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Pharmacotherapy of Acute Lung Injury and Acute Respiratory Distress Syndrome

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Abstract

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are characterized by rapid-onset respiratory failure following a variety of direct and indirect insults to the parenchyma or vasculature of the lungs. Mortality from ALI/ARDS is substantial, and current therapy primarily emphasizes mechanical ventilation and judicial fluid management plus standard treatment of the initiating insult and any known underlying disease. Current pharmacotherapy for ALI/ARDS is not optimal, and there is a significant need for more effective medicinal chemical agents for use in these severe and lethal lung injury syndromes. To facilitate future chemical-based drug discovery research on new agent development, this paper reviews present pharmacotherapy for ALI/ARDS in the context of biological and biochemical drug activities. The complex lung injury pathophysiology of ALI/ARDS offers an array of possible targets for drug therapy, including inflammation, cell and tissue injury, vascular dysfunction, surfactant dysfunction, and oxidant injury. Added targets for pharmacotherapy outside the lungs may also be present, since multiorgan or systemic pathology is common in ALI/ARDS. The biological and physiological complexity of ALI/ARDS requires the consideration of combined-agent treatments in addition to single-agent therapies. A number of pharmacologic agents have been studied individually in ALI/ARDS, with limited or minimal success in improving survival. However, many of these agents have complementary biological/biochemical activities with the potential for synergy or additivity in combination therapy as discussed in this article.

Keywords

ARDS; ALI; inflammatory lung injury; lung injury therapy; anti-inflammatory therapy; surfactant therapy; INO therapy; anti-oxidants; pharmacotherapy

1. INTRODUCTION

Clinical acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) can arise in patients of all ages from direct or indirect insults that induce pulmonary inflammation, damage the cells of the alveolocapillary membrane, and lead to severe acute respiratory failure. The American-European Consensus Committee (AECC) in 1994 defined clinical ALI as

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respiratory failure of acute onset with a PaO_2/FiO_2 ratio ≤300 mmHg (regardless of the level of positive end expiratory pressure, PEEP), bilateral infiltrates on frontal chest radiograph, and a pulmonary capillary wedge pressure <18 mmHg (if measured) or no evidence of left atrial hypertension [1]. ARDS was defined identically except for a lower limiting value of <200 mmHg for PaO_2/FiO_2 [1]. The AECC definitions of ALI/ARDS are widely-used and simple to apply, but also have serious deficiencies in discrimination. There is often not a good correlation between these broad clinical definitions and diffuse alveolar damage (DAD), which is widely considered to be a major characteristic histological feature of ALI/ARDS [2]. The AECC definitions also do not take into consideration variables such as the mode of ventilation and the level of PEEP, which can significantly influence oxygenation. The AECC definitions of ALI/ARDS are thus frequently supplemented by lung injury or critical care scores like the Murray score [3] or the APACHE II [4] in adults, and the PRISM (Pediatric RISk of Mortality score) [5,6], PIM (Pediatric Index of Mortality score) [7], or Oxygenation Index [8] in children. An alternative definition of ARDS by a recent Delphi consensus panel of senior investigators includes PEEP restrictions in defining hypoxemia, radiographic criteria for air space disease in two or more quadrants, and requires either quantitative compliance abnormalities or the presence of a predisposing condition [9]. Although the Delphi definition is more specific than the AECC criteria, it has been reported to be less sensitive [10].

Although ALI and ARDS encompass a broad spectrum of etiologies, it is important to consider specific causes of lung injury in targeting therapeutic agents. In particular, it is relevant to distinguish between ALI/ARDS from direct pulmonary causes as opposed to systemic (indirect, non-pulmonary) causes. As reviewed elsewhere [1,11–17], common direct pulmonary causes of ALI/ARDS include lung viral or bacterial infections, gastric aspiration, blunt thoracic trauma with lung contusion, meconium aspiration (infants), near-drowning, thoracic radiation, hyperoxia, and the inhalation of smoke or other toxicants. Common indirect (systemic) causes of ALI/ARDS include sepsis, closed space burn injury, hypovolemic shock, non-thoracic trauma, multiple transfusions, and pancreatitis. The pathology of ALI/ARDS is particularly complex in systemic insults like sepsis, where multi-organ involvement is common and extra-pulmonary inflammation is severe and pervasive as reflected by systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), or multiple organ failure (MOF) [4,18,19]. The severe systemic pathology in indirect forms of ALI/ARDS has the potential to significantly limit the effectiveness of pharmacological and other therapies that target pulmonary pathology compared to the case of ALI/ARDS caused by direct lung injury. As one example, post-hoc analyses in two recent clinical trials of surfactant therapy in ALI/ARDS suggest greater efficacy in direct as opposed to indirect forms of these syndromes [20,21].

Regardless of definition, ALI and ARDS affect a large number of patients and have a poor prognosis. The incidence of ALI/ARDS has been variably reported to be 50,000–190,000 cases per year in the United States [1,11–17,22]. The incidence of ALI in two recent studies has been estimated at 22–86 cases per 100,000 persons per year [16,17], with 40–43 percent of these patients having ARDS [16]. These studies primarily considered adults, and the incidence of ALI/ARDS is lower at 2–8 cases per 100,000 persons per year in the pediatric age group [23–26]. Survival statistics for patients with ALI/ARDS vary with lung injury etiology and age, but overall mortality rates in both adult and pediatric patients remain very substantial at 30–50% despite sophisticated intensive care [1,11–17,22,24–31]. The significance of distinguishing between the two clinical syndromes in a practical sense is uncertain, since a meta-analysis of 102 studies prior to 1996 suggested little or no difference in mortality rates between patients meeting criteria for ALI compared to ARDS [12]. This was also the conclusion in the recent NEJM article by Rubenfeld *et al.* [16], which reported mortality rates of 38.5% for ALI and 41% for ARDS, with an estimated 74,500 deaths per year and an aggregate 3.6 million hospital days of care in the United States.

There is clearly a significant need for improved treatments for ALI/ARDS in all age groups, and this review focuses on medicinal chemical interventions. Major emphasis in this article is on reviewing current medicinal chemical agents in the context of their biochemical and biological activities directed against specific aspects of the pathophysiology of acute inflammatory pulmonary injury in ALI/ARDS. The material presented is not only relevant for current clinical pharmacotherapy, but also will hopefully help to facilitate future work on chemistry-based drug discovery and the development of active new medicinal chemical agents for ALI/ARDS based on the targeting of specific biological and biochemical aspects of pathophysiology.

2. DIFFICULTIES OF DEVELOPING AND TESTING THERAPIES IN ALI/ARDS

Over the past two decades, a variety of interventions and intensive care strategies have been used in treating patients with ALI/ARDS. The current standard of clinical care for ALI/ARDS includes mechanical ventilation with lung protective strategies, coupled with judicious fluid management, adjunct nutritional support, and specific treatment of any known underlying cause of injury or disease. The only intervention to date that has clearly showed a survival benefit in controlled studies in adults with ARDS has been the adoption of low tidal volume ventilation strategies (6–8 ml/kg bodyweight) [32], an advance that is non-pharmacologic in nature. In addition, exogenous surfactant therapy with an active bovine-derived drug (Infasurf) has recently been shown to improve survival in pediatric patients up to age 21 with direct pulmonary ALI/ARDS [33].

