Review Article

The Pharmacology of Acute Lung Injury in Sepsis

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Acute lung injury (ALI) secondary to sepsis is one of the leading causes of death in sepsis. As such, many pharmacologic and nonpharmacologic strategies have been employed to attenuate its course. Very few of these strategies have proven beneficial. In this paper, we discuss the epidemiology and pathophysiology of ALI, commonly employed pharmacologic and nonpharmacologic treatments, and innovative therapeutic modalities that will likely be the focus of future trials.

1. Introduction

Acute lung injury (ALI) secondary to sepsis is the source of substantial morbidity and mortality in both adult [1, 2] and pediatric [3, 4] populations and is a major contributor to intensive care unit (ICU) costs [5]. ALI and acute respiratory distress syndrome (ARDS) are defined by well-established criteria (Table 1) [6] with sepsis and pneumonia being the two leading etiologies [2, 3].

As ARDS is associated with a risk of mortality of 26–44% in the adult population [1, 2] and 22% in the pediatric population [7], a host of therapeutic strategies have been attempted to alter the progression of ALI. While this review will focus on the pharmacology of ALI in sepsis, it will also provide brief summaries of nonpharmacologic treatment strategies. ALI will be used to refer to both ALI and ARDS unless treatments are specifically limited to patients with ARDS.

2. Pathophysiology of ALI in Sepsis

ALI, like sepsis, is a clinical description and common endpoint of many pathophysiologic processes and should be considered a syndrome and not a disease. In considering therapeutic strategies for ALI, clinicians attempt to treat these common processes, address underlying etiologic factors, and, when possible, tailor treatment to specific underlying pathology.

Classically, ALI has been described as progressing through three stages: exudative, proliferative, and fibrotic [8, 9]. Although different mechanisms of lung injury and severity of illnesses significantly influence the severity and duration of these stages [10], the three-stage model has remained largely intact for four decades and serves as a useful frame of reference for discussion.

Exudative. this initial stage of ALI encompasses the first seven days of illness and is marked by a net efflux of proteinaceous material from the intravascular to the alveolar spaces. By definition this efflux is related to increased capillary permeability (i.e., a reduced reflection coefficient) and not hydrostatic forces (i.e., an elevated left atrial pressure). The alveolar exudate reduces lung compliance and increases alveolar surface tension both by virtue of the increased viscosity of the exudate compared to air and by pulmonary surfactant neutralization [11–13]. As vascular leak occurs to varying degrees, lung compliance is heterogeneous leading to focal areas of atelectasis and the patchy bilateral infiltrate on chest X-ray classic of ALI. With positive pressure ventilation, this heterogeneous lung compliance leads to relative overdistention of more normal alveolar units and underinflation of lower compliance ones. Perfusion of inadequately ventilated lung units leads to pulmonary venous desaturation and the hypoxemia of ALI.
Table 1: Diagnostic Criteria for ALI and ARDS [6].

<table>
<thead>
<tr>
<th>ALI Criteria</th>
<th>ARDS Criteria</th>
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<tr>
<td>Acute Onset</td>
<td>Acute Onset</td>
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<tr>
<td>( P_{O_2}/FiO_2 \leq 300 \text{ mmHg} )</td>
<td>( P_{O_2}/FiO_2 \leq 200 \text{ mmHg} )</td>
</tr>
<tr>
<td>Chest Radiograph: Bilateral infiltrates</td>
<td>Chest Radiograph: Bilateral infiltrates</td>
</tr>
<tr>
<td>No evidence of left atrial hypertension</td>
<td>No evidence of left atrial hypertension</td>
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Proliferative. this second stage is a pathological fibroproliferative response to the initial injury and is classically defined as occurring during the second week. Until recently, endogenous fibroblasts were thought to mediate this response; however, emerging evidence suggests that transformation of injured epithelial cells to fibroblast-like cells (epithelial-mesenchymal transition) may play a prominent role [14]. ALI resulting from different mechanisms of injury has also been associated with the presence or absence of myofibroblasts [15, 16]. As myofibroblasts exhibit a substantially enhanced fibroproliferative response to cytokines such as transforming growth factor-\( \beta \) [17, 18], there may be a role for cytokine antagonism in these patients. Regardless of fibroblast origin or phenotype, the lung's ability to turn off the fibroproliferative response and begin tissue remodeling is a critical determinant of outcome.

