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The Pharmacology of Acute Respiratory Distress Syndrome

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is a common respiratory complication of critical severe illness or injury. Despite steady improvement in outcomes over the last three decades, ARDS remains a common cause of morbidity and mortality in pediatric and adult intensive care units. Due to its extensive burden, ARDS has been the focus of numerous multi-center clinical trials which have attempted to translate animal, *ex vivo,* and small single center studies into wider practice. Since the results of several of these large studies have been recently published, we sought to review the pharmacology of ARDS, summarize the major non-pharmacologic interventions shown to improve outcome, and update the reader on evolving therapies which may enter clinical practice in the coming decade.

Keywords: Acute lung injury; Acute respiratory distress syndrome; Critical care

Abbreviations: ALI: Acute Lung Injury; ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; iNO: Inhaled Nitric Oxide

Introduction

Acute lung injury (ALI) and the more severe acute respiratory distress syndrome (ARDS) are common complications in intensive care units (ICUs) being present in approximately 40% of admissions [1]. Although there is wide variability in reported mortality rates in the literature, the most recent comprehensive assessment determined that the average mortality from ARDS is approximately 40% [2]. Due to its high economic and societal burden, many pharmacologic and non-pharmacologic trials have been undertaken to reduce its associated morbidity and mortality. Due to the recent publication of several large trials focused on new pharmacologic therapies for ARDS, we sought to provide an updated guide for intensive care physicians and pharmacists.

What are Acute Lung Injury and Acute Respiratory Distress Syndrome?

Acute lung injury (ALI) is a syndrome of acute-onset hypoxemia and non-cardiogenic pulmonary edema in the setting of critical illness or injury. Acute respiratory distress syndrome (ARDS) is a more severe form of ALI. Despite a progressive decline in mortality rate reported in observational trials [3], ARDS is still associated with significant mortality in adult and pediatric intensive care units.

Traditionally, ARDS has been separated into three stages (Figure 1). In the exudative phase, reduced capillary and lung epithelial cell integrity permits the influx of protein-rich fluid into the alveolar space leading to surfactant neutralization [4-6]. In this phase inflammatory cells potentiate lung injury by release of inflammatory mediators [7,8]. In the proliferative phase, proliferation of lung interstitial cells thickens airspace walls and reduces diffusion capacity [9,10]. The proliferative stage can be followed either by resolution with near-normalization of pulmonary function [11] or progression to the third stage--the fibrotic stage. In this stage, lung interstitial cells synthesis increasing amounts of extracellular matrix leading to a progressive decline in lung function and often death [12]. In reality, there is substantial overlap of these three stages making it impossible to clearly define which is predominant in any given patient. This heterogeneity of disease phenotype likely accounts for why therapies targeted to specific aspects of the disease such as surfactant dysfunction, oxidative injury, or inflammation have shown limited effectiveness in large clinical trials.

How are ALI and ARDS Diagnosed?

ARDS was first described by Ashbaugh et al. in 1967 as syndrome of acute onset hypoxemia with bilateral chest infiltrates [13], but a commonly accepted definition of ALI and ARDS was not available until 1994 with the American-European Consensus Conference definition [14]. The AECC definition required:

1. Acute onset hypoxemia with an arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio of ≤ 300 (ALI) or ≤ 200 (ARDS).
2. Bilateral lung infiltrates on chest X-ray.
3. Absence of left atrial hypertension as evidenced by a pulmonary capillary wedge pressure of ≤ 18 cm mm Hg.

The AECC report further described ALI and ARDS as either direct (e.g. pneumonia, inhalational injury, or aspiration) or indirect (e.g. burns, trauma, sepsis).

