indirect lung insults [1]. Despite the heterogeneity of its causes, ARDS is characterized by a common final pathophysiologic pathway (non-cardiogenic pulmonary edema) and particular histopathology including diffuse alveolar damage, protein-rich alveolar edema, alveolar neutrophil influx, alveolar epithelium and capillary endo-

thelium injury with subsequent cell death, hyaline membrane deposition and microthrombi formation, type II alveolar cells, fibroblasts and myofibroblasts proliferation [2,3].

Due to its complex etiology and variable definitions, the exact ARDS incidence varies from 64.2 to 78.9 per 100.000 person years in the US, 75% of cases displaying a moderate or severe form [4,5]. In addition, ARDS accounts for 10% of intensive care unit admissions worldwide [6]. However, its incidence has been constantly declining during the last 20 years, mainly due to adoption of preventive measures for reduction of the nosocomial ARDS incidence [7,8,9]. ARDS mortality is between 26 and 58%, being influenced by disease severity (increases with hypoxemia severity) and etiology (lowest in trauma-induced ARDS, highest in sepsis related ARDS)[10]. Mortality remains still high even among ARDS survivors, many of them developing cognitive dysfunction, psychiatric illnesses or impaired physical and lung function, increasing the burden of the disease [11].

Despite its high incidence and severe outcomes, ARDS has no specific treatment, the only effective therapy currently being minimizing potentially harmful ventilation and avoiding a positive fluid balance. Thus, it becomes clear that the supportive measures designed for ARDS management are far from enough and a paradigm shift is fiercely needed. First, a better selection of patients at risk of ARDS and a bundle of measures adoption to prevent progression to ARDS is needed. Secondly, the discovery of an efficient therapy designed to reverse or modulate the characteristic proinflammatory and procoagulant response would certainly improve ARDS survival.

The focus of this article review is assessing the immunomodulatory pharmacotherapies employed for prevention or treatment of established ARDS and their effectiveness as stated in current literature.

### **Prevention therapies for ARDS**

Considering the multi-hit theory of ARDS pathogenesis and the fact that patients develop rarely ARDS since their hospital admission, but rather later during their hospitalization, recent studies have concluded that ARDS might be preventable and there is a window of opportunity when prevention could be employed in high-risk groups [9,12,13].

Several clinical scores have been developed in order to identify patients at high risk of ARDS. Currently, the best available tool, Lung Injury Prediction Score/LIPS evaluates multiple

predisposing conditions and risk modifiers and a cutoff value  $\geq 4$  has a sensitivity of 0.69, specificity of 0.78 [12]. Even SpO<sub>2</sub>/FiO<sub>2</sub> measured within 6h since admission can be a powerful risk predictor, while combining serum levels of angiopoietin-2 with LIPS improves its prediction power [14,15].

Apart from several supportive measures, bundled together in the Checklist for Lung Injury Prevention (CLIP), multiple systemic or inhalatory pharmacologic interventions targeting the pathophysiological pathways of ARDS are currently emerging [2,9].

### **Systemic preventive therapy**

#### ***Aspirin***

In preclinical studies it was shown that aspirin inhibits neutrophil-platelets interaction, decreases inflammation and edema, decreases intrapulmonary shunt and promotes resolution of inflammation through modulation of leukotriene and prostaglandins levels [16,17,18,19]. Although animal studies and several observational studies have returned positive results, the latest phase 2b randomized clinical trial has reported no effect of preventive aspirin administration on ARDS incidence at one week [20,21]. Even if administration of aspirin for ARDS prevention was ineffective, there is an ongoing phase 2 RCT that aims to study the effect of low dose aspirin as a treatment for ARDS (ClinicalTrials.gov ID: NCT02326350).

#### ***Steroids***

As potent anti-inflammatory agents, systemic steroids have long been proposed in clinical trials as the ideal molecule in ARDS management. Up to now, four randomized trials using high-dose methylprednisolone in septic shock patients considered to be at high risk of ARDS proved no benefit of steroid treatment and even a higher incidence of ARDS and mortality [22, 23]. However, these findings results should not be considered a drawback because studies were designed in the '90s and since that time better scores for ARDS risk evaluation have emerged and thus the possibility for better conducted prevention trials has flourished [24].