A major difficulty in testing and evaluating medicinal chemical therapies for ALI/ARDS is that clinical studies on agent efficacy in these syndromes are complicated by their multiple etiologies and heterogeneous cohort of affected patients (see preceding section). Although some of this heterogeneity can be reduced by considering direct versus indirect causes of ALI/ARDS, patients in both categories still vary in age and may also have significant co-morbid conditions such as diabetes, alcohol abuse, or other chronic pathologies particularly in the case of adults. Even if co-morbidities and extra-pulmonary pathology are absent or relatively minimal (e.g., as in otherwise healthy patients with direct forms of lung injury), the multifaceted pathophysiology of pulmonary injury itself is a complicating factor in efficacy assessments. An individual pharmacologic agent may in fact be effective in mitigating its intended target of pathology, but benefits to survival and other long term clinical outcomes may be obscured by remaining aspects of pathology. All these considerations complicate the design and analysis of clinical trials and reduce their resolving power. In general, evaluating therapies in ALI/ARDS requires multi-center studies of substantial size, with patient populations and outcome variables controlled with as much focus as possible. More complete discussion of factors affecting the design of clinical trials for testing single-agent and combination therapies in ALI/ARDS is given elsewhere [34].

Although developing and testing medicinal chemical interventions for clinical ALI/ARDS is certainly challenging, there is reason for optimism about the potential for more effective therapies of this kind. A significant amount of scientific information has now accrued concerning the mechanistic pathophysiology of acute and chronic pulmonary injury and inflammation, and this has identified a number of biological targets for pharmacologic agents. Moreover, extensive on-going research on acute and chronic lung injury at the cellular and molecular level can be expected to identify additional agents and targets for specific pharmacology as time progresses. The remainder of this article reviews current medicinal chemical agents used or potentially applicable for ALI/ARDS. Many of these agents have been shown to have significant beneficial effects in laboratory and animal model research on lung injury, although benefits to survival in human studies, particularly in adults, have not yet been seen. In at least some cases, this may reflect the limited resolving power of clinical trial

assessments in ALI/ARDS described above. In addition, factors relating to drug activity or delivery can help to explain the lack of clinical efficacy of specific agents, as discussed later for some exogenous surfactants.

The complex multifaceted pathology of ALI/ARDS may ultimately require mechanism-based combination interventions instead of single-agent therapy, as reviewed in detail by Pryhuber *et al.* [34]. Defining combination therapies for ALI/ARDS requires integrated basic and clinical research. Mechanistic studies of activity and interactions in animal and cell models are essential in screening, refining, and focusing specific combination therapies for ultimate clinical testing [34]. Combination therapy approaches in ALI/ARDS could include the use of multiple pharmacological agents together, as well as multimodal strategies that involve drug therapy plus non-pharmacologic interventions such as the use of specific modes or protocols of mechanical ventilation to enhance alveolar recruitment and minimize ventilator-induced lung injury) [32,34–46]. This article focuses on pharmacological agents, and detailed review of non-drug treatments such as low tidal volume and lung protective ventilation strategies, prone positioning, and conservative fluid management is not included.

3. MEDICINAL CHEMICAL TARGETS IN THE PATHO-PHYSIOLOGY OF ALI/ARDS

Rational medicinal chemical drug discovery and development for ALI/ARDS depends on pathophysiological understanding. Although ALI/ARDS is sometimes subdivided into early, mid, and late periods of pathology, pharmacotherapy for these syndromes is discussed here in terms of two major phases: the acute exudative phase and the later fibroproliferative phase. Occurring within 12–72 hours of the initiating lung injury stimulus, the exudative phase of ALI/ARDS is initially characterized by prominent interstitial and alveolar edema in association with an increased permeability in the alveolocapillary membrane (capillary endothelial cells and alveolar type I epithelial cells) that normally maintains a tight barrier and electrolyte balance [47–50]. Over the next 3–7 days, further alveolocapillary damage occurs, with denuding of basal lamina and the formation of intra-alveolar hyaline membranes containing plasma proteins, fibrin and cellular debris. Complement and coagulation cascades are activated, and multiple inflammatory cytokines/chemokines and reactive oxygen/nitrogen species are released [51]. Pulmonary blood flow and perfusion are reduced in acute exudative ALI/ARDS by thrombus formation, intravascular sequestration of leukocytes and platelets, and hypoxia-induced vasoconstriction. Surfactant activity can be impaired by several mechanisms including interactions with serum proteins and other inhibitors in edema [52–55]. Surfactant metabolism, including the production of surfactant apoproteins, may also be disrupted if alveolar type II cells are injured or become altered by the pulmonary inflammatory response. Potential targets for therapies in the acute exudative phase of ALI/ARDS include general hypoperfusion as well as ventilation/perfusion mismatching, surfactant dysfunction, arterial hypoxemia and edema, inflammation, oxidant injury, and cellular injury to the alveolar epithelium and capillary endothelium (Table 1).

The acute phase of ALI/ARDS is generally followed in survivors by a 1–3 week period of fibroproliferation and organization of previously deposited intra-alveolar and interstitial exudates [51]. In the fibroproliferative phase of ALI/ARDS, type II cells proliferate and line the alveolar wall, re-covering the basement membrane and migrating over organizing intra-alveolar hyaline membranes. These type II cells can present a chronic source of proinflammatory mediators (for details on the spectrum of inflammatory mediators in acute and chronic lung injury see Ref [56]). There is also proliferation and migration of fibroblasts into intra-alveolar exudates, along with differentiation of fibroblasts into myofibroblasts. Collagen-rich extracellular matrix material is deposited in the pulmonary interstitium, and fibrosis can start to become apparent. Alveoli are lost by accumulation of connective tissue

within septal walls and by dropout as collapsed distal airways and airsacs become sealed by organizing fibrin and hyperplastic epithelium. Vascular and perivascular smooth muscle cell proliferation also occurs, and pulmonary vascular area is reduced leading to pulmonary hypertension. In some areas of lung, there can be complete destruction of small arteries (obliterative endarteritis). Chronic inflammatory foci rich in polymorphonuclear cells are also typically present in the lung interstitium, potentially augmenting the destruction of neighboring alveolar structure.

The fibroproliferative phase of ALI/ARDS either slowly resolves, progresses, or remains static. The incidence of fibrosis following ARDS is noteworthy. One study using high-resolution computed tomography and lung function testing demonstrated pulmonary fibrosis in 13 of 15 patients examined 6–10 months after ARDS [57]. The extent of fibrotic pathology correlated with the severity of ARDS ($p<0.01$) and with the duration of mechanical ventilation with peak inspiratory pressures greater than 30 mmHg ($p<0.05$) or >70% inspired oxygen ($p<0.01$) [57]. This suggests that acute pulmonary injury impacts the development of fibrosis, and that ventilator- and hyperoxia-induced injury may be important factors. Even in the absence of clear fibrosis, it is common for patients recovering from ALI/ARDS to demonstrate reduced exercise tolerance and abnormalities in pulmonary function tests including diffusion capacity [58]. In contrast to therapies in the exudative phase of ALI/ARDS, interventions in the fibroproliferative phase must address pathophysiological elements of remodeling, repair and fibrosis [59–64] (summarized in Table 2). Details on specific pharmacological agents for the exudative and fibroproliferative phases of ALI/ARDS are given in following sections.