In response to criticisms regarding the invasiveness of left arterial atrial pressure measurements, the failure to account for positive end expiratory pressure (PEEP), and a high sensitivity but low specificity compared to autopsy findings [15], in 2012 the European Society of Intensive Care Medicine created the Berlin Definition of ARDS [16] which eliminated the term ALI, incorporated PEEP, and allowed for exclusion of cardiogenic pulmonary edema on less stringent grounds. The Berlin Definition of ARDS required:

1. Onset of hypoxemia within one week of insult.

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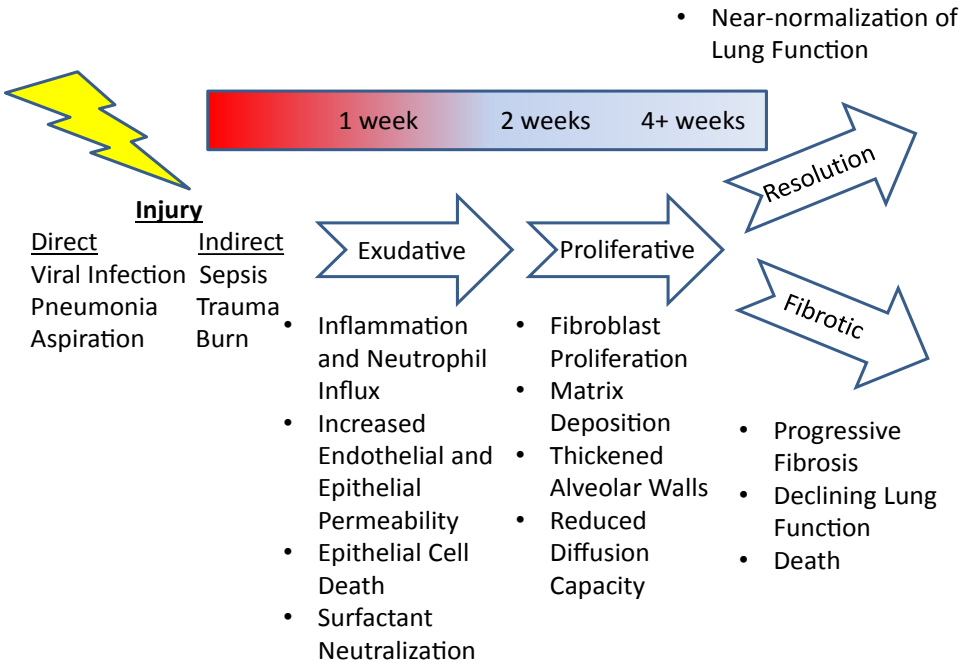

Figure 1: Time Course of Acute Lung Injury. Following a direct or indirect lung insult, the lung becomes inflamed with reduced integrity of endothelial and epithelial cell barriers. Influx of protein-rich fluid leads to surfactant neutralization which in turn reduces lung compliance. Epithelial cell death leads to basement membrane denudation which potentiates the inflammatory response. Within a week, the inflammatory response transitions to a fibro-proliferative one with increased numbers of pulmonary fibroblasts and matrix deposition in the alveolar interstitium. This also leads to reduced lung compliance as well as reduced gas diffusion capacity. Several weeks after the initial insult, there is either resolution of injury, or progressive fibrosis leading to progressively declining lung function and death.

2. Bilateral chest opacities not explained by lung collapse, effusion or nodules.
3. Pulmonary edema not fully explained by fluid overload or cardiac failure.
4. Mild, Moderate and Severe classification with.

a. Mild: PaO_2/FiO_2 200-299 with PEEP ≥ 5 cm H_2O.

b. Moderate: PaO_2/FiO_2 100-199 with PEEP ≥ 5 cm H_2O.

c. Severe: PaO_2/FiO_2<100 with PEEP ≥ 5 cm H_2O.

The Berlin Criteria provide a more accurate classification scheme which will be useful in future clinical trials. All of the clinical trials described in this review utilized the AECC criteria. In evaluating each study, clinicians should be cognizant of the study group and consider whether treatment effect could have been masked by group heterogeneity.

What are the Non-Pharmacologic Therapies for ALI and ARDS?

Arguably, the improvement in ARDS outcomes over the past three decades can be principally attributed to improved treatments for the triggers of ARDS and the development of strategies to minimize ventilator induced lung injury [17,18].

