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Emerging Therapies for the Prevention of Acute Respiratory Distress Syndrome

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Abstract

The development of the acute respiratory distress syndrome (ARDS) carries significant risk of morbidity and mortality. To date, pharmacologic therapy has been largely ineffective for patients with ARDS. We present our personal review aimed at outlining current and future directions for the pharmacologic prevention of ARDS.

Several available risk-stratification or prediction scores strategies for identification of patients at risk of ARDS have been reported. Although not ready for the clinical everyday use, they are and will be instrumental in the ongoing and future trials of pharmacoprevention of ARDS.

Several systemic medications established the potential role in ARDS prevention based on the preclinical studies and observational data. Due to potential for systemic adverse effects to neutralize any pharmacologic benefits of systemic therapy, inhaled medications appear particularly attractive candidates for ARDS prevention. This is because of their direct delivery to the site of the proposed action (lungs), while pulmonary epithelial surface is still functional.

We postulate that overall morbidity and mortality rates from ARDS in the future will be contingent upon decreasing the overall incidence of ARDS through effective identification of those at risk and early application of proven supportive care and pharmacologic interventions.

Keywords

ARDS; prevention

Introduction

ARDS is a clinicopathologic entity defined by acute onset, hypoxemia and characteristic chest radiographic findings (Ranieri, Rubenfeld et al. 2012). Despite the heterogeneous array of systemic and pulmonary insults that can serve as triggers to this devastating condition, ARDS is considered a distinct condition on the basis of a final common pathway in pathogenesis (Matthay, Ware et al. 2012) and corresponding histopathologic changes (Thompson 2014). Despite decades of research in treatment of ARDS, not a single effective pharmacological intervention emerged. Several common ARDS precipitants were elucidated including ventilator induced lung injury, septic shock, transfusion related lung injury and

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ventilator associated pneumonia (Estenssoro, Dubin et al. 2002), hence management of ARDS has focused on supportive care measures. These include improvements in recognition and timely management of severe sepsis and septic shock (Rivers, Nguyen et al. 2001; Yealy, Kellum et al. 2014), lung protective ventilation strategies (Acute Respiratory Distress Syndrome Network 2000), restrictive PRBC, platelet and FFP transfusion strategies (Gajic, Rana et al. 2007; Khan, Belsher et al. 2007; Toy, Gajic et al. 2012) the adoption of standardized VAP prevention "bundles" (Rosenthal, Rodrigues et al. 2012) and other institutional protocols such as the proposed Checklist for Lung Injury Prevention (CLIP, Figure 1) (Kor, Talmor et al. 2012). With these improvements in the delivery of supportive care, rates of nosocomial ARDS have been on the decline (Li, Malinchoc et al. 2011). However, mortality associated with ARDS has remained at the similar unsettlingly high ~40% rate for the past approximately 20 years. (Phua, Badia et al. 2009) These stagnant mortality data are certainly not reflective of a lack of interest in finding effective pharmacologic approaches to the treatment of ARDS. The cavalcade of investigational therapies showing promise in preclinical trials failed to demonstrate any meaningful clinical efficacy (Cepkova and Matthay 2006; Bosma, Taneja et al. 2010) when applied after the development of fully established ARDS. As such, a paradigm shift is occurring in how we approach the burden of ARDS, away from treatment and towards prevention of the fully established syndrome. (Ortiz-Diaz, Festic et al. 2013; Beitler, Schoenfeld et al. 2014) Parallels can be drawn to the other critical illness syndromes, of which sepsis have been the most studied and with the best resulting improvement in outcomes following adoption of early identification and goal-directed treatment principles. Since most of the ARDS cases develop 2–5 days after the hospital admission (Gajic, Dabbagh et al. 2011) there is a window of opportunity where early identification of patients at risk and improvements in supportive care, coupled with effective pharmacological interventions could potentially prevent or ameliorate ARDS in patients at risk. Hence, the key question: Can pharmacological intervention administered prior to the fully established ARDS prevent disease development and enhance outcomes in patients at risk? In order to answer this key question, we first have to find answers to the following: who are the patients at risk, when to apply the intervention, and what intervention? The first two questions were answered by the LIPS trial, to a certain degree. The final and perhaps the most important sub-question remains: What are the effective interventions? In order to identify a safe pharmacologic treatment as an effective intervention, the investigators ought to apply systematic translational research directed towards proven mechanistic pathways of ARDS pathophysiology.

Preventive Strategies

- Who and when?