4. PHARMACOTHERAPY FOR VENTILATION-PERFUSION INDUCED-HYPOXEMIA IN EXUDATIVE ALI/ARDS

One of the primary goals in treating acute respiratory failure in the exudative phase of ALI/ARDS is to improve alveolar ventilation (V_A) and the ratio to capillary perfusion (Q_c), i.e. to enhance V_A/Q_c matching. Selected pharmacologic agents for improving V_A/Q_c matching and arterial oxygenation are summarized in Table 3. These include inhaled vasodilators to increase blood flow to ventilated alveoli, selective vasoconstrictors to potentiate hypoxic vasoconstriction in non-ventilated regions of lung, exogenous surfactants to reduce alveolar surface tension and increase alveolar ventilation, anti-coagulants to antagonize thrombus formation and increase pulmonary blood flow, and β-2 agonists to reduce edema. A number of these agents have been used and tested clinically in single-agent therapy for ALI/ARDS, but a majority of them have not been examined in any detail in combination therapies.

4.1. Vasoactive Agents for Treating Acute Exudative ALI/ARDS

The ability to titrate dosing and the degree of pulmonary selectivity are major considerations in selecting vasoactive drugs for acute respiratory failure. Relatively few vasoactive agents have been identified that generate therapeutic pulmonary actions without significant systemic side effects if given intravenously [65]. The development of inhaled drugs such as nitric oxide and prostacyclin that can directly target the pulmonary vasculature in mechanically-ventilated patients has reduced systemic side effects and led to improved efficacy.

4.1.1. Inhaled Nitric Oxide (INO)—Nitric oxide, a naturally-occurring product identical to endothelial-derived relaxing factor [66–68], is an important endogenous mediator in several physiological processes *in vivo*. One of its most important cardiovascular actions is potent vasodilation, which results from decreased calcium in smooth muscle cell cytoplasm following an NO-dependent increase in cyclic-GMP. The activity of NO can be pharmacologic as well as physiologic. Inhaled NO (INO) affects gas exchange by increasing blood flow in ventilated areas to improve V_A/Q_c matching. Due to its high affinity for hemoglobin, INO is active

principally in ventilated lung regions with relatively little diffusion into neighboring non-ventilated tissues. INO has been used in the therapy of several pediatric and adult lung diseases ([69–71] for review). A major established therapeutic use of INO is in pulmonary hypertension of the newborn [69,72–74]. INO has also been shown to reduce pulmonary artery pressures and/or pulmonary vascular resistance in a number of animal models of acute pulmonary injury [75–80], making it relevant for patients with ALI/ARDS. Clinical studies have shown that INO improves arterial oxygenation and reduces pulmonary artery pressure in adults with ARDS [81–89] and in infants or children with acute respiratory failure [90–96]. The efficacy of INO has also been reported to be additive with those of PEEP [97] and patient prone positioning [98].

Michael *et al.* [87] studied 40 patients with ARDS, and reported improved oxygenation for the first 24 hours in those receiving INO plus conventional therapy compared to conventional therapy alone. The double-blind trial of Dellinger *et al.* [85] from the multi-center INO in ARDS Study Group involved 177 patients with ARDS and compared 3 dosages of INO with placebo. Several measures of acute lung function (e.g., PaO_2, FiO_2, PaO_2/FiO_2 ratio, PEEP, mean airway pressure) were improved in patients receiving INO [85]. However, Dellinger *et al.* [85] reported no difference in mortality rate or in the number of days alive following mechanical ventilation in patients treated with INO. The authors suggested that “larger phase III studies are needed to ascertain if the acute physiologic response (to INO) can lead to altered clinical outcome.”

One drawback to INO therapy is that some patients require a prolonged treatment and withdrawal course, likely due in part to down-regulation of endogenous NO production. Since therapeutic NO is currently delivered primarily through mechanical ventilation circuits, this necessitates prolonged ventilation. However, recent studies administering INO through nasal cannula circuits suggest that alternative delivery systems could allow more gradual weaning of the gas and earlier extubation [99]. Adverse effects of NO therapy such as methemoglobinemia, production of peroxynitrate, increased pulmonary edema and rebound pulmonary hypertension have also been noted in some clinical studies [81,86,87]. A Cochrane Library review on the use of INO for treating acute hypoxic respiratory failure identified five studies assessing over 500 patients that demonstrated no statistically significant effect of INO on mortality but indicated a transient improvement in oxygenation [100]. The authors of the Review called for future INO studies “to stratify patients by their primary disorder, to assess the importance of combined modalities, and to specifically evaluate clinically relevant outcomes [100].”

Further vascular smooth muscle relaxation and reduction in pulmonary hypertension may be accomplished with selective phosphodiesterase inhibitors such as sildenafil and more recent inhibitors of phosphodiesterase (PDE) V [101,102]. These inhibitors reduce cGMP metabolism and hence may act in combination with nitric oxide to enhance smooth muscle relaxation and reduce pulmonary hypertension [103]. Case reports and animal research support the efficacy of such drugs especially in refractory or INO-dependent pulmonary hypertension [104,105]. The selectivity of PDE inhibitors appears to be in part dose dependent, with higher doses more likely to induce systemic hypotension. The PDE III inhibitor milrinone has also been observed to reduce acute pulmonary hypertension [106].

4.1.2. Prostacyclin and other Vasodilatory Prostaglandins—Prostacyclin is a microcirculatory vasodilator and inhibitor of platelet aggregation used for several indications in neonatal and adult medicine. When aerosolized, its vasodilatory action in ventilated areas should be similar to INO in improving V_A/Q_c matching without promoting systemic hypotension. Consistent with this, aerosolized prostacyclin improved acute respiratory function to the same degree as INO in several studies in patients with ARDS [107–109].

Another vasodilatory prostaglandin, PGE_1, also has been shown to give improvements similar to those of INO when delivered by aerosol to patients with ARDS [110]. These results suggest that aerosolized prostacyclin or similar drugs could be viable therapeutic alternatives to INO. Additionally prostacyclin may have some advantages over NO as it is easier to administer and has harmless metabolites. However it is more expensive and has not shown any survival benefit in human trials [107].

4.1.3. Selective Vasoconstrictors Used in Combination with Inhaled Vasodilators—

The activity of INO and other inhaled vasodilators in treating acute respiratory failure in ALI/ARDS may be further enhanced by specific vasoconstrictors (e.g., [65,111,112] for review). The mechanistic rationale for this is that selective vasoconstrictive drugs can reinforce the natural hypoxic vasoconstriction of the pulmonary vasculature in poorly ventilated regions. In principle, selective constriction of blood vessels in under-ventilated alveoli allows a larger fraction of pulmonary blood flow to be redirected to ventilated areas to improve V_A/Q_c matching. The use of vasoconstrictive agents also has the potential for negative effects, since excessive or inappropriate vasoconstriction would further impair an already compromised gas exchange process. Several clinical studies have shown that co-administration of INO and almitrine bismesylate, a selective pulmonary vasoconstrictor, can enhance the efficacy of INO in improving arterial oxygenation or reducing the level of mechanical ventilatory support in patients with ARDS [112–118]. Caution is warranted with the use of almitrine because of a potential increase in pulmonary arterial pressure and right ventricular loading [119]. However, promising results from the concurrent use of INO and almitrine support the concept of using rational combinations of vasoactive agents in treating ALI/ARDS. Phenylephrine has also been reported to generate improvements in acute respiratory function in ARDS patients responding to INO [120], although the mechanisms involved have been questioned [121].