Methods aimed at minimizing ventilator-induced lung injury are termed the "Lung Protective Strategy." In this strategy, PEEP is used to maintain alveolar recruitment (keep the alveoli open) while peak inspiratory pressures are limited by using smaller tidal volumes and tolerating elevated arterial carbon dioxide levels (termed permissive hypercapnia). One of the few positive trials in ARDS demonstrated that 6 mL/kg tidal volume reduced ARDS mortality by 9% compared to 12 mL/kg tidal volumes [19]. Use of higher levels of PEEP or oscillatory ventilation improved oxygenation [20-22] but did not improve outcome with a trend towards increased mortality in adult patients randomized to oscillatory ventilation [21]. Likewise, both prone positioning and lung recruitment maneuvers (a temporary increase in airway pressure to open atelectatic alveoli) improved oxygenation but not ventilator days or mortality [23-25]. The fluid and catheters treatment trial (FACTT) demonstrated that a restrictive fluid strategy reduced ventilator days but not mortality compared to a more liberal fluid management strategy [26]. Extracorporeal membranous oxygenation (ECMO) was shown to improve mortality in an adult trial where ARDS patients were randomized to conventional management or transport to a central ECMO center; however, there was no difference in ECMO and control groups within that referral center [27].

In summary, the only proven non-pharmacologic therapies for ARDS are the use of low tidal volume ventilation and a restrictive fluid management strategy.

What Local-Acting Pharmacologic Therapies Are Available for ARDS?

Surfactant Replacement Therapy

Acute lung injury leads to surfactant neutralization and reduced lung compliance. The surfactant recovered from BAL fluid in patients with ARDS demonstrates alterations in both the phospholipids and protein profiles which reduce its ability to decrease surface tension [28]. Exogenous surfactant has a long history and documented benefits for use in neonates with surfactant deficiency secondary to prematurity [29], and numerous animal trials demonstrating improvement in induced lung injury models led to a series of randomized trials in adult and pediatric ARDS.

Despite promising initial studies involving small numbers of patients, large randomized clinical trials of surfactant replacement therapy in adult ARDS have been negative. The pooled data of two multicenter, randomized, double-blind trials performed in North America, South Africa, and Europe (448 patients) with ARDS found that surfactant protein c-enriched recombinant surfactant did not improve survival or increase ventilator-free days. However, the authors observed an improvement in gas exchange during the 24 hour treatment period [30]. The use of nebulized synthetic surfactant in a multicenter, prospective, randomized, double-blind, placebo controlled study of 725 adults with sepsis-associated ARDS demonstrated no improvement in oxygenation, 30 day survival, length of ICU stay, or ventilator-free days [31]. The most recent adult surfactant trial randomized 418 ARDS patients to placebo or endotracheal administration of a porcine-derived surfactant and demonstrated trend towards worse outcomes in adults receiving surfactant [32].

The role of surfactant replacement in pediatric ARDS has recently become clear. While preliminary trials suggested benefit of surfactant replacement in pediatric ARDS due to direct lung injury, a recent larger trial failed to show benefit. In 1999, Willson et al. [33] performed a multi-center, randomized, and controlled trial that included 42 pediatric patients that were given Calfactant® at a dose of 80 ml/m^2 endotracheally for the treatment of acute hypoxic respiratory failure. They observed improvement in oxygenation, reduced ventilator days, and decreased length of stay in the intensive care unit [33]. This study was included in a 2007 meta-analysis that included a total of 314 pediatric patients enrolled in six randomized controlled trials in which subjects were given surfactant for either ALI/ARDS and found a reduction in mortality (RR=0.7; 95% CI=0.4 to 0.97, P=0.04) and a 2.5 day increase in ventilator free days (95% CI=0.3 to 4.6 days; P=0.02) [34]. However, a recent randomized, blinded, placebo-controlled trial performed in 24 children's hospitals in six different countries was terminated early for futility after interim analysis of the data collected from 110 patients was evaluated. The trial included children from 37 weeks post-conceptual age to 18 years with acute lung injury or acute respiratory distress syndrome due to direct lung injury. Subjects were given up to three doses of 30 mg/cm of height of Calfactant® or placebo within 48 hours of intubation. At the second interim analysis, the only significant difference between the groups was hospital-free days (10.4 in treatment vs. 6.4 in surfactant; p=0.01). There was no immediate difference in oxygenation and mortality did not differ between groups [35].