Fibrotic. two to three weeks following the initial injury, the lung parenchyma either undergoes tissue remodeling leading resolution or the fibroproliferative response is not turned off and fibrosis results. Patients who initiate lung remodeling typically will have near-normalization of pulmonary function six months later [19]. Patients who fail to initiate lung remodeling experience progressive fibrosis which leads to worsening respiratory insufficiency and death weeks to months later. In the adult population, some patients experience initial improvement in lung function only to develop idiopathic pulmonary fibrosis months to years later. Idiopathic pulmonary fibrosis also leads to progressive respiratory insufficiency and death over the course of several months to several years [20].

3. Nonpharmacologic Therapies for ALI

There is no cure for ALI. Treatment is entirely supportive and aims to maintain adequate oxygenation and ventilation while minimizing secondary lung injury. The strategies by which this is done are briefly outlined below.

3.1. The Lung Protective Strategy. The “Lung Protective Strategy” refers to three interventions intended to minimize secondary lung injury in patients with ALI who require mechanical ventilation. These interventions are (1) reduction of tidal volumes (volutrauma), (2) minimization of airway pressures (barotrauma), and (3) application of the minimum end expiratory pressure to prevent airway collapse (atelectrauma) [21]. A large multicenter study on ARDS showed that a 6 mL/kg tidal volume resulted in a 9% reduction in mortality compared to a 12 mL/kg volume [22]. The use of high PEEP-low fractional inspired oxygen [23], oscillatory ventilation [24, 25], or newer ventilator modes such as airway pressure release ventilation [26] have not been shown to improve mortality. There is no mortality data available on other ventilator modes such as neurally adjusted ventilator assist (NAVA) or volume support ventilation, although these modes (as well as others) have shown improvements in secondary outcomes such as oxygenation, duration of mechanical ventilation, or patient-ventilator synchrony [27].

3.2. Alveolar Recruitment. By virtue of the heterogeneous compliance seen in ALI, positive pressure ventilation results in overdistention of lower compliance areas of lung and underinflation of others. Maximizing alveolar recruitment should minimize these disparities. “Recruitment maneuvers” refer to several techniques that increase mean airway pressure temporarily to open closed alveoli. Prone positioning recruits dependent lung segments. Both recruitment maneuvers [28] and prone positioning [29, 30] have been shown to improve oxygenation but not survival.

3.3. Fluid Management Strategies. Adequate fluid resuscitation is a key determinant of survival in septic shock. However, fluid-overload has been associated with poorer outcomes in ALI [31]. In a recently completed randomized trial comparing liberal to restrictive fluid management after initial resuscitation, patients in the restrictive arm had significantly reduced duration of mechanical ventilation and reduced intensive care stay but no reduction in mortality [32]. Furosemide was part of the management algorithm of this trial (FACTT). To date, no trial has investigated the isolated use of furosemide in ALI, but combining albumin replacement with furosemide administration in the context of hypoproteinemia improved fluid balance and oxygenation but not mortality [33, 34]. There is an emerging consensus that after initial resuscitation, achieving a negative fluid balance is important in improving outcomes in sepsis-related ALI [35].

3.4. Extracorporeal Membranous Oxygenation. The use of ECMO in ALI is associated with survival in 57% of pediatric patients [36]; however, disappointing results in two early adult trials dampened enthusiasm in that population [37, 38]. A recent adult trial randomizing patients with severe ARDS to standard of care at the admitting facility versus transfer to a single ECMO center showed better outcomes in those treated with ECMO; however, no difference in outcomes was noted between the ECMO group and the conventional ventilation group at the referral center [39]. Whether the increased use of ECMO in adults seen during the H1N1 influenza pandemic [40] persists is yet to be seen.

3.5. Pumpless Extracorporeal Oxygenation and Carbon Dioxide Removal. In patients with adequate cardiac output, extracorporeal oxygenation and CO\(_2\) removal devices can
reduce the ventilator work required to maintain acceptable 
P\textsubscript{a}O\textsubscript{2} and P\textsubscript{a}CO\textsubscript{2} levels. There is currently no FDA-approved
device for this indication; however, several are approved for
use in Canada and Europe. The devices have an advantage
over traditional extracorporeal membranous oxygenation
in that they require less anticoagulation and cause less
hemolysis [41, 42].

4. Pharmacologic Therapies for ALI

The history of pharmacologic treatments for ALI is marked
by many therapies that showed benefit in animal and small
human trials but failed in larger human trials. Whether
this is due to our inability to identify ALI subgroups or
the immutability of ALI pathophysiology is a matter of
conjecture.