4.2. Exogenous Surfactant Therapy for Acute Phase ALI/ARDS

The rationale for exogenous surfactant therapy in ALI/ARDS is primarily to reverse surfactant dysfunction (inhibition), although surfactant deficiency is also treated by this intervention. Abnormalities in surfactant in lung lavage from patients with ALI/ARDS are well-documented [122–129], and exogenous surfactant therapy has a strong rationale based on extensive biophysical research showing that raising surfactant concentration can overcome inhibition by endogenous compounds present in injured lungs ([52,53,130–132] for review). In addition, the ability of exogenous surfactants to improve pulmonary mechanics and function has been established in multiple animal models of ALI/ARDS including acid aspiration [133–135], meconium aspiration [136–139], anti-lung serum [140], bacterial or endotoxin injury [141–146], vagotomy [147], hyperoxia [148–152], *in vivo* lung lavage [153–158], N-nitroso-N-methylurethane (NNNMU) injury [159–161], and viral pneumonia [162,163]. Consistent with these laboratory findings, surfactant therapy has been shown to be successful in infants with ARDS-related lung injury associated with meconium aspiration or pneumonia [164–172], as well as in children and young adults with ALI/ARDS [33,173,174]. Particularly impressive is the recent double-blind, placebo-controlled study by Willson *et al.* [33] in 153 pediatric patients up to age 21 yrs with ALI/ARDS, which demonstrated not only lung functional benefits but also a substantial improvement in survival following treatment with the bovine-derived surfactant Infasurf®. Aside from low tidal volume ventilation as noted earlier [32], this is one of the few controlled studies to show substantive survival improvements in patients with ALI/ARDS.

Several small pilot studies have also documented improved respiratory function (oxygenation) in adults with ALI/ARDS [175–179]. However, controlled clinical trials in adults have been less successful. By far the largest prospective controlled study of surfactant therapy in adults

with ARDS was definitively negative [180]. Anzueto *et al.* [180] administered nebulized Exosurf® vs. placebo to 725 adults with ARDS secondary to sepsis and found no improvement in any measure of oxygenation and no effect on morbidity or mortality. However, interpretation of these negative results is confounded because both laboratory and clinical studies have documented that Exosurf® has low activity compared to animal-derived surfactants [181–190], and this surfactant is no longer marketed in the United States. In addition, aerosolization has not been shown to be as effective as airway instillation in delivering surfactant. Gregory *et al.* [191] reported only small benefits in oxygenation in a controlled trial in adults with ARDS who received four 100 mg/kg doses of Survanta®, but with no overall advantage in survival in the 43 surfactant-treated patients studied. However, this exogenous surfactant contains only very small amounts of surfactant protein (SP)-B [192], which is known to be the most active apoprotein in native surfactant [193–201]. A more recent study by Spragg *et al.* [21] using recombinant SP-C surfactant (Venticute®) in adults with ARDS showed immediate improvements in oxygenation, but no improvement in duration of mechanical ventilation, lengths of stay, or mortality. Post-hoc analysis did suggest, however, that the response in the subgroup of patients with ARDS due to "direct lung injury" was positive [21], and a follow-up prospective study in this category of patients is currently underway. Exogenous surfactant therapy in ALI/ARDS requires the use of the most active clinical surfactant drugs plus effective delivery methods. In addition to animal-derived surfactants such as Infasurf, highly-active new synthetic lipid/peptide lung surfactants are currently being developed that have significant potential advantages in manufacturing, economy, and purity compared to biological products [202–207]. Such synthetic surfactants include preparations with novel physicochemical properties like phospholipase-resistance [203–207], which may be of particular importance in ALI/ARDS where these lytic enzymes can be elaborated in high concentrations in the interstitium and alveoli [208–214].

4.3. INO Plus Exogenous Surfactant in Combination Therapy

The rationale for combination therapy with INO and exogenous surfactant is based on their complementary mechanisms of action in improving ventilation/perfusion matching and gas exchange. INO dilates the vasculature in ventilated lung units, while surfactant improves ventilation by decreasing surface tension and enhancing alveolar stability and recruitment. Exogenous surfactant therapy would theoretically increase the ventilated lung area accessible to INO, while the latter would increase the perfusion of these ventilated areas. Additive improvements in lung function from the simultaneous use of INO and exogenous surfactant have been demonstrated in premature surfactant-deficient lambs with congenital diaphragmatic hernia [215], as well as in animal models of ALI/ARDS [216–221]. A stepwise, multiple regression analysis of neonates with hypoxic respiratory failure being weaned from INO has demonstrated that therapeutic surfactant significantly enhanced oxygenation reserve [222]. Clinical benefits have been reported from exogenous surfactant therapy and INO in a small case series in full-term infants with severe acute respiratory failure [223]. These findings support more extensive study of combination therapy with surfactant and INO in ALI/ARDS. This is also the conclusion of a review of newborns < 5 days old and ≥ 35 weeks gestation diagnosed with hypoxemic respiratory failure (oxygenation index >15) from meconium aspiration, sepsis/pneumonia or persistent pulmonary hypertension in the eras preceding (1993–1994) and following (1996–1997) the simultaneous availability of high frequency oscillatory ventilation, INO and exogenous surfactant [224]. The simultaneous availability of these therapies was associated with a reduced percentage of infants requiring rescue therapy with ECMO (42.8% vs. 27.7%) that was not fully attributable to the reported efficacy of the individual agents alone [224]. Prospective controlled clinical trials on the combined use of INO and exogenous surfactant have not yet been done in pediatric or adult patients with ALI/ARDS.

4.4. Agents to Enhance Pulmonary Blood Flow by Reducing Intravascular Coagulation

Therapies that reduce vascular obstruction have the potential for synergy with agents that dilate the pulmonary vasculature (INO) or increase alveolar ventilation (exogenous surfactant) [225]. Pulmonary vascular obstruction can occur in patients with ALI/ARDS from leukocyte and platelet aggregation and later fibrin deposition [226]. Intravascular coagulation can reduce blood flow, decrease the functional area of the pulmonary vascular bed, and lead to increased mismatching of ventilation and perfusion. In addition, intra-alveolar coagulation may promote fibrin deposition and provide a matrix for organizing inflammatory cells and fibroblasts contributing to the later development of pulmonary fibrosis. Administration of the anti-coagulants tissue factor pathway inhibitor (TFPI) or site-inactivated factor VIIa has been reported to protect gas exchange and compliance, reduce pulmonary edema and hypertension, and preserve renal function in a baboon model of gram-negative sepsis [227]. Systemic proinflammatory cytokine responses including production of interleukin (IL)-6 were also reduced by anticoagulant therapy [227]. A preliminary report of a small Phase 2 clinical trial of septic patients treated with TFPI indicated reduced cytokine levels and a roughly 35% survival advantage in the ARDS subgroup in association with a measurable anti-coagulant effect [228]. Mortality has also been found to be significantly reduced in a large study of patients with severe sepsis treated with anti-thrombotic protein C (APC), a selective endogenous anticoagulant that is rapidly depleted in septic shock [229]. Additionally healthy patients treated with activated protein C have shown a decrease in lung inflammation and inhibition of coagulation after endotoxin exposure [230,231]. A multicenter phase II study of activated protein C in ALI/is expected to be completed in 2008.