Although surfactant replacement therapy clearly has a role in the care of neonates with respiratory distress syndrome, it does not have a role for routine use in pediatric and adult patients with ARDS. This difference is likely due to the surfactant neutralization of ARDS compared to the surfactant deficiency of neonatal respiratory distress syndrome.

Inhaled Beta-2 Agonists

In patients with acute lung injury and the acute respiratory distress syndrome, lung endothelial cell damage and inflammation increase vascular permeability leading to pulmonary edema. Treatment with β2-agonists may increase the rate of clearance of pulmonary edema by increasing cyclic-AMP which increases chloride and sodium transport and improves the reabsorption of alveolar fluid. This effect has been well documented in in animals and human lung explants [36].

Despite promising animal and single-center human studied, β2-agonist therapy was not shown to be beneficial in two randomized trials. The first was a multicenter, placebo-controlled, parallel-group, randomized trial of intubated and mechanically ventilated adult patients. Within 72 hours of ARDS onset, the subjects were treated with intravenous salbutamol 15 mcg/kg/hour (n=162) or placebo (n=164) for up to 7 days. Recruitment was stopped after the second interim analysis because of safety concerns. The investigators found that salbutamol increased 28 day mortality with increased rates of tachycardia and arrhythmia [37]. In 2011, a randomized, placebo-controlled trial evaluating the use of aerosolized albuterol for the treatment of acute lung injury that included 282 patients on mechanical ventilation found that aerosolized albuterol did not reduce ventilator free days or improve mortality. The authors did note an increase in ventilator free days in patients who presented with shock, but there was no change in mortality rate in this subset of patients [38].

Despite the promising data observed in animal and *ex vivo* lung models, β2-agonists have not shown benefit in the treatment of ALI and ARDS in clinical trials. However, there may be a subset of patients, including those with a history of airway reactivity and those presenting in shock, who may benefit from this therapy. Furthermore, efficacy in a younger patient population without the cardiovascular risks of adult ICU patients has not been evaluated.

Inhaled Nitric Oxide

Inflammation and disruption of the alveolar-capillary membrane results in ventilation and perfusion mismatch in the setting of ARDS. Inhaled nitric oxide selectively vasodilates vascular smooth muscle in ventilated areas of the lung to help redistribute blood flow away from areas of low ventilation and therefore decrease mismatching [39].

Case reports and small trials have found that iNO improved oxygenation and pulmonary vascular resistance in patients with acute lung injury. However, no differences in mortality or duration of mechanical ventilation were demonstrated in studies of large numbers of patients. In a meta-analysis of 1,237 patients with ALI or ARDS from 12 trials receiving iNO between 1 and 40 ppm, investigators found no significant reduction in mortality, duration of ventilation, or ventilator-free days. Interestingly the authors did not find a reduction in pulmonary arterial pressure. However, iNO did improve oxygenation [40]. A systematic review of five randomized, controlled trials of inhaled nitric oxide vs placebo for acute hypoxemic respiratory failure (including ALI, ARDS, and other diagnoses) in adults and children concluded that inhaled nitric oxide improved oxygenation for up to 72 hours but had no effect on mortality or the duration of mechanical ventilation [41].

The current body of evidence does not support the use of inhaled nitric oxide as standard therapy for the treatment of ALI or ARDS. However, it can improve oxygenation and reduce pulmonary arterial pressure and may be beneficial in patients with severe hypoxemia or concurrent pulmonary hypertension.

What Systemic Pharmacologic Therapies are Available for ALI?

Corticosteroids

Corticosteroids have multiple mechanisms by which they can slow the inflammatory cascade associated with ALI and ARDS. By binding to the glucocorticoid receptor, corticosteroids suppress gene transcription of pro-inflammatory cytokines, enhance expression of anti-inflammatory proteins, and inhibit neutrophil activation and adhesion to endothelial cells [42]. Early studies utilized corticosteroids in an attempt to prevent progression of ALI to ARDS and potentially reverse the inflammatory damage to prevent fibrosis.