4.1. Corticosteroids. The use of corticosteroids for ALI has
been the subject of multiple trials [43–47] with one of them
being a multicenter randomized trial [47]. The therapeutic
rationale for their use is to blunt fibroproliferation. Many
dosing regimens of corticosteroids have been reported, but
the regimen in the largest trial [47] used a 2 mg/kg loading
dose of solu-medrol, 0.5 mg/kg every 6 hours for 14 days,
0.5 mg/kg every 12 hours for 7 days, and then a taper
dependent on the patient’s clinical status. In the above
trial, the intervention group experienced improvements in
oxygenation and ventilator-free days, but no improvement
in mortality. However, on subset analysis, there was a
significantly increased risk of mortality in patients given
solumedrol more than 14-days after ARDS onset and a
trend towards improved mortality in those treated 7–14
days from ARDS onset. A meta-analysis of patients treated
with corticosteroids before day 14 showed improvement in
outcomes [48]. A trial from the same authors suggested
benefit in starting corticosteroids within 72 hours of ARDS
onset [45]. No trials have been performed to compare
timing of initiation, dosing, or duration of drug admin-
istration. Particularly in the context of sepsis, early, high-
dose steroid administration may slow pathogen clearance,
induce myopathy, increase the risk of secondary infections,
and slow wound healing. The literature supports the use of
corticosteroids in ALI prior to 14 days from ALI onset. Their
use should be considered in this context after a careful risk-
benefit analysis.

4.2. \(\beta\)-Agonists. Apart from their bronchodilator prop-
erties, \(\beta\)-receptor signaling increases alveolar type-I cell
aquaporin-5 expression and aids in alveolar fluid reab-
sorption [49]. In vitro, ex vivo, and preliminary human
studies suggest that \(\beta\)-agonist therapy increases alveolar
fluid reabsorption and improves lung compliance [50–53].
A large randomized trial using aerosolized albuterol every 4
hours in mechanically ventilated adult patients with ARDS
was terminated for futility. However, a smaller randomized
trial using salbutamol infusion improved lung water and
plateau airway pressures [54], leading some to speculate
that inadequate drug delivery may have blunted therapeutic
benefit in the larger trial.

4.3. Furosemide. Independent of its diuretic actions, fu-
rosemide has been shown in animal studies to improve lung
function in ALI [55]. This may be secondary to the anti-
inflammatory effects of furosemide, particularly its ability to
reduce tumor necrosis factor-\(\alpha\) levels [56].

4.4. Neuromuscular Blockade. Neuromuscular blockade us-
ing nondepolarizing agents is highly associated with the
development of ICU myopathy, particularly in the adult
population [57]. In combination with sedation and anal-
gesia, they are generally used to facilitate ventilation and
oxygenation in the most severe cases of ARDS. However,
a recent single-center trial has suggested some intrinsic
benefit of neuromuscular blockade in the first 48 hours of
mechanical ventilation with increased ventilator-free days
and reduced time in the ICU [58]. The mechanism by which
this occurs is unclear.

4.5. Surfactant Replacement Therapy. Pulmonary surfactant
improves pulmonary compliance by reducing alveolar sur-
face tension in lower compliance alveoli thus promoting
more uniform alveolar inflation. Surfactant replacement
therapy is clearly beneficial in premature neonates with
respiratory distress syndrome [59, 60] and also benefits
neonates with lung injury secondary to infections [61]. Large
randomized studies using surfactant replacement in adults
have been unequivocally negative and some have tended
towards harm [62–65]. Several factors may account for these
differences.

1. Infants, particularly premature infants appear to
be surfactant-dependent to maintaining alveolar
benefit. A normal adult has a surfactant pool
size of about 22 mg of phospholipid per kg. An infant
without RDS has a pool size of about 60 mg/kg and an
infant with RDS has a pool size of less than 15 mg/kg
[66]. Surfactant depletion is a negative predictor of
extubation success in premature infants [67].

2. The developing lung does not begin alveolarization
until approximately 35 weeks after conceptional age
[68], and alveolarization continues through toddler-
hood [69]. Pores of Kohn (alveolar) and Canals of
Lambert (bronchiolar) develop at approximately one
and five years of age respectively and contribute sub-
stantially to the maintenance of alveolar recruitment
in the context of lung injury [70]. The lung therefore
becomes able to maintain alveolar recruitment with
progressively less surfactant with improved alveolar
development.