#### ***Statin***

Originally developed for the treatment of dyslipidemia, statins are shown to exhibit immunomodulatory effects [2,22]. Although pre-clinical studies have returned positive outcomes

[25,26], prospective observational human studies have revealed mixed results, some investigators proving that prehospital statin use might be protective against sepsis and acute lung injury [27], while others failing to prove any statistically significant benefit [29]. In addition, a recent 2016 meta-analysis has concluded that prior statin therapy does not lower the risk of developing ARDS [30].

### **Angiotensin-converting enzyme (ACE)**

As pulmonary angiotensin-converting enzyme activity may play a role in ARDS pathogenesis, renin-angiotensin-aldosterone system (RAAS) blockers have sparked researchers' interest [31]. Although animal studies have reported a benefit of RAAS blockers in ARDS prevention [32,33], conflicting results have issued from human observational studies: while some suggested a protective effect of prehospital therapy with these agents [34], investigators analyzing the LIPS cohort proved that, apart from conferring no benefit, outpatient therapy with RAAS blockers may actually increase mortality in ALI patients [35].

### **Vitamin D**

Vitamin D is a modulator of immune responses with controversial antioxidant activity [36]. Vitamin D deficiency was associated with an exaggerated alveolar inflammation, epithelial damage, hypoxia and a higher risk of acute respiratory failure in critically ill patients [37,38]. Lower levels of vitamin D matched an increased prevalence of ARDS but without any influence on mortality [39].

### **Carnosine**

Carnosine, a small dipeptide with antioxidant activity which shows promising results in suppressing pulmonary edema, tissue injury and inflammation in a murine model, while decreasing reactive oxygen species production in vivo, with potential benefits in suppressing the onset and progression of ARDS [40].

### **Dilmapimod and bevacizumab**

Newly employed molecules for ARDS prevention are dilmapimod (SB-681323) and bevacizumab. SB-681323 is a selective inhibitor of p38 alpha mitogen-activated protein kinase, able to reduce lung injury due to pancreatitis and burns in preclinical studies. A phase 2a ran-

domized clinical trial investigating its efficacy in preventing ARDS in trauma patients has proven increased tolerability and a reduced incidence of ARDS in the study cohort [41]. Bevacizumab, a recombinant humanized monoclonal antibody inhibiting vascular endothelial growth factor A, was also the subject of a phase 2 clinical trial for ARDS prevention, recently withdrawn due to a lack of funding [42].

## **Inhaled preventive therapies**

### **Corticosteroids**

Although results from previous studies using intravenous administration of corticosteroids were not promising, the advent of inhaled delivery steroids, bypassing the systemic side-effects of corticotherapy, has yielded positive results in attenuating lung injury in animal models [43].

### **Combined corticosteroids and beta-agonists**

The anti-inflammatory effect of both beta-agonists and inhaled corticosteroids raised the hypothesis of using them in tandem. In a phase IIa trial the combined inhaled therapy increased oxygenation, lowered ARDS incidence and shortened hospital length of stay whilst *proving to be the first safe and effective intervention in preventing/ameliorating ARDS* [44].

### **Heparin**

One mechanism in the physiopathology of ARDS is the fibrin accumulation/deposition via local inflammation and coagulation impairment. The anti-inflammatory effects of heparin are due to its binding to other "heparin binding proteins" such as complement proteins, interferons, fibroblast growth factor and other cytokines [45]. In smoke inhalation-associated ALI, inhaled anticoagulation regimens improve survival and decrease morbidity [46].

## **Therapies for ARDS treatment**

### **Neuromuscular blocking agents**

Until recently, a "less is more" strategy has been applied to neuromuscular blocking agents (NMBA) in ARDS. NMBA use influences ARDS mortality through a mild anti-inflammatory effect, respiratory muscles oxygen consumption's decrease, arterial and mixed venous oxygenation's increase and ventilator-induced lung

injury (VILI) prevention [47]. Cisatracurium, a nondepolarising NMBA has been shown to inhibit inflammatory responses and to regulate the immune functions in sepsis in a murine model by [48]. NBMA treatment is associated with decreased level of the epithelial and endothelial lung injury biomarkers and attenuate systemic inflammation in patients with severe ARDS [49]. In present, NMBA are part of the recommended pharmaceutical arsenal employed to treat acute ARDS.

