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Prevention of ARDS

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Abstract

Purpose of review—The paucity of effective therapeutic interventions in patients with the acute respiratory distress syndrome (ARDS) combined with overwhelming evidence on the importance of timely implementation of effective therapies to the critically ill patients have resulted in a recent shift in ARDS research. Increasingly, efforts are being directed towards early identification of patients at risk with a goal of prevention and early treatment, prior to development of the fully established syndrome. The focus of this review is on the prevention of ARDS in patients without this condition at the time of their healthcare encounter.

Recent findings—The primary thematic categories presented in this review article include: Early identification of patients at risk of developing ARDS, optimization of care delivery and its impact on the incidence of ARDS, pharmacological prevention of ARDS, prevention of postoperative ARDS, and challenges and opportunities with ARDS prevention studies.

Summary—Recent improvements in clinical care delivery have been associated with a decrease in the incidence of hospital acquired ARDS. Despite the initial challenges, research in ARDS prevention has become increasingly feasible with several randomized controlled trials on ARDS prevention completed or on the way.

Keywords

ARDS; prevention; quality improvement

Introduction

Almost 40 years after the initial description of acute respiratory distress syndrome (ARDS) (1) only a few interventions demonstrated the outcome benefit in this devastating complication of critical illness or injury. The current therapy is largely supportive, including lung-protective mechanical ventilation(2-4) and restrictive fluid and blood products administration.(5) However, these “supportive” therapies do not reverse the pathophysiological processes underlying ARDS; rather they limit further iatrogenic injury to

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lungs in patients with prevalent ARDS. Therefore, current supportive therapies for ARDS are perhaps better regarded as prevention of further complications or worsening of the underlying disease (tertiary prevention) rather than effective therapies for inflammatory lung edema.

The relative lack of effective therapeutic interventions in ARDS combined with overwhelming evidence on the importance of timely implementation of effective therapies in the setting of critical illness has resulted in a recent shift in ARDS research. More specifically, research efforts are increasingly being directed towards the early identification of patients at risk with a goal of prevention before ARDS is fully established. In 2010, an NHBLI workshop on future clinical research in acute lung injury (ALI) recommended development of strategies to perform ALI prevention trials.(6) In 2013, the Acute Respiratory Distress Syndrome (ARDS) Network was retired and replaced with the Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-014.html, accessed on August 21, 2014). This paradigm shift in ARDS research emphasizes the increasingly recognized importance of ARDS prevention. The focus of this review is prevention of ARDS in patients without lung injury at the time of the healthcare encounter.

Early identification of patients at risk of developing ARDS

In order to study plausible interventions and treatments for the prevention of ARDS, a key barrier is its relatively low (∼1%) prevalence among hospitalized patients.(7) A recent multicenter observational cohort study of 5,584 patients from 22 hospitals, identified key predisposing conditions and risk modifiers for ARDS and refined and validated a prediction model to identify patients at high risk for ARDS at the time of hospital admission.(8) Based on routinely available clinical data, a novel Lung Injury Prediction Score (LIPS) at a cutoff of ≥4 demonstrated a positive predictive value for ARDS of 18% with a negative predictive value of 97% (Figure 1). While the suboptimal predictive accuracy does not support its use in everyday clinical practice, LIPS has enabled enrollment in novel clinical trials of ARDS prevention (actively recruiting LIPS-A, NCT01504867 and LIPS-B, NCT01783821). Using similar methodologies, two surgical lung injury prediction models (SLIP and SLIP-2) have also been developed for the identification of patients at high risk of postoperative lung injury.(9, 10)

Notably, there have been other recent attempts to predict early ARDS. Levitt and al. derived an Early Acute Lung Injury Score, dependent on the oxygen requirement, respiratory rate and presence of immunosuppression in patients with bilateral infiltrates on chest imaging. (11) The score performed similarly to the LIPS, was not limited to the first 6 hours of hospitalization and is relatively simple to calculate. In a secondary analysis of the LIPS cohort, we have shown that the ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen (SpO2/FiO2) is an independent predictor of early ARDS development, even after adjustment for age, comorbidities, the APACHE 2 score and all other LIPS variables.(12) The main limitation to the clinical use of SpO2/FiO2 in prediction of ARDS is the lack of standardized measurement of FiO2 in spontaneously breathing patients.