The first critical step in instituting an effective primary prevention program was to identify the population most likely to glean benefit from the prophylactic intervention. The Lung Injury Prediction Score (LIPS) (Gajic, Dabbagh et al. 2011) is currently the best available tool for risk stratification of patients presenting to the hospital without ARDS. To evaluate this prediction model, LIPS investigators prospectively enrolled 5584 patients admitted for sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery and

included comorbid conditions such as alcohol abuse, DM, obesity, physical exam and laboratory findings [Figure 2]. Using a cutoff LIPS score of ≥4, the authors found an 18% positive predictive value and 97% negative predictive value with an overall incidence of Acute lung injury (ALI) or ARDS of 6.8%. The patients destined to develop ARDS in the hospital did so most frequently beyond 48 hours of hospitalization so any future intervention should be applied within the first 24 hours after the admission to allow it sufficient time to exhibit its protective effect.

A number of other scoring systems for risk stratification with regard to development of ARDS have been proposed. Secondary analysis of the LIPS data have revealed that SpO2/FiO2 ratio, a single (composite) variable from the LIPS, is an independent risk factor for progression to ARDS. (Festic, Bansal et al. 2013). Levitt et Al reported an Early Acute Lung Injury (EALI) score, based on the oxygenation impairment, radiographic abnormalities and presence of concomitant immunosuppression (Levitt, Bedi et al. 2009). This risk score may be more applicable to hospitalized patients already developing early lung injury. Specific to the postoperative population, the Surgical Lung Injury Prediction model, SLIP and refined SLIP-2, have shown similar utility in predicting which surgical patients are at the highest risk for development of ARDS (Kor, Warner et al. 2011), (Kor, Lingineni et al. 2014). While none of these prediction models appear ready for everyday use in clinical practice, they represent useful tools for enrollment in clinical trials investigating pharmacological strategies for ARDS prevention.

Pharmacologic Preventive Strategies

- What interventions?

Key components in the common final pathogenic pathway to ARDS include dysregulated inflammation, maladaptive platelet activation, dysfunction of the coagulation cascade, endothelial and epithelial barrier dysfunction, and failure of T-cell/macrophage mediated clearance of activated neutrophils and necrotic debris [Figure 3]. (Matthay, Ware et al. 2012). As we have begun to elucidate the individual components leading to the full-blown ARDS syndrome, several potential therapeutic targets have emerged [Table 1].

Systemic delivery

Aspirin

Several observations regarding the role of activated platelets as ‘instigators’ of endothelial dysfunction (Yiming, Lederer et al. 2008) and neutrophil chemotaxis and degranulation (Zarbock and Ley 2009) in animal models of ARDS have made aspirin an attractive potential agent. Furthermore, animal models specifically investigating the use of aspirin have been promising. In a “two hit” murine model of ARDS that included transfusion related acute lung injury and endotoxinemia, control mice were compared to platelet depleted and aspirin treated mice (Looney, Nguyen et al. 2009). In this study, the platelet-depleted and aspirin treated mice had similarly significant improvements in progression to ARDS and in mortality versus control. Song et al. demonstrated amelioration of the thromboxane-mediated pulmonary hemodynamic changes in aspirin treated mice with endotoxin-induced ARDS (Song, Suzuki et al. 2004). And in an acid-induced “aspiration”

murine ARDS model, Zarbock and colleagues demonstrated that aspirin decreased neutrophil chemotaxis across pulmonary endothelium, decreased the degree of pulmonary edema and improved oxygenation in mice (Zarbock, Singbartl et al. 2006).

The results of two observational studies in humans have thus far shown conflicting results with a possible trend towards a benefit of aspirin therapy for the prevention of ARDS. The charts of patients admitted to the medical ICU at Mayo Clinic in Rochester, Minnesota in 2006 with at least one known risk factor for ALI (ARDS) were reviewed. Prehospital use of antiplatelet medication was found in this series to be associated with a lower hazard ratio of ARDS development (HR 0.34, 95% CI 0.13 – 0.88) (Erlich, Talmor et al. 2011). A secondary analysis of 3814 patients (after excluding surgical patients) from the LIPS cohort showed a trend towards a protective effect from aspirin which did not achieve statistical significance after propensity score matching (OR for development of ARDS 0.7, 95% CI = 0.48 – 1.03, p =0.07) (Kor, Erlich et al. 2011). In another recently published propensity score analysis of 1149 patients admitted to the surgical or medical ICU at a tertiary care facility, Chen et al. found prehospital aspirin use to be associated with a significantly lower risk of developing ARDS versus matched controls even after adjusting for propensity scores for prehospital aspirin use (Chen, Janz et al. 2014)