3. The leak of serum proteins into the alveolar space
leads to surfactant inactivation in ARDS [13], whereas the principle problem in RDS is surfactant
deficiency.
4.6. Inhaled Nitric Oxide. Nitric oxide (NO) is a free-radical with a half-life of a few seconds produced by several different isoforms of nitric oxide synthase throughout the body. It is a potent pulmonary vasodilator and is currently FDA approved for use in pulmonary hypertension [76]. In conditions in which there is a large degree of pulmonary shunting (such as ALI), theoretically, inhaled NO may be used to increase pulmonary blood flow to ventilated units and improve ventilation-perfusion matching. In addition, some clinicians believe that NO may treat the secondary pulmonary hypertension seen in ALI. A recently conducted meta-analysis on the use of inhaled nitric oxide in adults and children with ALI, including fourteen randomized control studies, concluded that inhaled nitric oxide improves oxygenation but does not reduce length of ventilation, ICU stay, or mortality [77]. The general use of NO for ALI should be discouraged, although it may benefit a subset of patients with ALI.

4.7. Ω-3 Fatty Acids. Oxidative damage due to high fractional inspired oxygen is thought to be a substantial source of continued injury in ALI. Ω-3 fatty acids possess antioxidant properties and animal and small human trials administering supplemental Ω-3 fatty acids showed improvement in outcomes [78, 79]; however, a large randomized trial using an Ω-3 fortified enteral formula was terminated early for futility. Many confounders in the trial such as feeding intolerance, a low-mortality rate in the control group, and use of a fortified formula instead of supplements may lead to further studies in this area.

4.8. Liquid Ventilation. Perfluorocarbons are inert, low-surface tension liquids that have a high oxygen-carrying capacity. They may be used either to fill the lungs partially or completely. When they are used to fill the lungs completely (tidal liquid ventilation), liquid in a reservoir is oxygenated and cycled through the lung by active inspiration and exhalation. Traditional ventilation is used in partial liquid ventilation and the perfluorocarbons act as a surfactant with the benefit of having high gas solubility coefficients [80]. Case series demonstrate the feasibility of using liquid ventilation in neonates [81–84], but it showed neither benefit nor harm in industry-sponsored adult trials. Further investigations are required before making recommendations regarding its use [85].

4.9. Activated Protein C. Multisystem organ failure (MSOF) is a common consequence of sepsis with the lung being one of the first organ systems typically involved. The pathophysiology of MSOF is complex but involves the development of diffuse microvascular thrombosis leading to local ischemia, cellular dysfunction, and cell death. Protein C is an endogenous anticoagulant that cleaves activated factors V and VIII. Levels are often pathologically low in sepsis [86]. A large multicenter randomized trial involving adult and pediatric patients with sepsis found a small but significant improvement in mortality in adults with a moderate organ dysfunction, but the pediatric arm of the trial was stopped early due to bleeding complications [87]. The use of activated protein C specifically for ALI is still in the preclinical phase [88].

4.10. Mesenchymal Stem Cells. MSCs are nonhematopoietic progenitor cells identified by a host of surface markers, reside in the bone marrow, and display a fibroblast-like phenotype in cell culture. MSCs were found safe in a Phase I trial of patients with acute myocardial infarction with patients receiving the MSCs having faster resolution of symptoms [89] and have shown promise in improving survival in sepsis [90] and acute kidney [91] injury among other conditions. Animal models of lung injury suggest that either intravascular [92, 93] or intratracheal [94] administration of MSCs improve lung function. Despite early concerns about engraftment [95], it now appears that although these cells traffic to the lung interstitium they do not exhibit long-term engraftment [93]. A human trial using MSCs in adults with severe ARDS is currently being developed.

5. Conclusions

ALI is a common complication of sepsis. Despite multiple trials, the only therapy that has demonstrated clear benefit with regards to mortality is the employment of low tidal volume ventilation strategy. Although no mortality benefit was demonstrated, a restrictive fluid strategy is well supported. Arguably, only two drugs, solumedrol and furosemide, have shown therapeutic benefit. Among the other therapies listed, their general use cannot be advocated but may be beneficial to select patients. We do not yet have the ability to phenotype ALI in a clinically meaningful way. As ALI is common in ICUs and associated with significant morbidity, mortality, and cost, investigators will continue to explore new pharmacologic and nonpharmacologic therapies despite a long history of disappointments.

References


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