Nevertheless, the broad availability and the simplicity of SpO2/FiO2 calculations are obvious advantages.

Improvements in clinical care delivery and the impact on ARDS development

Importantly, ARDS is rarely present at the time of the initial healthcare encounter. Rather, it typically develops during the hospital course, usually between days 2 and 5 in patients with predisposing conditions or risk factors.(8) Therefore, ARDS may be thought of as an iatrogenic complication with the potential for avoidance with optimal care delivery. Hospitalized patients are frequently exposed to various potentially harmful factors that may modify the inherent risk of ARDS development. This concept is often referred to as the multi-hit theory of ARDS pathogenesis. The number of such “hits” or harmful in-hospital exposures is directly proportional to the likelihood of ARDS development.(13) If one accepts these plausible concepts, two essential conclusions arise: 1) there is a window of opportunity for ARDS prevention that begins at the time of the initial healthcare encounter; and 2) by limiting high-risk exposures, ARDS may be preventable.

Olmsted county data experience

A retrospective, population-based study of Olmsted County residents reported a decrease in the incidence of hospital-acquired ARDS by more than half during the 8-year evaluation interval. Although causal relationships could not be determined, multiple changes in critical care structure and care delivery were implemented concurrent with the falling rate of ARDS. (14) Notably, the decrease in ARDS incidence was observed despite a stable incidence of community-acquired ARDS, an increase in the population's severity of illness and comorbid burden, and a higher prevalence of predisposing conditions for ARDS over the same 8-year period. The ARDS case-fatality rate over this same interval did not change, highlighting a potentially more meaningful opportunity for ARDS prevention when compared to the treatment of established ARDS. Several of the factors associated with ARDS development in this study, have been confirmed in other pertinent publications.(15-17) In a single-center study of ventilated patients without ARDS at the onset of mechanical ventilation, we have shown the importance of high tidal volume ventilation(15), which has been confirmed in a recent meta-analysis.(18) The importance of restrictive transfusion, use of male-donor predominant plasma transfusion(16) as well as timely treatment of sepsis,(17) have all been subsequently confirmed.

Other factors that can serve as potential prevention targets

The role of atelectasis and recumbency in ARDS pathogenesis, particularly in obese patients, has recently been highlighted.(19) This intriguing perspective focuses on the adverse effects of body position, spontaneous and mechanical hyperventilation on surfactant, surface tension and development of atelectasis (Figure 2). Therefore, the modification of current care relative to patient positioning and sedation may impact surfactant dysfunction and resulting atelectasis, ultimately mitigating risk for ARDS.

Gastric to pulmonary aspiration was identified as a principal cause of hospital-acquired ARDS back in 1980s.(20) In the LIPS cohort, aspiration represented one of the most common major risk-factors for ARDS.(21) Additional potentially modifiable risk factors include the use of strict lung-protective ventilation at the outset (NCT02070666), neuromuscular blockade,(3) limitation of oxygen support with lower oxygen saturation targets,(22) targeted fluid resuscitation and restrictive transfusion of blood products,(23) avoidance of hyperventilation in spontaneously breathing patients and striving for early extubation and early mobilization,(19) among others. All of these interventions have the potential to limit unnecessary and potentially harmful "hits" that may eventually result in fully established ARDS.

Checklist for Lung Injury Prevention

To be truly effective in mitigating the occurrence of ARDS, the simple identification of potentially modifiable factors is not sufficient. It is important to ensure that best evidence is not only disseminated, but implemented in a timely manner and continually assessed for their use and impact.(24-26). To this extent, LIPS investigators have formulated and implemented the Checklist for Lung Injury Prevention (CLIP),(27) which contains the key elements for standardizing the care of patients at risk enrolled in clinical trials of ARDS (Figure 3).

Pharmacological prevention

In addition to the improvements in clinical care delivery, we must continue efforts to identify effective new therapies that target the pathophysiological pathways underlying ARDS. Figure 4 provides a list of emerging pharmacological interventions for ARDS prevention.(28)

Inhaled medications

The notion of delivering medications with preventative potential directly to the lungs, thereby avoiding systemic side effects, is very attractive. Perkins et al. recently investigated inhaled salmeterol for ARDS prevention.(29) Over a 3-year period, they recruited 362 patients undergoing esophagectomy in 12 centers in the United Kingdom. Though the incidence of ARDS did not differ between salmeterol and placebo groups, postoperative adverse events (primarily pneumonia) were less frequent in the former. Additionally, in a translational substudy of 53 patients, salmeterol reduced several biomarkers of alveolar inflammation and epithelial injury.