The need for prospective, randomized double-blind human data with regards to aspirin in prevention of ARDS is already being addressed. The Lung Injury Prevention Study with Aspirin (LIPS-A) has been completed (NCT 01504867) with the results forthcoming. This was a phase II double-blind, placebo controlled, multi-center trial comparing aspirin (325mg ×1 day followed by 81 mg ×6 days) to identically appearing placebo. Eligible enrollees were hospitalized adults with a LIPS score of ≥4 at the time of admission. Development of ARDS is the primary outcome and all enrolled patients received CLIP-based support for the standardization of care and avoidance of known nosocomial secondary hits.

Systemic Steroids

Systemic steroids have been shown to possess pleiotropic anti-inflammatory properties; 1) They reduce pro-inflammatory cytokines, chemokines, adhesion molecules and receptors, (Frieri 1999) 2) Increase anti-inflammatory mediators, (Kovalovsky, Refojo et al. 2000) 3) Increase activated protein C (Seam, Meduri et al. 2012), 4) Reduce inducible nitric oxide (iNO) expression (Yu, Ouyang et al. 2009), and 5) Inhibit fibroblast proliferation and collagen deposition (Thompson 2003). The last characteristic specifically may play role in tertiary prevention of excessive fibrosis as complication of fully established ARDS. The main limitation of use of systemic steroids in ARDS is their association with adverse effects, which potentially might offset their beneficial anti-inflammatory effects. Furthermore, studies that looked into role of steroids in the prevention of ARDS were conducted prior to standardization of the lung protective mechanical ventilation; they used different durations of therapy and employed different definitions of ARDS, which further complicated the already heterogeneous characteristics of patients with ARDS. Therefore, it is not surprising that these studies showed conflicting results, hence the equipoise for systemic steroid use in ARDS prevention continue (Brian, Rolf et al.)s. Future studies will have to evaluate which groups of patients at risk and at what point in the course of the disease will favorably

respond to systemic steroids. Perhaps, biomarkers will play the important role in attempts to answer these questions. For example, Steinberg et al, in a subgroup analysis of a randomized controlled trial showed that patients randomized to steroids with higher levels of procollagen peptide III, a marker of fibroproliferation, had significantly better survival.

Statins

It has long been appreciated that the biologic effects of statins extend beyond their ability to lower LDL levels. These so-called pleiotropic effects include ischemic stroke prevention, decreased vascular smooth muscle proliferation and reduced reactive oxygen species production; these effects are thought to be mediated by the inhibition of several isoprenylated proteins or isoprenoids (Liao 2002; Arnaud, Veillard et al. 2005; Greenwood and Mason 2007). Murine models have demonstrated a role for statins in the prevention of ARDS (Jacobson, Barnard et al. 2005). Prospective observational human studies have revealed conflicting results; with some suggesting that prehospital statin use is protective against ALI/ARDS in patients with sepsis (Kruger, Fitzsimmons et al. 2006; Falagas, Makris et al. 2008; O'Neal, Koyama et al. 2011) and others showing no clear benefit (Bajwa, Malhotra et al. 2012). A recently complected large, multicenter, randomized, double blinded prospective clinical trial comparing rosuvastatin to placebo in patients with sepsis-associated ARDS failed to show any meaningful benefit of statin therapy in fully established ARDS (Truwit, Bernard et al. 2014).

The discordance between prehospital statin use and a trend toward benefit and the lack of benefit seen with initiation of statins in established ARDS is likely multifactorial. Whether initiation of statins at the time of hospitalization for those at high risk but before the development of ARDS would be beneficial merits further research.

RAAS blockers

There is compelling evidence to suggest that a prominent role in the development of ARDS is played by local pulmonary vascular angiotensin converting enzyme (ACE) activity. For example high levels of ACE have been isolated from broncheoalveolar lavage fluid in subjects with ARDS versus non-ARDS controls (Idell, Kueppers et al. 1987). Additionally, homozygosity for the polymorphism in the gene encoding ACE associated with higher enzyme activity levels has been shown to be an independent risk factor for the development of ARDS (Marshall, Webb et al. 2002). Elegant in vitro studies have linked angiotensin II, the downstream product of ACE activity, to human lung fibroblast collagen production in a bleomycin-toxicity model. This was attenuated by ACE inhibitor or angiotensin receptor blocker therapy (Marshall, Gohlke et al. 2004). As such, inhibition of the renin-angiotensin aldosterone axis has been of interest as a potential target for prevention of ARDS, and there have been encouraging preclinical data in this regard.