### **Macrolide antibiotics**

Animal models studies of ARDS suggest that macrolides possess immunomodulatory and anti-inflammatory effects. In vitro experiments macrolides reduce TNF $\alpha$ , IL1 $\beta$  and IL6 levels in a dose dependent-manner [50]. They also limit immune complex-induced lung injury in rats by inhibiting the inducible nitric oxide synthase gene expression and cytokine release [51]. Moreover, macrolides are used for their immunomodulatory effects in chronic lung diseases that include diffuse panbronchiolitis, cystic fibrosis, chronic obstructive pulmonary disease and asthma [52]. A low-dose and long-term macrolide treatment showed a reduction in IL1 $\beta$  and IL8 levels of the bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis [53].

These non-bacterial effects of macrolide treatment may also be advantageous in the treatment of ARDS. Although to date there are no randomized clinical studies, several secondary analysis studies have associated the use of macrolides with beneficial effect and even decreased mortality. Walkey et al analyzed the data collected from an ARDS Network RCT - Lisofylline and Respiratory Management of Acute Lung Injury Trial. Use of erythromycin and azithromycin within the first 60 hours of ALI diagnosis, for a median period of 4 days was associated with lower 180-day mortality and shorter time to successful discontinuation of mechanical ventilation [54]. Similarly, Kawamura et al found that use of intravenous azithromycin starting within 24 h of ARDS diagnosis is associated with a lower mortality and a shorter time of mechanical ventilation [55]. Simonis et al found that low-dose erythromycin, prescribed for another reason than infections, was associated with reduced 30-day mortality in the group of patients with low inflammatory biomarkers levels or non-pulmonary type of ARDS [56].

### **Granulocyte/macrophage colony-stimulating factor**

The resident alveolar macrophages' response to pathogen recognition consist of

TNF $\alpha$  release which induces epithelial granulocyte/macrophage colony-stimulating factor (GM-CSF) expression[57]. GM-CSF regulates surfactant homeostasis, modulates the immune functions of alveolar macrophages and dendritic cells and promotes epithelial repair processes in viral infections as well as bacterial pneumonia[58,59]. Moreover, patients who survive ARDS have higher concentrations of GM-CSF in their bronchoalveolar lavage fluids. In a RCT including 131 patients with ARDS, intravenous GM-CSF has been administered for 14 days, showing no improvement in ventilator-free days, 28-day mortality or organ failure[(60)].

However, a report on six patients with pneumonia-associated ARDS who received inhalational GM-CSF revealed a significant improvement of oxygenation, an increase in lung compliance and a decrease in morbidity scores. Furthermore, a RCT that evaluates the efficacy and safety of inhaled GM-CSF in patients with pneumonia associated ARDS is ongoing (ClinicalTrials.gov ID: NCT02595060).

### **Vitamin C**

Vitamin C administration in critical patients decreases the vasopressor therapy and mechanical ventilation duration, without affecting on 30-day mortality[61]. Data about its effect on ARDS patients are quite limited, with only a few case reports published in the literature (first in 2016), but with positive results [62,63,4]. There is currently an ongoing 2017 study that evaluates the impact of high dose of Vitamin C, 10 grams per day, on ARDS patients.

### **Ineffective therapies**

Multiple physiological mechanisms are disturbed within the ARDS, and so many adjuvant therapies have been used over time in an attempt to restore the normal function of the morphological unit of the lung. Many of them have proved ineffective.

#### **Antioxidants**

Over the last 20 years, many studies have shown that oxidative stress has negative impact on the evolution of critical patients, and so it has been considered that antioxidant medication can improve the outcome of critical patients. In 2013, Jain M showed that the effect of antioxidants can be both positive and negative, depending greatly on time and dose administered[65].

#### **N acetylcysteine**

N acetylcysteine is one of the most used antioxidants in intensive care units. N-ace-

tyl-cysteine (NAC) is a known compound that reduces oxidative stress by maintaining intracellular stores of reduced glutathione. NAC has been shown to exhibit prophylactic effects on the development of LPS-induced ALI in animal models, limiting TNF $\alpha$  production, as well as decreasing fibroproliferation in ventilation-induced lung injury[66,67]. Adhikari et al demonstrated that short-term mortality was not influenced by NAC administration in ARDS[68]. More, if non administered during the first 24 hours of ARDS, NAC produced myocardial depression[69]. In a meta-analysis from 2017, it was noted that the time spent in the ICU was reduced without influencing the 30-day mortality and gas exchange (PaO<sub>2</sub> / FiO<sub>2</sub>) in patients receiving NAC[70].