4.5. Drugs to Improve Alveolar Fluid Clearance

A good deal of recent interest has focused on ways to clear alveolar edema during the acute phase of ARDS. The clearance of fluid from the alveolar space has been shown to be crucial for the successful resolution of ARDS and associated respiratory failure [232–234]. Patients with ARDS have impaired alveolar fluid clearance [232,233], and those better able to clear extravascular lung water (EVLW) demonstrate a survival advantage [233,234]. Salbutamol or related β-2 agonists have the potential to improve alveolar fluid clearance in ARDS by upregulating sodium transport mechanisms on the alveolar epithelial cells [49,232,235]. In addition, β-2 agonists cause pulmonary vasodilation and reduce the edema-promoting hydrostatic driving force for fluid transport across capillaries [236]. Based on data in β-2 knockout mice [237] and volunteers at risk for high altitude pulmonary edema [238], a single center double-blind study (BALTI) was recently conducted on the use of salbutamol in patients with ARDS [239]. Results showed that patients receiving salbutamol had significantly lower levels of EVLW [239]. As a result of these findings, the ARDS network is now initiating a multi-center randomized, controlled study using β-2 agonists in ALI/ARDS [234].

5. PHARMACOTHERAPY TARGETING INFLAMMATION OR OXIDANT INJURY IN EXUDATIVE ALI/ARDS

Over-exuberant inflammation is generally a prominent feature of the exudative phase of ALI/ARDS. The overproduction of pro-inflammatory cytokines, chemokines, growth factors, and reactive oxygen/nitrogen species by activated leukocytes and resident lung cells can sometimes be more harmful than the initial stimulus causing lung injury. Increased levels of pro-inflammatory mediators and reactive chemical species have been found in lavage fluid, plasma, and blood cells from patients with ALI/ARDS (e.g., [240–248]). Persistent elevations of pro-inflammatory cytokines in BAL and plasma from patients with ALI/ARDS have also been shown to be predictive of poor clinical outcome [246–248]. This provides a rationale for therapies with anti-inflammatory agents or antioxidants in ALI/ARDS to complement interventions targeting ventilation/perfusion abnormalities described in the preceding section.

Medicinal chemical agents targeting inflammation and oxidant pathology that have been studied in humans or animals with ALI/ARDS or sepsis are summarized in Table 4. Agents targeting specific inflammatory mediators or pathways include antibodies or soluble receptors for tumor necrosis factor (TNF)-α [249–253], IL-8 [254–256], and CD40 ligand (CD40L) [257,258]. Also studied have been receptor antagonists for IL-1 (IL-1Ra) [259–262], and antibodies against bacterial products such as endotoxin [263,264]. In addition, pentoxifylline has been found to have anti-inflammatory properties of potential utility in ALI/ARDS and sepsis [265–276], and oxidant injury has been targeted by agents like N-acetylcysteine (NAC) [277–285] and recombinant superoxide dismutase (SOD) [286–288]. Corticosteroids, which have broad anti-inflammatory activity, have been found to be ineffective and even potentially harmful in early exudative ALI/ARDS (for review see [289]). However, corticosteroids are discussed later for potential use in the fibroproliferative phase of lung injury.

5.1. Anti-TNFα Antibodies, Receptor Antagonists, or Soluble Receptors

TNFα is an important early pro-inflammatory mediator of acute pulmonary injury ([290–292] for review). TNFα not only has direct cellular actions, but also induces other proinflammatory mediators like IL-1β and promotes the recruitment of activated neutrophils into the lungs. The correlation between levels of TNFα and the development of ALI/ARDS is highest when this cytokine is measured in edema or BAL fluid [240–242]. Anti-TNFα or TNFα receptor blockade has been shown to reduce the severity of lung injury in several animal models [250,293–295]. Acute benefits have also been reported following the delivery of monoclonal anti-TNFα antibodies to patients with ARDS or sepsis, but long term outcomes including survival were not significantly improved [249,251,252]. However, since TNFα is crucial in the innate antibacterial response, a failure to be more selective in choosing patient groups to receive anti-TNF therapy may have contributed to this lack of long term benefit. Antibodies to TNFα and receptor blockade strategies including the use of soluble TNF receptors (e.g., Enbrel) appear to be well tolerated in patients, and agents antagonizing the activity of this cytokine are potential candidates for use in combination therapies for ALI/ARDS.

5.2. Anti-IL-8 Antibodies

IL-8 is a potent chemoattractant cytokine (chemokine) for neutrophils, and has been studied as a marker for ALI/ARDS in high-risk patients [246,296–299]. IL-8 has also been shown to affect neutrophil apoptosis [300]. IL-8 levels are markedly elevated in pulmonary edema from patients with ARDS compared to lung fluid from healthy volunteers or patients with hydrostatic edema [246,296–298]. High IL-8 levels in lavage also correlate with increased mortality in patients with ALI/ARDS [246], and with a high risk for development of ARDS [297]. IL-8 levels in lavage do not correlate with the persistence of ARDS [299], suggesting more importance in the pathogenesis of acute disease. Early treatment with anti-IL-8 antibodies has been found to reduce lung injury and mortality in animal models of acid aspiration [254] and endotoxemia [255,256]. Antibodies to IL-8 have not yet been studied in single-agent or combination therapies in patients with ALI/ARDS.

5.3. Anti-CD40L

CD40 is a 50 kD receptor that was once thought to be expressed only on bone marrow-derived cells, but is now known also to be present on pulmonary fibroblasts [257,301–303]. Fibroblast CD40 serves as an activation structure for the synthesis of pro-inflammatory cytokines through interactions with CD40 ligand (CD40L), which is found on T lymphocytes and mast cells. A monoclonal anti-CD40L antibody termed MR1, which disrupts the CD40-CD40L interaction, has been shown to reduce the severity of hyperoxic lung injury and radiation-induced lung injury in mice [257,258]. In radiation-induced lung injury, treatment with MR1 not only

improved acute injury, but also reduced fibrosis [258]. Caution is suggested, however, by a subsequent study in CD40- and CD40L-deficient mice (−/−), which failed to show improvements in oxygen-induced injury in the absence of CD40 activity [304]. Anti-CD40L reagents for humans are in the testing phase by several pharmaceutical firms for diseases such as idiopathic thrombocytopenic purpura, but they have not been studied clinically in single or multi-agent therapies for ALI/ARDS.

5.4. Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

GM-CSF is a novel agent that has been shown to play an important role in the development and homeostasis of alveolar macrophages. Recombinant GM-CSF has been shown to reduce lung injury and mortality in an animal model of neutropenic Candida sepsis [305], and a small randomized phase-II study of GM-CSF in patients with severe sepsis and ALI/ARDS showed an improvement in oxygenation over a period of 5 days [306]. A randomized controlled trial of a 14 day course of GM-CSF in ALI/ARDS is currently ongoing at the University of Michigan.

5.6. Pentoxifylline

The xanthine derivative pentoxifylline is a phosphodiesterase inhibitor with multiple physiological effects. Pentoxifylline has direct vasodilatory activity, and it also affects erythrocyte deformability [307,308]. However, its major beneficial actions in ALI/ARDS appear to relate to its ability to raise cyclic adenosine monophosphate (cAMP) levels [309–311], inhibit free radical formation [265], and antagonize the production and actions of TNFα [272,275,276,312,313]. Pentoxifylline has been shown to mitigate ALI/ARDS in multiple animal models [265–271], as well as to reduce levels of TNFα and improve cardiopulmonary function in patients with sepsis [272–276]. However, pentoxifylline and related phosphodiesterase inhibitors have not yet been evaluated in large clinical trials in adults with ALI/ARDS.