For example in a rat model of chemically induced ARDS, captopril therapy markedly improved several surrogate markers of severity of ARDS including circulating endothelial cells, PaO2, and wet to dry lung weight ratio (Liu and Zhao 2002). In another ARDS model using rats subjected to ventilator induced lung injury, captopril significantly reduced markers of inflammation and apoptosis versus in untreated controls. (Wosten-van Asperen,

Lutter et al. 2008) In a similarly designed study, Yao showed losartan to be effective at mitigating the ventilator-induced lung injury in rats (Yao, Feng et al. 2008)

Human data are somewhat conflicting but suggest a protective effect of ACE inhibitor or angiotensin receptor blocker (ARB) therapy in selected populations. In a large prospective trial, chronic ACE inhibitor use was associated with lower rates of pneumonia versus placebo, however this benefit was limited only to Asian population (Ohkubo, Chapman et al. 2004). In her review of the interplay between diabetes, hyperglycemia and therapies commonly prescribed for diabetic patients, Honiden noted that the decreased rate of mortality from community-acquired pneumonia noted among Caucasians chronically taking ACEI/ARB therapy only extended to diabetic patients (Honiden and Gong 2009). Interestingly, diabetic patients have been shown to be at decreased risk of developing ARDS compared to non-diabetic patients (Yu, Christiani et al. 2013). A retrospective review of 1423 patients admitted to ICU in Rochester, Minnesota showed a statistically significant reduction in the risk of developing ARDS in those patients taking ACEI/ARB therapy chronically prior to hospitalization, with an odds ratio of 0.49, 95% CI 0.25 – 0.94 (Trillo-Alvarez CA 2009). The LIPS cohort study however did not find any statistically significant decrease in the incidence of ARDS among patients at high risk for developing ARDS taking an ACEI/ARB prior to hospitalization. On the contrary, the data suggested a trend towards worsening mortality outcomes for those patients taking ACEI/ARB therapy who developed ARDS (Watkins TR 2011).

These disparate findings perhaps highlight the interplay between genetic and environmental factors in the pathogenesis of ARDS and the need for ongoing prospective research investigating, which patients could benefit from the use of ACEI/ARB therapy for the prevention of ARDS, if any.

PPAR agonists

Peroxisome proliferator-activated receptors (PPAR) are a family of intracellular receptors which translocate to the nucleus and modulate gene expression in response to ligand binding. These are well known for their effects with regard to glucose and lipid metabolism but are also important mediators of cellular proliferation and inflammation and are expressed in vascular endothelium, smooth muscle cells and various leukocytes (Brown and Plutzky 2007). Animal models have shown PPAR gamma to be implicated in the inflammation associated with asthma, COPD and pulmonary fibrosis (Belvisi and Hele 2008). As such PPAR agonists, particularly the thiazolidinediones have gained attention as having potential utility in the prevention of ARDS. There is ample animal data to suggest a role may exist for thiazolidinedione therapy in the prevention of ARDS. Rosiglitazone has been shown to protect lung tissue in bleomycin toxicity, endotoxemia, pancreatitis, and hyperoxia (Honiden and Gong 2009).

To date no prospective human studies involving the use of PPAR agonists have been performed. The association of thiazolidinedione with worsening congestive heart failure in diabetic patients might have resulted in less interest in investigating this class of drugs.

Inhaled Delivery

The appeal of aerosol or nebulized delivery systems for medications lies in the ability to potentially deliver effective doses of agent while minimizing or wholly avoiding systemic side effects. Parallels can be drawn to inhaled medications already available for an array of chronic pulmonary disorders or bronchopulmonary infections.

Inhaled Corticosteroids

Investigators have examined the preventative and therapeutic roles of inhaled corticosteroids (ICS) in animal models of acute lung injury (ALI) through direct and indirect pulmonary insults. ((Forsgren, Modig et al. 1990; Walther, Jansson et al. 1992; Walther, Jansson et al. 1993; Wang, Zhang et al. 2002; Wang, Zhang et al. 2004; Jansson, Eriksson et al. 2005). Despite heterogeneity in their methodology, these investigators have reported remarkably uniform observations with regard to the ability of ICS to attenuate lung injury. Related to this, ICS are commonly used medications with an excellent safety profile in humans; however, to date no investigators have performed randomized studies of ICS for the prevention or early treatment of ARDS in human subjects. In a secondary analysis of the LIPS cohort, pre-hospitalization ICS exhibited raw protective signal towards ARDS development. Even though signal weakened after comprehensive adjustment with propensity matched analysis, the estimate of effect remained consistent suggesting clinical equipoise and implications for further investigations in role of ICS in ALI/ARDS prevention. (Festic, Ortiz-Diaz et al.)