The ongoing Lung Injury Prevention Study with Budesonide and Beta agonist formoterol (LIPS-B) is the first phase 2 clinical trial to study inhaled corticosteroids in combination with a long-acting beta agonist for prevention of ARDS (NCT01783821). In addition to direct anti-inflammatory properties,(30, 31) these drugs may act synergistically to improve peripheral delivery of the drugs.(32) In LIPS-B trial, the patients at risk for ARDS, as judged by a high LIPS score (≥4) are recruited less than 12 hours from their presentation to the hospital, and receive inhaled medications or identically appearing placebo twice daily for up to 10 doses. The primary aim of the study is to inform whether the treatment with inhaled

budesonide and formoterol can alleviate pulmonary dysfunction in patients at risk for ARDS.

In a small clinical trial enrolling 50 patients requiring mechanical ventilation for longer than 48 hours, inhaled heparin was associated with fewer days of mechanical ventilation when compared to placebo.(33) Experimental and observational clinical data suggested that inhaled anticoagulants might be associated with improved survival in patients with smoke inhalation-induced lung injury.(34) Several animal studies have demonstrated potential of nebulized hypertonic saline to ameliorate inflammatory and oxidative stress pathways of lung injury(35, 36) and the phase I/II clinical trial is on the way.

Systemic medications

Dysregulated inflammation, coagulation and oxidative stress play central roles in ARDS pathophysiology (37) and future mechanistic ARDS prevention trials are likely to target these pathways. In addition, platelet activation has been increasingly linked to both ARDS development and resolution.(38, 39) Both animal data and observational studies suggest aspirin can modulate these platelet-mediated processes and prevent or attenuate lung injury.(40-43) Given its wide availability, good safety profile, potential to decrease both inflammation and vascular permeability, and potential impact on immune function, aspirin is a prime candidate for prevention of ARDS by systemic delivery. The ongoing NIH-sponsored multicenter randomized placebo-controlled, LIPS-A trial (NCT01504867), will address whether the daily administration of aspirin up to 7 days can prevent or attenuate ARDS in patients at risk.(27)

Other systemic medications have shown to be effective in ameliorating lung injury and are being currently investigated. A selective inhibitor of p38 alpha mitogen-activated protein kinase plays a major role in the regulation of the inflammatory cytokines. It is currently being investigated in a multicenter clinical trial accruing patients at risk for ARDS due to trauma (NCT00996840). Efficacy in ARDS prevention of bevacizumab, a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor A, has also been studied in an ongoing clinical trial (NCT01314066).

Prevention of postoperative ARDS: experimental clinical laboratory for prevention studies

ARDS is a common and frequently lethal cause of postoperative respiratory failure, accounting for approximately 35% of cases.(44) The overall incidence of postoperative ARDS is estimated at approximately 3%,(44) but rates vary greatly for different surgical procedures.(8, 9) Specifically, complex cardiac, thoracic and aortic vascular surgeries have been consistently associated with the highest-rates of postoperative ARDS. Likewise, emergency surgery also appears to portend increased risk for this life-threatening postoperative respiratory complication.(10, 45) Notably, postoperative ARDS has been associated with up to 45% mortality.(44)

As in the non-surgical setting, a key barrier to preventing postoperative ARDS has been our inability to identify those at greatest risk. In an effort to address this limitation, recent

investigations have reported prediction models that can be used to identify a more targeted study population with greater risk for developing postoperative ARDS.(9, 46) More recently, a prediction model has been developed for more heterogeneous surgical populations including those undergoing both elective and emergency surgery as well as those with concomitant major risk factors for ARDS.(10)

The perioperative environment provides a unique opportunity to better understand ARDS mechanisms. Specifically, the above-mentioned ARDS prediction models can be used to facilitate the identification of patients at particular risk for postoperative ARDS prior to their surgical procedure. In doing so, patients may be enrolled before the major risks for ARDS have been experienced. As a result, ARDS pathogenesis can be studied from a relatively healthy (preoperative) state to the full ARDS phenotype, in contrast to patients who are admitted through the emergency department.