5.7. Thromboxane Synthase and 5-Lipoxygenase Inhibitors

Various cells of the pulmonary circulation including endothelial cells release metabolites of arachidonic acid including the thromboxanes and leukotrienes. While thromboxanes cause platelet aggregation and vasoconstriction, leukotrienes cause broncho-constriction and act as powerful neutrophilic chemokines. Ketoconazole, a synthetic antifungal inhibits thromboxane and leukotriene synthesis, and thus may be of benefit in antagonizing this aspect of the inflammatory response in ALI/ARDS. Three clinical trials have shown that Ketoconazole when given prophylactically prevented ARDS in high-risk patients, and in one of these studies there was an observed mortality benefit in those receiving prophylaxis [314–316]. A large ARDS network study using 400 mg/day Ketoconazole early in the course of ALI/ARDS was unable to show any difference in gas exchange, ventilator-free days, or mortality [317] However, the use of Ketoconazole in the prophylactic mode in high risk patients was not addressed in this latter study and considering a lower dose of Ketoconazole was used, this strategy still remains of potential therapeutic value based on the earlier clinical findings [314–316].

5.8. N-Acetylcysteine (NAC)

NAC is a precursor for glutathione (GSH), an antioxidant present in significant levels in the normal lung [318–320]. GSH has many biological actions, ranging from oxidant protection to participation in metabolic pathways such as those involving inflammatory mediator synthesis [321]. Lavage from patients with ALI/ARDS is deficient in GSH [244], and GSH levels are also below average in some pulmonary fibrotic disorders [322]. Increased intracellular levels of GSH reduce production of pro-inflammatory cytokines like TNFα and IL-1 [318,323]. In addition to promoting GSH production, NAC also has direct antioxidant properties because of

its thiol group, and it can scavenge reactive oxidants including hydrogen peroxide, superoxide anion, and hypochlorus acid [323]. Animal studies indicate that NAC has significant protective effects against acute pulmonary injury from hyperoxia, endotoxin, or GSH synthesis inhibition [277–282]. NAC has been reported to improve respiratory function but not survival in adults with ALI/ARDS [283–285]. A double-blind, placebo-controlled study in 48 patients at five centers found that treatment with NAC or procysteine (2-oxo-4-thiazolidinecarboxylic acid, a cysteine analog and GSH precursor) increased cardiac index and decreased the number of days of ALI without improving mortality [285]. However, an ARDS Network trial of procysteine for patients with ARDS was terminated early due to lack of evidence of efficacy [285]. No adverse side effects have been reported from the use of NAC in patients with ALI/ARDS, consistent with the broad experience with this drug as an antidote for acetaminophen overdose. No studies to date have investigated the utility of NAC in combination therapies for ALI/ARDS.

5.9. Superoxide Dismutase (SOD) and Related Antioxidants

SOD acts to catalyze the conversion of superoxide anion to hydrogen peroxide [320,324, 325], which is subsequently converted to water by GSH peroxidase or by catalase, a tetrameric, heme-containing enzyme [320,325]. SOD exists primarily in three physiological forms: cytoplasmic SOD (Cu,Zn-containing), mitochondrial SOD (Mn-containing), and extracellular SOD (Cu-containing) [324,325]. The levels of extracellular SOD are relatively high in lung and brain tissue [326,327], and it has been speculated that this form of SOD may have a particular role in pulmonary anti-oxidant defense [287]. Cellular forms of SODs (cytoplasmic, mitochondrial) also have important anti-oxidant activity. In therapeutic applications involving the delivery of exogenous SODs to decrease superoxide anion, it is important to take into account that resulting increases in H_2O_2 could lead to hydroxyl radical production if the physiologic ability to scavenge H_2O_2 is exceeded. Animal studies show that hydroxyl radical production can cause oxidant-mediated lung injury as severe as that from superoxide [328]. A number of studies have shown that exogenously administered anti-oxidant enzymes, particularly when encapsulated in lipid vesicles (liposomes) or conjugated to polyethylene glycol to prolong biological half-life and aid delivery to cells, can protect against oxidant damage and mitigate the severity of acute pulmonary injury [288,329–334]. The majority of these studies have involved delivery of Cu,Zn-SOD by tracheal instillation [288,329,330, 332–334], although intraperitoneal injection has also been used [331]. Recombinant forms of several human SODs are available for clinical use in ALI/ARDS [286–288]. These enzymes have not been studied in any detail in combination therapies, although instillation of SODs with exogenous surfactant has been suggested as one approach to treating acute pulmonary injury [286,335]. In addition to SODs, several other anti-oxidant agents have been studied in therapeutic applications for lung injury. This includes EUK-8, a synthetic low molecular weight compound with SOD-like and catalase-like activity [336,337].

5.10. Immunonutrition

Providing early and appropriate enteral nutrition to critically-ill patients is a clinical standard of care. Enteral nutrition containing eicosapentaenoic acid (EPA, fish oil), gamma-linolenic acid (GLA, borage oil), and anti-oxidants including Vitamins E and C (termed collectively as immuno-nutrition), has been shown to reduce the days of mechanical ventilation, intensive care requirements, and the incidence of extra-pulmonary organ failure in patients with ARDS [338]. In retrospective subgroup analysis from this trial, it was also shown that levels of IL-8 and leukotriene B4 in bronchoalveolar lavage fluid were reduced in patients given enteral nutrition enriched in EPA and GLA [339]. A meta analysis of twelve randomized clinical trials using enteral formulas containing antioxidants suggested a reduction in infectious complications, but no observed differences in mortality [340]. Further studies are needed to

define more fully the specific benefits of anti-oxidants in enteral nutrition regimens for patients with ALI/ARDS.

6. AGENTS TARGETING THE FIBROPROLIFERATIVE PHASE OF ALI/ARDS

As discussed earlier (Section III, Table 2), interventions in the fibroproliferative phase of ALI/ARDS must primarily address pathophysiological elements of remodeling, repair and fibrosis as opposed to acute issues of cardio-respiratory instability. Current understanding of fibroproliferative lung injury suggests that therapeutic agents need to enhance repair (e.g., angiogenesis and alveolar secondary crest formation) while inhibiting fibroblast proliferation, differentiation, and interstitial matrix deposition. The necessity to include epithelial rescue in therapies for ALI/ARDS has been emphasized [63], although the detailed roles of epithelial cells in chronic lung injury remain unclear. Epithelial cell inflammatory mediator production and surfactant metabolism must also be normalized. Selected agents targeting various aspects of pathophysiology in fibroproliferative ALI/ARDS are summarized in Table 5 and are discussed below.

6.1. Agents to Reduce Persistent Inflammation in Fibroproliferative ALI/ARDS

Persistent inflammation is characteristic of patients that progress to fibroproliferative or fibrotic lung disease following acute exudative ALI/ARDS. Some anti-inflammatory agents already discussed for the acute phase of lung injury may have utility against these aspects of fibroproliferative phase pathology in combination therapies. In addition, anti-inflammatory agents like corticosteroids appear to have increased benefits in fibroproliferative lung injury compared to acute injury. During the early exudative phase of ALI/ARDS, corticosteroids are ineffective and even potentially harmful in patients [341,342]. In contrast, multiple studies have found improved outcomes for patients with established, fibroproliferative ARDS treated with corticosteroids over a prolonged course [343–350]. For example, Meduri *et al.* [349, 350] reported that patients who had no improvement in lung injury scores and were deemed non-responders at day 7 of acute ALI/ARDS had reduced inflammation and significant improvements in lung injury and survival following prolonged corticosteroid treatment. More recently the ARDS network published less positive results for methylprednisolone in patients with ARDS of at least 7 days duration [351]. Results showed that although there was a reduction in ventilator-free days, there was a significant increase in mortality at 60 and 180 days [351]. The use of inhaled rather than systemic corticosteroids in the fibroproliferative phase of ARDS to attempt to minimize drug-associated toxicity is currently under investigation.