Beta Agonists

Besides dysregulated inflammation, another hallmark of ARDS involves accumulation of protein-rich exudative edema fluid in the airspaces of the lung. Beta agonists increase the rate of vectorial transport of salt and water across normal epithelium as well as in animal models of ALI. (Matthay, Folkesson et al.) As such, beta agonists may be effective as a preventative therapy due to their ability to enhance resolution of pulmonary edema fluid and maintain endothelial barrier functions under baseline conditions. (Matthay, Folkesson et al.). The first ARDS prevention randomized controlled study of beta agonists have been recently reported. Perkins et al. studied 362 patients undergoing esophagectomy in 12 centers in the United Kingdom over a 3-year period. The incidence of ARDS did not differ between salmeterol and placebo groups, however, postoperative adverse events (primarily pneumonia) were significantly less frequent in the intervention group. Moreover, in a substudy of 53 patients with available plasma samples, salmeterol reduced several biomarkers of alveolar inflammation and epithelial injury. (Schein, Bergman et al. 1987)

Combined inhaled corticosteroids and beta agonists

Given the bronchodilating as well as anti-inflammatory properties of beta agonists, it has been proposed that they may act in synergy when used in combination with ICS. Seventy percent of patients on ICS in the secondary analysis of LIPS cohort (Festic, Ortiz-Diaz et al.) were concomitantly receiving inhaled beta agonists. Based on this experience, investigators initiated a multi-center, double-blind, placebo-controlled, randomized trial evaluating the combined effect of early administered budesonide and formoterol on lung function in

patients at risk of ARDS (NCT01783821). This trial has been designed to test the previous observational study results and provide essential data for a future multi-center phase-III trial.

Heparin/Thrombolytics

The interplay between local alveolar inflammation and dysregulated coagulation with fibrin deposition/accumulation is integral to the pathogenesis of ARDS. This makes agents targeting the coagulation cascade attractive potential therapeutic options. Although systemic administration of anticoagulant medications would possess the same proposed effect, it carries significant risk of bleeding complications, leading to the investigation into use of inhaled anticoagulant medications.

Heparin is unique in its ability to bind not only antithrombin III, but dozens of other so-called 'heparin binding proteins' such as complement proteins, interferons, fibroblast growth factor and other cytokines (Young 2008). These biologic actions likely mediate the previously documented but not completely understood anti-inflammatory effects of heparinoids. Miller et al. recently published a review of available human and animal data relating to the use of inhaled heparin and heparin related compounds in smoke inhalation injury. Collectively these data show decreased morbidity and may suggest potential mortality benefit for the use of inhaled heparin in smoke inhalation injury without increasing markers of coagulopathy or increasing the risk of bleeding complications (Miller, Elamin et al. 2014). Whether these data will have generalizable applications to the at-risk ARDS population remains to be seen, and further investigation into the utility of routine use of inhaled heparin in smoke inhalation injury is merited and already registered in the clinicaltrial.gov database (#NCT014548690).

In a murine model of hemorrhagic shock, it has been shown that microthrombus formation precedes the subsequent accumulation of leukocytes and is likely due to sluggish blood-flow in the low-pressure pulmonary circulation (Conhaim, Mangino et al. 2010). As such, inhaled thrombolytic therapy has been of interest for prevention of ARDS and has been studied in rat models showing mitigation of microthrombus formation and subsequent leukocyte accumulation (Conhaim, Watson et al. 2014).