Challenges and opportunities of ARDS prevention studies

The design and conduct of ARDS prevention trials pose numerous challenges. Patients need to be identified, consented and enrolled very early in their hospital course. For example, the inhaled medications in LIPS-B trial are to be delivered not later than 4 hours after the randomization, regardless of the time of the day (or night). The time-sensitive nature of these interventional trials raise challenges that require innovative patient enrollment strategies (e.g. novel informatics approaches to patient identification(47)), different approaches to informed consent (surrogate, phone, deferred or community consent) as well as multispecialty collaboration (emergency medicine physicians, hospitalists, intensivists, anesthesiologists, surgeons, pharmacists, respiratory therapists, etc).

In addition to the challenges of early identification and enrollment, there are other barriers that must be addressed as well. While the development of ARDS is a logical primary outcome, the relatively low positive predictive value of the prediction scores poses limitations. Specifically, only a small proportion of patients at risk will progress to fully established ARDS, which increases the sample size requirement, duration and associated cost of the clinical trials. Therefore, the use of alternative, surrogate outcomes may be considered. Particularly attractive seems to be derangement in oxygenation, given its increasingly recognized importance in likelihood for the development as well as prognosis of ARDS.(11, 12, 48) Alternatively, an extravascular lung water measurement could potentially be a useful surrogate outcome.(49, 50) However, an intervention that positively affects surrogate outcome might not necessarily improve but rather could pose harmful effect on patient-important outcomes.(2)

Conclusion

The importance of ARDS prevention has been increasingly recognized by the scientific community. Identifying patients at risk for ARDS early in their healthcare encounter and improvements in care delivery for those deemed to be at risk of this life-threatening syndrome have been associated with reduced incidence of ARDS among hospitalized

patients. Moreover, systematic testing and implementation of pharmacological prevention strategies has a potential to further decrease the burden of ARDS.

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Key points

- Novel risk prediction tools can assist in timely identification of patients at risk of developing ARDS.
- Improvements in clinical care delivery have been associated with decreased incidence of hospital acquired ARDS.
- Prevention and early treatment of ARDS is a current priority in investigative efforts to curtail this devastating syndrome.

Predisposing Conditions	LIPS Points	Examples
		i. Patient with history of alcohol abuse with septic shock from pneumonia requiring FIO2>0.35 in the emergency room:
Shock	2	
Aspiration	2	
Sepsis	1	
Pneumonia	1.5	Sepsis + shock + pneumonia + alcohol abuse + FIO2>0.35
High risk surgery*		
Orthopedic spine	1	1 + 2 + 1.5 + 1 + 2 = 7.5
Acute abdomen	2	
Cardiac	2.5	
Aortic vascular	3.5	
High risk trauma		ii. Motor vehicle accident with traumatic brain injury, lung contusion and shock requiring FiO_2 >0.35
Traumatic brain injury	2	
Smoke inhalation	2	
Near drowning	2	
Lung contusion	1.5	Traumatic brain injury + lung contusion + shock + FiO_2 >0.35
Multiple fractures	1.5	
		2 + 1.5 + 2 + 2 = 7.5
Risk modifiers		
Alcohol abuse	1	
Obesity (BMI >30)	1	iii. Patient with history of diabetes mellitus and urosepsis with shock
Hypoalbuminemia	1	
Chemotherapy	1	
FiO_2 >0.35 (>4 L/min)	2	Sepsis + shock + Diabetes
Tachypnea (RR >30)	1.5	
SpO2 <95%	1	1 + 2 - 1 = 2
Acidosis (pH <7.35)	1.5	
Diabetes mellitus**	-1	

Abbreviations: BMI=body mass index; RR=respiratory rate; SpO2=oxygen saturation by pulse oximetry.

*Add 1.5 points if emergency surgery; †Only if sepsis present.

Figure 1.

Lung Injury Prediction Score (LIPS) calculation worksheet.