The results of clinical trials evaluating the use of corticosteroids have had mixed results. Several studies have concluded that corticosteroids reduce the duration of mechanical ventilation but have no positive effect on mortality or prevention of ARDS, and other trials have shown improvement in survival and reduction in the duration of mechanical ventilation.

A randomized, double-blind, placebo controlled trial of 90 patients by Meduri et al. [43] evaluated the administration of methylprednisolone within 72 hours of the onset of ARDS for up to 28 days of therapy and found a significant reduction in inflammatory markers, improvement in lung injury, reduction in duration of mechanical ventilation, ICU stay, and ICU mortality. There was no increased rate of infection in the treatment arm. The steroid protocol used was a loading dose of 1 mg/kg followed by 1 mg/kg/day from day 1 to day 14, 0.5 mg/kg/day from day 15 to day 21, 0.25 mg/kg/day from day 22 to day 25, and 0.125 mg/kg/day from day 26 to day 28. The taper was advanced to 0.5 mg/kg/day if the patient was successfully extubated within the first 14 days of therapy [43]. A randomized, double-blind, placebo controlled trial performed in 180 patients with ARDS diagnosed for at least 7 days compared 21 days of methylprednisolone to placebo and found no 60 day mortality benefit. This study utilized a similar treatment protocol to that used in the Meduri trial. In patients who were started on steroids on day 14 or later of illness, there was an increase in mortality. However, methylprednisolone did increase ventilator-free days and improved oxygenation, lung compliance, and blood pressure. They found no increase in infection rates, but steroids were associated with a higher rate of neuromuscular weakness [44]. However, a secondary analysis of the 60 day survivors of this study found no association with methylprednisolone and the incidence of neuromuscular weakness [45]. A systematic review and meta-analysis that included five cohort studies and four randomized, controlled trials for a total of 648 total patients showed a trend toward mortality reduction. The review also noted improvement in length of ventilator-free days, length of ICU stay, multiple organ dysfunction scores, lung injury scores, and improvement in oxygenation. The authors found no increase in infection or neuromuscular weakness. The authors did note significant heterogeneity between the studies which is important when interpreting the results of meta-analysis especially those including a small number of trials [46].

The routine use of corticosteroids in patients with persistent acute respiratory distress remains controversial. If corticosteroids are initiated, it may be most beneficial to do so before day 14 of ARDS onset. Other medications that increase the risk of neuromuscular weakness, such as neuromuscular blockers, should be avoided if possible in patients on prolonged course of corticosteroids. Steroids should also be used with caution in patients confirmed or presumed infection.

Neuromuscular Blockade

The principal rationale for the use of neuromuscular blockers in patients with ALI and ARDS is to facilitate mechanical ventilation and reduce asynchrony with the ventilator. In general, as the severity of ARDS increases the use of neuromuscular blockers tends to increase [47].

A randomized, controlled, multicenter trial that included 56 adult ICU patients with ARDS compared 48 hours of neuromuscular blockers to placebo and found a higher PaO_2/FiO_2 ratio that was sustained for up to 120 hours after randomization. The investigators also found a reduction in ventilator support requirements and concluded that NMBs are associated with a sustained improvement in oxygenation in patients with ARDS [48]. These results were replicated in a larger randomized by Papazain et al. [49] in a double blind, multicenter trial that included 340 adult patients within 48 hours of onset of severe ARDS. The investigators randomly assigned patients to cisatracurium or placebo for 48 hours. They found a decrease in 90 day mortality after adjusting for baseline severity of lung injury, and there was a statistically significant decrease in 28 day mortality in the NMB group. They found no difference in ICU-acquired neuromuscular weakness [49].

Neuromuscular blockers should be considered to facilitate mechanical ventilation and reduce asynchrony with mechanical ventilation. The majority of trials report use for only 48 hours early in the course of ARDS. The safety and sustained benefit has not been fully investigated, so their use for extended periods may cause increased long term complications especially if used with corticosteroids or aminoglycoside antibiotics [50,51].