Hypertonic saline

Hypertonic saline has been established as a safe and effective tool in the management of cystic fibrosis (Elkins, Robinson et al. 2006), and non-CF bronchiectasis (Kellett and Robert 2011). It is postulated that in addition to its effects on sputum viscosity, the efficacy of nebulized hypertonic saline is due at least in part to its ability to inhibit neutrophil and macrophage mediated cytokine production (Cuschieri, Gourlay et al. 2002), (Zallen, Moore et al. 2000), (Deitch, Shi et al. 2003). In a rat model of traumatic shock, Wohlauer et al. demonstrated a convincing protective effect of inhaled hypertonic saline against pulmonary vascular permeability, neutrophil chemotaxis, matrix metalloprotease activity, IL-8 activity and histologic changes consistent with ARDS (Wohlauer, Moore et al. 2012). A recent preclinical study demonstrated the cytoprotective effect of extracellular hypertonicity induced by aerosolized hypertonic saline on alveolar resident cells, resulting in their resistance to injury. (Brian, Rolf et al.). Although routine use of *intravenous* hypertonic

saline for resuscitation of hypovolemic shock in trauma was shown not to improve mortality (Bulger, May et al. 2011) owing to disturbance of coagulation cascade, *inhaled* hypertonic saline is unlikely to have this systemic effect. A prospective study is being planned by the LIPS investigators.

N-Acetyl Cysteine

N-Acetyl Cysteine (NAC) is known for its ability to reduce the burden of oxidative stress by maintaining intracellular stores of reduced glutathione (Lauterburg, Corcoran et al. 1983). There is considerable evidence that oxidative stress stemming from depleted glutathione stores contributes to the pathogenesis of ARDS (Soltan-Sharifi, Mojtahedzadeh et al. 2007). In one small prospective clinical trial enrolling patients with smoke inhalation injury, the combination of inhaled NAC, heparin and albuterol were superior to albuterol and placebo with respect to mortality and lung injury scores (Miller, Rivero et al. 2009). Two additional clinical trials enrolling patients with active ARDS or undergoing esophagectomy (high risk surgery) have shown promise for intravenous NAC with regards to surrogate markers of pulmonary morbidity (Zingg, Hofer et al. 2007), (Soltan-Sharifi, Mojtahedzadeh et al. 2007). Owing to its well-established safety profile and promising preliminary clinical data, NAC should be of particular interest moving forward.

On The Horizon

Myriad additional agents are at various stages of preclinical and/or clinical investigation with regard to their potential use in the prevention of ARDS. Focus of our attention to these agents is not all inclusive as this area of research is rapidly evolving.

In a recently published, industry-sponsored phase 1/2 trial, Interferon-β-1a (FP-1201) showed promising, significant results with regard to improving oxygenation and 28 day mortality (OR 0.19, 95% CI 0.03 – 0.72) in 37 patients receiving treatment vs 59 matched controls with established ARDS. The proposed mechanism is via decreased vascular leakage through upregulation of pulmonary capillary CD73 (Bellingan, Maksimow et al. 2014).

Mesenchymal stem cell (MSC) therapy has been shown in animal models of sepsis to reduce markers of inflammation and incidence/severity of ARDS (Mei, Haitsma et al. 2010), and decrease histopathologic evidence of ARDS in ex-vivo and in-vitro studies using human lungs and lung tissue (Lee, Krasnodembskaya et al. 2013). An additional recently published study using human MSC in a rat ARDS model improved lung compliance, oxygenation, alveolar edema and promoted return to normal lung architecture (Hayes, Masterson et al. 2014). MSC have been shown to lead to more efficient tissue repair, and their use in ARDS is an exciting clinical prospect. One challenge of translating this promising bench research to the clinical setting is the optimal route of delivery of stem cell therapy; which in animal models has shown promise via the intravenous and intratracheal routes. Two clinical trials are ongoing (NCT01775774, NCT01902082) to assess the optimal doses of IV MSC therapy, and an additional phase 1 trial (NCT01632475) is underway assessing the safety of intratracheal administration of MSC in neonates with severe bronchopulmonary dysplasia (Lee, Rocco et al. 2014).

It has been postulated that at least part of the protective effects of exogenous MSC administration is mediated via their ability to secrete Keratinocyte Growth Factor (KGF) (Zhu, Feng et al. 2014). As such, KGF has been under investigation as a therapeutic agent in and of itself. Pretreatment with KGF prior to pulmonary acid injury in mice decreased markers of inflammation (Yano, Deterding et al. 1996). The mechanism by which KGF protects pulmonary epithelial cells from apoptosis and promotes survival and epithelial integrity has been elucidated in exquisite detail (Bao, Wang et al. 2005). KGF therefore may prove to have direct applications in the prevention of ARDS.

Curcumin, a natural phenol found in the spice turmeric has gained attention for its potential ability to modulate mammalian inflammation. In a murine model of virally induced ARDS, pretreatment with curcumin significantly reduced a number of surrogate severity markers of ARDS (Avasarala, Zhang et al. 2013). There has been interest among LIPS investigators to further study prospectively curcumin for ARDS prevention (personal communication, Ruxana Sadikot, MD).