### **Glutamine**

Most literature data suggest that glutamine administration either has no benefit or it has a negative effect on the evolution of critical patients[71]. However, in 2016, an experimental study on rat or mice lungs with ARDS suggests that glutamine administration could be beneficial in ARDS[72].

### **Vitamin E**

Vitamin E is an antioxidant incorporated in cell membranes with the role of protecting polyunsaturated fatty acids against peroxidation demonstrating a decrease in its concentration in patients with ARDS, along with increased plasma levels of lipoperoxides[73]. A study which included critically ill surgical patients revealed a decrease in the incidence of ARDS and pneumonia, as well as a decrease in the duration of hospitalization and mechanical ventilation, mortality rates and proinflammatory cytokine levels in the bronchoalveolar lavage fluid in the case of patients receiving prophylactic, enteral, vitamin C and vitamin E in the first 24 hours – either postoperatively or after trauma[74]. A similar study on critically ill patients demonstrated that the simultaneous enteral administration of vitamin C and vitamin E had no impact on the reduction in ARDS incidence, but had a positive impact on the duration of mechanical ventilation and all-cause mortality[75]. However, there are no studies evaluating the effectiveness of the administration of vitamin E as a single agent in the prevention and/or treatment of ARDS.

### **Beta-carotene**

Beta-Carotene is a membrane antioxidant with pro-oxidative properties at partial pressures of oxygen greater than 150 mmHg, with a decreased plasma concentration in ARDS[76].

Although the association of beta-carotene with other antioxidants and omega 3 or GLA fatty acids has been studied, without improving the outcome, the administration of beta-carotene as treatment has not been yet evaluated[77].

### **Omega 3**

Omega 3 (n-3) fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) lead to the formation of eicosanoids that are less reactive and less inflammatory than the ones formed by omega 6 (n-6) fatty acids. The n-6 gamma-linolenic acid (GLA) associated to omega 3 fatty acids reduces the production of leukotriene and increases the production of prostaglandin E<sub>1</sub>. [78]. There is an inverse correlation between the risk of developing ARDS and the levels of omega-3 and GLA fatty acids. Previous studies have demonstrated the relation between dietary supplementation with EPA and GLA and the reduction of lung inflammation, as well the improvement of clinical outcome[79]. Despite this evidence, a multicenter RCT published in 2011 has not shown any association between the dietary supplementation with EPA, GLA, DHA or antioxidants (vitamin C, vitamin E, beta carotene, zinc, selenium, taurine, L-carnitine) and the improvement of clinical outcome, pulmonary physiology, and systemic inflammatory markers. Moreover, this supplementation turned out to be potentially harmful by decreasing the number of ventilator-free and ICU-free days[77].

### **Statins**

Since statins have an anti-inflammatory effect and interfere with endothelial modulation, they have been thought to have a positive effect on ARDS. Multiple literature studies have shown that statin use has had no impact on mortality, mechanical ventilation duration or ICU hospitalisation[80,81]. In 2018, Feng made a meta-analysis to show that although statin use does not have a direct effect on mortality and sepsis, it reduced the number of days of mechanical ventilation, the SOFA score[82].

### **Surfactant**

Surfactant's use in ARDS in children, raised the hypothesis of its effectiveness also in the ARDS in adult patient. A meta-analysis including 1270 patients showed that the surfactant's use had no impact on mortality but produced an improvement in oxygenation[83]. In 2019, Shan-Shan and his team concluded after 11 studies involving 3038 patients that there was no improvement in mortality or oxygenation in patients treated with exogenous surfactant[84].

### **Keratinocyte growth factor**

Keratinocyte growth factor (KGF) is specifically secreted by fibroblasts and is one of the factors contributing to the re-epithelization of alveolar cells, especially type II pneumocytes, thus reducing capillary permeability and alveolar edema. In a first study, keratinocyte growth factor administration has been shown to produce an alveolar medium that augments the healing of cellular lesions, which means that its use in ARDS may be beneficial[85]. But McAuley and his colleagues found that the mortality rate was higher in the KGF group than in the placebo group[86].