A variety of anti-inflammatory compounds other than corticosteroids may be useful in treating fibroproliferative lung injury, but little direct clinical testing of potential agents has been done to date. A case series of 5 premature infants with BPD, a chronic fibrotic lung disease due to premature birth, has suggested reduced oxygen requirements, improved compliance, and reduced airway resistance following treatment with nebulized pentoxifylline [352]. This uncontrolled clinical experience supports further research on phosphodiesterase inhibitors as potentially relevant for fibroproliferative ALI/ARDS.

6.2. Agents to Re-Establish Matrix Deposition and Turnover in Fibroproliferativ

ALI/ARDS—Myofibroblast and endothelial cell invasion of the provisional matrix formed by protein exudation and coagulation initiates a “fibrosing alveolitis” and fibrotic interstitial foci in injured lungs. Fibroblast activation, migration, proliferation and collagen production in lung injury is augmented by cytokines and growth factors including transforming growth factor beta (TGFβ), platelet derived growth factor (PDGF), and TNFα. Agents under consideration to inhibit fibroblast-dependent fibrosis include antagonists to PDGF, inhibitors of TGFβ-mediated matrix protein production, and agents to promote fibroblast apoptosis including

PDGF tyrosine kinase inhibitors such as relaxin and lovastatin [353–355]. Other biologics like anti-CD44 antibody, which reacts with the cell-surface matrix receptor located on invading fibroblasts, may also promote apoptosis and resolution of fibroproliferation [356]. Additional agents that could potentially reduce fibroblast activity and restrict matrix formation include cytotoxic drugs like cyclophosphamide [357] or azothioprine [358], as well as interferon gamma and beta, colchicine, pirfenidone and D-penicillamine ([59,64], for review). However, despite the contributions of fibroblasts to chronic lung injury, it is not clear that inhibition of these cells will be effective in mitigating or reversing disease. Moreover, some degree of fibroblast activity and matrix deposition likely protects pulmonary architecture and enhances remodeling and repair, so that the use of cytotoxic agents targeting these cells has potential risks as well as benefits.

Two groups of enzymes that appear to be important in fibroproliferative lung injury are the matrix metalloproteinases (MMPs) and their negative regulators, the tissue inhibitors of metalloproteinases (TIMPs). These enzymes are thought to participate in establishing a balanced distribution of matrix to support normal pulmonary structure and function, as opposed to the relatively disorganized interstitial network that constitutes scarring or fibrosis in injured lungs. An imbalance between the activities of MMPs and TIMPs in injured lungs may thus promote abnormal composition, distribution or organization of matrix proteins and contribute to fibrosis. MMPs including collagenases and gelatinases have been found to be reduced in lavage from patients with ARDS and interstitial pulmonary fibrosis, while TIMPs were increased especially in fibrotic loci [359]. On the other hand, MMP activity has been found to be increased in mice with bleomycin-induced fibrosis [360]. Although MMPs and TIMPs are clearly relevant for fibroproliferative lung injury, a better basic research understanding of the regulation and balance of these enzymes in healthy and injured lungs is needed to allow the development of pharmacologic agents directed at related aspects of lung injury pathology in ALI/ARDS.

6.3. Agents to Improve Perfusion or Hypertension in Fibroproliferative ALI/ARDS

Pulmonary hypertension induced by arterial muscularization and fibrous narrowing or replacement of the microcirculation frequently contributes to the morbidity and mortality of chronic lung injury. Concomitant with these airway changes, platelet aggregation and fibrin-rich microthrombus formation within the vasculature cause increased pulmonary vascular resistance and pulmonary hypertension. Hypoxic pulmonary vasoconstriction and endogenous vasoconstrictors also contribute to the development of pulmonary hypertension in patients with ALI/ARDS [361]. A number of agents to improve pulmonary blood flow are under study in basic research, including endothelin (ET-1) receptor antagonists, prostaglandin derivatives, and anti-coagulants that could potentially be combined with (or replace) the conventional use of oxygen and vasodilating agents to reduce pulmonary vascular resistance in fibroproliferative ALI/ARDS (e.g., [362–364]). Studies using the endothelin receptor antagonist Tezosentan in a sheep model of endotoxin induced lung injury have demonstrated that treated animals exhibit reduced pulmonary edema, pulmonary hypertension and hypoxemia [364]. However, therapies with these agents are still in the developmental stage and have not been tested clinically in ALI/ARDS.

7. SUMMARY

Developing optimal pharmacotherapy for the severe clinical syndromes of ALI/ARDS ultimately depends on a detailed understanding of the pathophysiology of acute pulmonary injury, coupled with discovery-based medicinal chemical research and focused drug activity testing in cells, animals, and patients. To aid in future basic and applied medicinal chemistry research on new agents, this paper has reviewed current pharmacotherapy for ALI/ARDS in

the context of single-agent and combination therapies. Although current pharmacotherapy has not been highly successful in increasing survival in ALI/ARDS particularly in adults, improved mechanistic understanding of the pathogenic mechanisms involved in the individual insults responsible for acute and chronic lung injury have identified multiple biochemical and biological targets for future drug discovery and development. A number of agents including GM-CSF, activated protein C, active exogenous surfactant, and several vasoactive, anti-inflammatory, and anti-oxidant drugs are presently under clinical investigation as described in preceding sections. A variety of additional agents directed at specific biological aspects of acute and chronic lung injury are also being examined in continuing cell, molecular and animal research. The development of improved pharmacotherapy for ALI/ARDS should also benefit from the now-recognized importance of focusing many pulmonary-acting therapies on direct as opposed to indirect forms of these clinical syndromes.

In addition to single-agent treatments for ALI/ARDS, the possible benefits of combination therapies that simultaneously attack multiple aspects of pathophysiology are also becoming more widely appreciated. Individual pharmacological agents address only limited aspects of the complex, multifaceted pathophysiology of lung injury. The efficacy of an agent in mitigating its targeted element of disease can thus be obscured in terms of overall survival by other remaining elements of disease in critically-ill patients with ALI/ARDS. Several agents currently tested only as individuals may prove to have greater efficacy in improving survival or other long term outcomes when incorporated into combination therapies based on mechanistic understanding. Such therapies could potentially include combining multiple pharmacological agents having mechanistic synergy or additivity, or combining a pharmacological treatment with specific non-drug interventions such as different modes or strategies of mechanical ventilation or fluid balance.

Developing optimal medicinal chemical agents and combination therapy strategies for ALI/ARDS requires continuing complementary basic science and clinical research. Further chemistry-based laboratory research focusing on the discovery of new agents is essential, as are detailed cell and animal model studies testing putative agents for their activity alone and in mechanistically-complementary combinations. Direct clinical testing of new promising agents is of course crucial, although clinical trials in ALI/ARDS are complicated by the heterogeneity of patient populations and the multiple etiologies and broad pathology of lung injury. A rational approach to drug discovery and development that integrates findings on mechanistic activity and agent efficacy in basic research to facilitate the design and analysis of focused clinical trials will be necessary for defining optimal pharmacotherapies for ALI/ARDS-related lung injury in patients of all ages.