Adrenomedullin, a vasoactive peptide hormone initially isolated from pheochromocytoma tissue has been gaining interest as a potential biomarker for ARDS and may have therapeutic potential. Rat models of ARDS have shown exogenous adrenomedullin to be a potent inhibitor of lung injury in gut ischemia/reperfusion (Dwivedi, Wu et al. 2007) as well as endotoxinemia (Itoh, Obata et al. 2007). The potential role of this agent for humans remains to be seen and to our knowledge the only ongoing research using human subjects involves its use as a biomarker in various conditions.

Conclusion

Years of research on pharmacologic therapy for established ARDS have not yielded a single effective medication. However, this might not have been in vain. Many of the previously studied pharmacologic compounds, as well as new ones, when used early in the disease evolution may prove effective in the prevention of ARDS. We especially favor medications that have been proven to be safe, inexpensive and widely available. As such, these medications should be first studied in smaller, phase 2 trials that are much more feasible.

The completed LIPS-A trial and ongoing LIPS-B trial have already demonstrated the feasibility of early administration of systemic and inhaled medications to patients deemed at risk for ARDS development, frequently started while the patient is still in the emergency room. We postulate that overall morbidity and mortality rates from ARDS in the future will be contingent upon decreasing the overall incidence of ARDS through effective identification of those at risk and early application of proven supportive care and pharmacologic interventions.

Investigators, however, need to change the way of conducting randomized clinical trials to discern effective interventions. Some of the proposed strategies should include the following: smaller phase II trials of relatively homogenous patient populations, assessment of outcome variables other than mortality, focus on patient-centered outcomes including

longer-term outcomes, pragmatic and adaptive clinical trials, as well as the “platform” trials, which could simultaneously evaluate multiple treatments efficiently.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clip Elements	Definition
Lung protective mechanical ventilation	Tidal volume between 6-8 mL/kg predicted body weight and plateau pressure <30 cm H2O; PEEP≥5 cm H2O, minimize FiO2 (target O2 saturation 88-92% after early shock)
Aspiration precautions	Intubation supervised by experienced providers, elevated head of the bed, oral care with chlorhexidine, gastric acid neutralization in those not receiving tube feeds
Adequate empiric antimicrobial treatment and source control	According to suspected site of infection, health care exposure, and immune suppression
Limiting fluid overload	Modified ARDS Network FACCT protocol(National Heart, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials et al. 2006) after early shock
Restrictive transfusion	Hemoglobin target >7 g/dL
Assess readiness for extubation	Limit continuous sedation and perform spontaneous breathing trial as soon as feasible

Figure 1.
Checklist for Lung Injury Prevention

	LIPS Points	Examples
Predisposing Conditions		
Shock	2	
Aspiration	2	
Sepsis	1	(*1*) Patient with history of alcohol abuse with septic shock from pneumonia requiring $FI_{O_2} > 0.35$ in the emergency room: Sepsis + shock + pneumonia + alcohol abuse + $FI_{O_2} > 0.35$ 1 + 2 + 1.5 + 1 + 2 = 7.5
Pneumonia	1.5	
High-risk surgery*		
Orthopedic spine	1	
Acute abdomen	2	
Cardiac	2.5	
Aortic vascular	3.5	
High-risk trauma		(*2*) Motor vehicle accident with traumatic brain injury, lung contusion, and shock requiring $FI_{O_2} > 0.35$ Traumatic brain injury + lung contusion + shock+ $FI_{O_2} > 0.35$ 2 + 1.5 + 2 + 2 = 7.5
Traumatic brain injury	2	
Smoke inhalation	2	
Near drowning	2	
Lung contusion	1.5	
Multiple fractures	1.5	
Risk modifiers		
Alcohol abuse	1	
Obesity (BMI > 30)	1	(*3*) Patient with history of diabetes mellitus and urosepsis with shock Sepsis + shock + diabetes 1 + 2 − 1 = 2
Hypoalbuminemia	1	
Chemotherapy	1	
$FI_{O_2} > 0.35$ (> 4 L/min)	2	
Tachypnea (RR > 30)	1.5	
$Sp_{O_2} < 95\%$	1	
Acidosis (pH < 7.35)	1.5	
Diabetes mellitus†	−1	

Definition of abbreviations: BMI = body mass index; RR = respiratory rate; Sp_{O_2} = oxygen saturation by pulse oximetry.

* Add 1.5 points if emergency surgery.

† Only if sepsis.