From: Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. American Journal of Respiratory & Critical Care Medicine. 2011;183(4):462-70. [8]

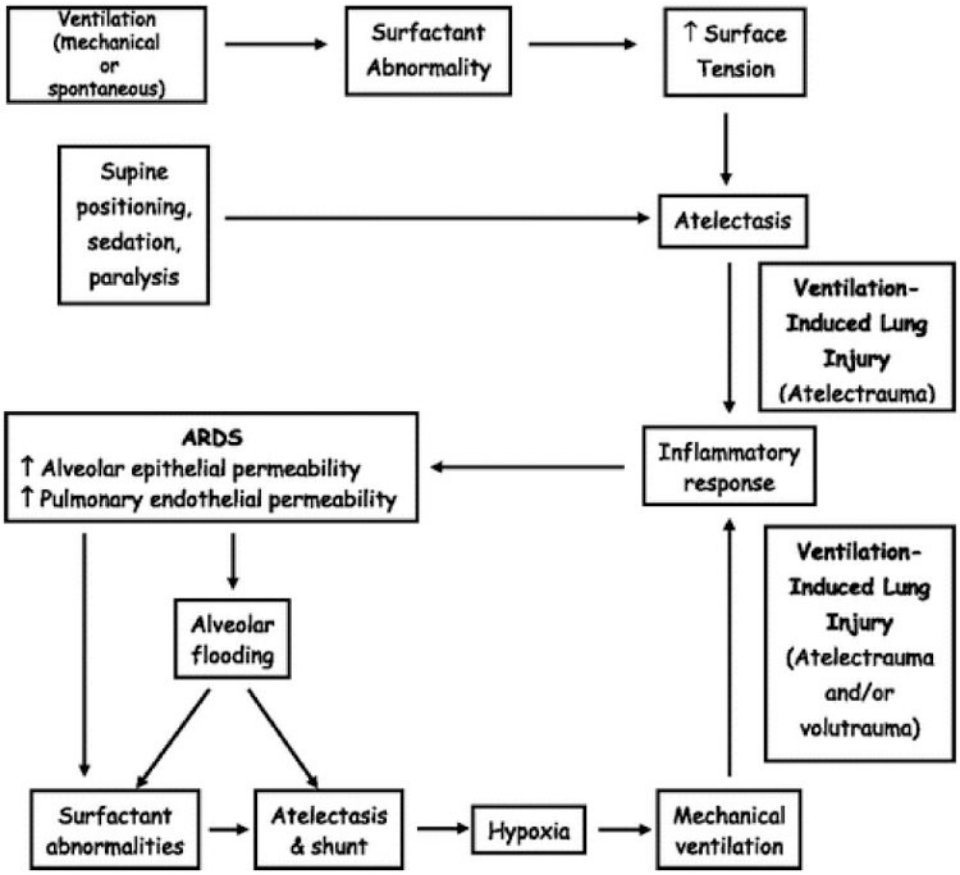

Figure 2.

Proposed alternative pathophysiology of ARDS.

From: Albert RK. The role of ventilation-induced surfactant dysfunction and atelectasis in causing acute respiratory distress syndrome. Am J RespCrit Care Med 2012;185(7):702-708. [19]

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, 2006 #124} 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

Abbreviations: PEEP=positive end-expiratory pressure; FiO2=fractional inspired oxygen concentration.

Figure 3.
Checklist for Lung Injury Prevention (CLIP).

Medication	Mechanism of action	Animal Studies	Human Studies
Aspirin	Inhibition of platelet mediated cyclooxygenase metabolism involved in bronchoconstriction and vasoconstriction and inhibits 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.
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.	Older studies performed in the 1980s show no benefit in administering short course high-dose steroids.
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.	No published human studies.
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.	No published human studies.
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.	One published human study,(29) no difference in ARDS incidence but less pulmonary complications, mainly pneumonia.Another study found treatment prevented high altitude pulmonary edema.
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 have not been consistent. One study showed a protective effect while 2, including largest cohort, did not.
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.	Two observational studies showed a protective effect.
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.

Figure 4.

Emerging pharmacological therapies for ARDS prevention.

Modified from: Ortiz-Diaz E, Festic E, Gajic O, Levitt JE. Emerging pharmacological therapies for prevention and early treatment of acute lung injury. Seminars in Respiratory and Critical Care Medicine. 2013:34(4):448-458. [28]