### **Neutrophil elastase inhibitor (sivelestat)**

Neutrophil elastase is a serine protease that is capable of degrading elastin, collagen and pulmonary surfactant, as well as inducing pro-inflammatory cytokines. Sivelestat, a drug approved in Japan and South Korea, slows down the lung injury progression by inhibiting the pathophysiological pathways, as shown in several studies on animals. The decrease in plasma levels in neutrophil elastase activity linked to sivelestat administration was not associated to PaO<sub>2</sub> / FiO<sub>2</sub> ratio or SOFA score[87]. STRIVE multicenter study from 2004, a double-blind, placebo-controlled trial, demonstrated that the administration of sivelestat in patients diagnosed with acute lung injury does not improve the 28-day mortality rate or the number of ventilator-free days. Moreover, the all-cause mortality rate at 180 days was significantly higher among patients treated with sivelestat[88]. A further meta-analysis from 2010 of randomized controlled trials, revealed that sivelestat does not decrease mortality in critically ill patients with ARDS[89].

### **Beta agonist**

Studies on animals have demonstrated the resolution of pulmonary edema by increasing sodium transport through the alveolar epithelium, mediated by beta 2 receptors[90]. Clinically, the administration of inhaled salmeterol led to a reduction in the incidence of high-altitude pulmonary edema[91]. Based on these findings, scientists started wondering whether beta 2 agonists could be used in the treatment of ARDS. The first randomized clinical trial, Albuterol to Treat Acute Lung Injury (ALTA), did not reveal any differences between patients

treated with albuterol (salbutamol) and placebo in ventilator-free days number, mortality before hospital discharge, as well as occurrence of cardiac arrhythmias[92]. The second study, BALTI-2, studied efficiency of continuous intravenous administration of beta 2 agonists (salbutamol) in ARDS, but had to be discontinued due to an increase in the 28-day mortality rates in the salbutamol group[93].

### **Prostaglandin E1**

Earlier studies, performed on a small number of patients, have demonstrated the beneficial effects of prostaglandin E in reducing pulmonary and systemic vasoconstriction, increasing arterial oxygen tension, cardiac output, oxygen delivery and oxygen consumption, as well as increasing pulmonary compliance and decreasing ventilator dependence[94]. Subsequently, a randomized multicenter clinical trial compared the intravenous administration of liposomal prostaglandin E with placebo in patients with ARDS. The treatment based on prostaglandin E shortened the time of improvement of the PaO<sub>2</sub> / FiO<sub>2</sub> ratio, but did not, however, reduce mortality rates or the number of ventilator-free days[95]. PGE1 administration through inhalation improved oxygenation, lowered pulmonary artery pressure, caused arterial hypotension as a side effect, but a clinical benefit cannot be demonstrated[96].

### **Nitric oxide**

Inhaled nitric oxide causes selective pulmonary vasodilation with improved matching of perfusion with ventilation, as well as decreased pulmonary artery pressure, without causing systemic vasodilation[97]. Despite the transient improvement in oxygenation, a Cochrane systematic review revealed that NO administered through inhalation did not have any benefit in terms of survival rates. Furthermore, inhaled NO was associated with a higher incidence of impairment of renal function[98].

### **Recombinant human activated protein C (rhAPC)**

Starting from the close link between inflammation and clotting, it has been demonstrated that alveolar deposits of fibrin and vascular microthrombi perpetuate alveolar inflammation and alveolar capillary barrier dysfunction[99]. Furthermore, ARDS patients have been shown to exhibit a decrease in plasma levels of protein C and an increase in plasma levels of inhibin-1

plasminogen activator – the magnitude of these quantitative changes correlates with mortality, ventilator support and organ dysfunction[100]. Despite this findings, a RCT concluded that administering rhAPC to patients with ARDS neither improved the pulmonary leak index, assessed by measuring the intravascular-alveolar transport ratio of the transferrin-bound isotope  $^{67}\text{Ga}$ , nor did it bring clinical benefits[101].

### Conclusions

Despite multiple pharmacological therapies investigated with encouraging experimental and early clinical results, to date there are few effective agents for prevention and treatment of ARDS. The heterogeneity of the therapeutic measures studied is linked to the heterogeneity of the ARDS syndrome that might require a more targeted or personalized management addressed to different biologic pathways activated in each type of ARDS illness. The principles of ARDS treatment should include a valuable method of identifying at-risk subjects and selecting those most likely to benefit from early interventions to prevent progression, diagnosis criteria and specific etiological treatment and finally, ARDS severity classification. All measures must be undertaken simultaneously in order to improve survival.

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