Figure 2.
Lung Injury Prediction Score calculation

Table 1

Emerging therapies for the prevention of ARDS and previous studies.

Medication	Mechanism of action	Animal Studies	Human Studies
Aspirin	Inhibition of platelet mediated cyclooxygenase metabolism involved in platelet-neutrophil-endothelial interactions.	Mice treated with aspirin have less pulmonary platelet and neutrophil sequestration. Also treated animals have improved survival and decreased lung weights.	Observational studies conflicting in terms of their findings. The largest cohort found a non-significant trend toward a protective effect. LIPS-A trial completed, awaiting results.
Systemic Corticosteroids	Multi-potent; inhibit inflammatory cytokines; induced apoptosis of macrophages; maintain endothelial cellular barrier.	Majority show improvement of hypoxemia, pulmonary vascular pressure and extra-vascular lung water.	Studies performed in the 1980s in heterogenous groups of patients showed no benefit in administering high-dose steroids. Subgroup analysis of RCT suggest using biomarkers may help with patient selection.
Inhaled Heparin	In addition to potentiating anti-thrombin-III, inhibits adhesion of neutrophils to endothelium and degrades intravascular and bronchial fibrin.	Conflicting results with improvement of hypoxemia histology scores and shunt fraction.	Suggest morbidity/mortality benefit in smoke inhalation injury patients; RCT currently enrolling patients.
Inhaled Corticosteroids	Same as systemic corticosteroids. In theory, might spare patients from hyperglycemia, myopathy, super-infection, etc.	Most studies conducted in mice indicate that physiological surrogates are improved by treatment prior to or after direct/indirect lung injury.	Subgroup analysis of LIPS-A cohort suggest protective effect of baseline ICS against development of ARDS. LIPS-B recruiting.
Inhaled Hypertonic Saline	Inhibition of neutrophil activation/ chemotaxis and macrophage cytokine production	Rats with trauma show less pulmonary vascular permeability, neutrophil chemotaxis, matrix metalloprotease activity, IL-8 activity and ARDS at necroscopy.	Intravenous hypertonic saline shown to have no benefit in trauma patients, likely due to effects on coagulation cascade. Prospective study forthcoming from LIPS investigators.
Inhaled beta-agonists	Enhanced alveolar fluid clearance and inhibits neutrophil adhesion to the endothelium.	Improved pulmonary mechanics; decrease neutrophil sequestration, inflammatory cytokine concentrations and enhanced surfactant secretion.	LIPS-B ongoing; no difference in ARDS incidence but less pulmonary complications among high risk surgical patients, mainly pneumonia.
Statins	Decreases inflammatory cytokine levels, adhesion molecule expression, and neutrophil proliferation.	Improvement in oxygenation, hemodynamic surrogates, neutrophil sequestration and decreased cytokine concentration.	Human observational studies show inconsistent effects of prehospital statin use with regards to development of ARDS. Statin therapy for treatment of established ARDS has been shown to be ineffective.
Thrombolytic Therapy	More rapid resolution of pulmonary microthrombi	Rat studies showing mitigation of pulmonary microthrombus formation and decreased neutrophil chemotaxis	No human studies published to date
N-Acetyl Cysteine	Repletes intracellular stores of reduced glutathione, decreasing oxidative stress.	In vivo studies elucidating the mechanism of NAC.	Mitigated mortality and lung injury scores in patients with smoke inhalation injury.
Renin-angiotensin axis blockers	Angiotensin-2 positively modulates nuclear factor-κβ gene expression. ACE type 2 receptor with angiotensin as its ligand, prevents endothelial damage.	Effective in preventing endothelial damage and inflammatory cytokine expression.	Observational studies showed a protective effect among specific populations including Asians and diabetics

Medication	Mechanism of action	Animal Studies	Human Studies
Peroxisome Proliferator Receptor agonists	Nuclear receptor superfamily related to the retinoid, steroid and thyroid receptors with three subtypes. They decrease inflammatory cytokine expression, neutrophil and macrophage chemotaxis plus inhibit oxidative burst in neutrophils.	Decreased wet to dry ratios, inflammatory cytokine expression and improved static compliance.	No human studies to date.
Curcumin	Up-regulation of PPAR-γ in various inflammatory cells (neutrophils, monocytes, T lymphocytes, endothelial and epithelial cells). Down-regulation of inflammatory transcription factors, enzymes and cytokines.	Decreased wet to dry ratios, and inflammatory cytokine secretion.	No human studies to date.