Statins

HMG CoA-reductase inhibitors are known to modulate the inflammatory response [52,53] and are associated with reduced ICU mortality in patients with infective endocarditis [54] and in elderly patients admitted to the ICU [55]. The ARDSnet investigators evaluated whether rosuvastatin therapy improved clinical outcomes in critically ill patients with sepsis-associated ARDS. This was a randomized, placebo-controlled, double-blind, multicenter trial in which patients either received enteral rosuvastatin 40 mg once followed by 20 mg daily or placebo. The study was stopped for futility after 745 patients were enrolled. They found no significant difference in 60 day mortality or ventilator-free days. Rosuvastatin therapy was associated with increased renal failure and hepatic failure [8]. Despite the anti-inflammatory effects of HMG CoA-reductase inhibitors, they are not associated with improved outcomes in patients with sepsis mediated ARDS and may increase the incidence of renal and hepatic failure.

What Pharmaconutrition Strategies are Available in ARDS?

Omega-3 Fatty Acid Supplementation

The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may increase the production of anti-inflammatory prostaglandins and leukotrienes [56]. Patients with ALI have lower than normal levels of omega-3 fatty acids [57].

The OMEGA study randomized 272 adults from 44 hospitals who were within 48 hours of onset of ALI requiring mechanical ventilation that were starting on enteral nutrition to either receive omega-3 fatty acids, gamma-linolenic acid, and antioxidant supplementation or placebo in a double blind fashion. The study was stopped early for futility after 143 were enrolled in the treatment arm and 129 were randomized to placebo. The investigators found a significant increase in plasma levels of EPA, but subjects in the treatment arm required longer mechanical ventilation and ICU stay, had more non-pulmonary organ failure, and resulted in more days with diarrhea. There was no difference in adjusted 60 day mortality [58]. Enteral supplementation with omega-3 fatty acids, gamma-linolenic acid, and antioxidants cannot be routinely recommended for patients with ARDS.

What Future Pharmacologic Therapies May Become Available for ARDS?

Current therapies and strategies for ARDS largely focus on mitigating ongoing injury and slowing the inflammatory cascade. Emerging therapies focus on improving endothelial and epithelial

integrity and using cell-based therapies to reverse lung inflammation. In animals [59] and human lung explants [60] keratinocyte growth factor (KGF) improves epithelial cell survival and reduces the accumulation of alveolar fluid in experimental lung injury. Other therapies aimed at improving endothelial or epithelial barrier integrity have shown promise in animals but have not been tested in human systems [61]. Bone marrow stromal cells that adhere to plastic surfaces after bone marrow aspirate and are often termed mesenchymal stem cells (MSCs). MSCs have shown promise in attenuating injury after myocardial infarction [62] and have been shown to attenuate lung injury in animal models [63-65]. MSCs are currently in Phase 1 trial in adults with ARDS (NCT01775774). Continued improvement in ARDS outcomes will depend upon developing novel therapies targeted to central pathogenic pathways and targeting patient populations more precisely so as to target therapies to sub-populations of ARDS patients most likely to benefit.

Conclusions

ARDS continues to be associated with high rates of morbidity and mortality in both adult and pediatric intensive care units. To date, the only therapies proven to improve outcomes are low tidal volume ventilation, a conservative fluid administration strategy, initiation of corticosteroid therapy before day 14 of illness, and early, limited use of neuromuscular blockade. A host of therapies have been shown to improve oxygenation but not patient outcomes.

How can therapies which significantly impact a meaningful surrogate outcome such as oxygenation not reduce ventilator free days or mortality? As the developers of the Berlin criteria point out, careful selection of a target population is essential to demonstrating the effect of an intervention [16]. Interventions will be unable to demonstrate a meaningful effect in less sick patients, and in extremely ill patient any intervention will fail to alter the eventual outcome. Given the heterogeneity of ARDS, perhaps it is not surprising that many of the therapies found beneficial in small trials failed to show benefit when tested in larger more heterogeneous populations. In any given patient, the extensive literature available on therapies for ARDS can only inform clinical decision making; it cannot dictate which decisions are right or wrong.

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