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Table 1

Potential Biological Targets For Pharmacotherapy In The Acute Exudative Phase Of Ali/Ards

Target	Contributing abnormalities or processes	Examples of relevant biological activities for medicinal chemistry agents*	Desired outcomes
Hypoperfusion and ventilation/ perfusion mismatching	Hypoxic vasoconstriction, inappropriate vasodilation, microvascular occlusion	Selective vasodilators, selective vasoconstrictors, anti-thrombotic agents	Vasodilate ventilated lung tissue regions, vasoconstrict non-ventilated lung tissue, reduce microvascular thrombosis
Surfactant dysfunction or deficiency	Physicochemical inhibitors of lung surfactant in edema or inflammation, or injury to type II pneumocytes	Active exogenous surfactants	Improve alveolar stability to reduce edema, and normalize P-V mechanics
Over-exuberant inflammation	Activation/recruitment of inflammatory leukocytes, over-production of pro-inflammatory mediators and decreased production of modulatory mediators	Cytokine or chemokine antagonists, soluble receptors, antioxidants, or other blockers of specific inflammation	Mitigate over-exuberant mediator activity and production while maintaining physiologic innate pulmonary host defense
Arterial hypoxemia	Decreased gas exchange, increased alveolar permeability, decreased resorptive capacity of the alveolocapillary membrane	Agents that increase alveolar and interstitial fluid clearance, increase compliance, or increase alveolar ventilation or gas exchange efficiency	Reduce alveolar and interstitial interstitial edema, increase arterial oxygenation without without increasing permeability injury
Death/injury of cells in airways and alveolocapillary membrane	Loss of normal ciliated airway epithelium alveolar type I cells, and microvascular endothelial cells	Cell protective agents that antagonize injury-induced changes in metabolism, differentiation, or growth	Reduce cell death and the severity of cellular injury

*Specific agents of possible utility in single or combination therapies in the acute exudative phase of ALI/ARDS are discussed in the text (Sections IV and V). Note that many of the biological targets in Table 1 are interdependent (e.g., surfactant dysfunction contributes to ventilation/perfusion abnormalities, arterial hypoxemia, edema, and abnormal lung mechanics). Similarly, many of the therapies noted will affect overlapping targets (e.g., vasoactive agents, exogenous surfactants, and agents to reduce edema will improve arterial oxygenation, compliance, and ventilation/perfusion mismatching and mitigate cell injury). Adapted from [34].

Table 2

Potential Biological Targets for Pharmacotherapy in Fibroproliferative/Fibrotic Phase ALI/ARDS

Target	Contributing abnormalities or processes	Examples of relevant biological activities for medicinal chemistry agents*	Desired outcome(s)
Persistent (chronic)	Persistent leukocytic activation, increased production of reactive enhance oxygen/nitrogen species and pro-inflammatory mediators	Agents that decrease the levels or activities of pro-inflammatory cytokines and chemokines chemokines, reduce reactive species, increase neutrophil apoptosis, or antagonize chronic neutrophil activity	Decrease over-exuberant inflammation and allow the initiation of normal tissue repair
Fibrosis	Fibroblast proliferation and invasion, and increased interstitial matrix deposition	Agents to enhance fibroblast apoptosis, reduce matrix formation, or increase matrix remodeling	Improve remodeling and repair in the lung interstitium
Pulmonary hypertension	Microvascular thrombosis, loss of vascular cross sectional area, decreased pulmonary capillary blood flow, and muscularization of distal small vessels	Agents to reduce microvascular thrombosis, enhance regrowth of microvascular network, and reduce perivascular smooth muscle proliferation	Improve revascularization and vascular repair to increase alveolar and interstitial perfusion
Hypoventilation and loss of gas exchange surface	Airway reactivity and obstruction, loss of functional respiratory airways & alveoli	Agents to dilate airways, clear secretions, normalize mucin production and consistency, promote differentiation of Clara cells to ciliated bronchiolar cells, or to enhance alveolarization	Improve pulmonary airflow, reduce airway resistance, increase alveolar ventilation
Alveolar epithelial cell abnormalities	Type I cell loss and type II cell proliferation and/or alteration	Agents to promote type II cell to type I cell differentiation, normalize type I/II cell numbers and functions, or protect alveoli against further injury	Normalize alveolar membrane permeability and cellular functions

*See text (Section VI) for presentation and discussion of current pharmacologic agents targeting several of the tabulated biological pathways in fibroproliferative phase ALI/ARDS. The development of new and more effective medicinal chemical agents and agent combinations targeting the biological pathways in Tables 1 and 2 for exudative and fibroproliferative phase ARDS is particularly important and challenging, as described in the text. Adapted from [34].

Table 3

Examples of Current Pharmacologic Agents with the Potential to Improve Ventilation-Perfusion Matching, Alveolar Ventilation, and Arterial Hypoxemia in ALI/ARDS

Pharmacologic agents to increase perfusion of ventilated alveoli
Inhaled nitric oxide (INO)
Inhaled prostacyclin (PGI_2)
Pharmacologic agents to decrease perfusion of poorly ventilated alveoli
Almitrine
Pharmacologic agents to increase alveolar ventilation and stability
Exogenous surfactants
Pharmacologic agents to reduce vascular obstruction
Anti-coagulants
Tissue factor pathway inhibitor (TFPI)
Site-inactivated factor VIIa
Inhibitors of neutrophil recruitment
Inhibitors of platelet aggregation
Endothelin-1 receptor antagonists
Pharmacologic agents to improve alveolar fluid clearance and reduce edema
Beta-2 agonists (e.g., Salbutamol)

See text (Section IV) for specific reference citations to studies using these agents individually in ALI/ARDS, as well as their potential use in combination therapy approaches.

Table 4

Examples of Current Pharmacologic Agents with the Potential to Target Inflammation or Oxidant Injury in Exudative ALI/ARDS

Pharmacologic agents with anti-inflammatory effects
Anti-TNF-α
Anti-IL-8
Anti-CD-40
Pentoxifylline
Ketoconazole
Pharmacologic agents with anti-oxidant properties
N-acetylcysteine
Cu, Zn Superoxide dismutase (liposome encapsulated)
Nutritional pharmacologic agents
Eicosapentaenoic acid
Gamma linolenic acid
Vitamins E, C

See text (Section V) for specific reference citations to studies using these agents individually in ALI/ARDS, as well as their potential use in combination therapy approaches.

Table 5

Examples of Current Pharmacologic Agents with the Potential to Target Persistent Inflammation, Matrix Deposition, or Improve Pulmonary Blood Flow in the Fibroproliferative Phase of ALI/ARDS

Pharmacologic agents with anti-inflammatory effects
Corticosteroids
Pharmacologic agents affecting matrix deposition and turnover
Anti-TGF β
Anti-PDGF
Cyclophosphamide
Azothioprine
TIMPs
Pharmacologic agents to improve pulmonary blood flow
Tezosentan
Prostacyclin
Anticoagulants

See text (Section VI) for specific reference citations to studies using these agents individually in ALI/ARDS, as well as their potential use in combination therapy approaches.