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Acute respiratory distress syndrome (ARDS) is a common complication of critical illness or injury associated with significant morbidity and mortality. The pathogenesis of ARDS involves mechanical and inflammatory injury to the lungs that causes marked derangement in alveolar-capillary permeability and the passage of protein-rich edema fluid into the air spaces. ARDS usually occurs in a context of uncontrolled response to local or systemic inflammation and most recently two endotypes of ARDS—namely, hyperinflammatory and hypoinflammatory—have been identified with different therapeutic responses and prognoses. The clinical pathogenesis is often multifactorial, with complex interaction of risk factors and risk modifiers (Fig. 15.1).

### PREDISPOSING CONDITIONS

Sepsis, pneumonia, and shock are the most common conditions predisposing to ARDS. However, only a minority of these patients with these disorders actually have ARDS (Fig. 15.2). Other typical predisposing conditions include gastropulmonary aspiration, trauma, and massive blood product transfusion. Atypical respiratory infections, including viral (influenza) and fungal (Pneumocystis jiroveci, Histoplasma spp., Blastomyces spp.) infections, are unusual but important causes of ARDS, especially in patients with compromised immune systems. Several pathogens, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome-coronavirus, and epidemic H1N1 influenza, have attracted widespread attention, and confer increased risk for ARDS. Additional patient risk factors include gastroesophageal reflux disease, chronic silent aspiration, and drug exposures.

Observational studies and clinical trials have noted a distinct subtype of ARDS without known risk factors. Of note, these patients may have better prognoses.

Certain host genetic variants have been associated with development of sepsis and ARDS, including mutations in the surfactant protein B. Recently, a genome-wide association study comparing 232 African-American patients with ARDS and 162 at-risk control subjects identified selectin P ligand gene (SELPLG) as a novel ARDS susceptibility gene. Genetic associations have been generally difficult to replicate, and the role of genetic predisposition in development of ARDS is presently unclear.

### RISK MODIFIERS

Sepsis in alcoholics is associated with a distinctly high risk of ARDS. Chronic alcohol use carries a twofold to threefold increase in ARDS development. The exact mechanism of this association remains unknown, but it may be related to a reduction in the antioxidant capacity of the lung. In addition, acute and chronic consumption of alcohol cause an increase in the systemic levels of adenosine and a dose-dependent reduction in alveolar fluid clearance through stimulation of the adenosine type 1 receptor, adding to the lung injury. A 2014 study in trauma patients demonstrated that the risk of ARDS increased in direct proportion to the blood alcohol content.

A history of tobacco exposure (including second-hand smoking) has been associated with an increased risk of ARDS in trauma patients. Another study found an independent dose–response association between current cigarette smoking and subsequent development of ARDS. Hypoalbuminemia is a well-known marker of acute or chronic illness or malnutrition and poor surgical outcomes. It was also found to be an independent risk factor for ARDS. This appears to be mediated by decreases in plasma oncotic pressure with increased pulmonary permeability in the critically ill, independent of underlying cause and fluid status.

Hypercapnic acidosis protects against ventilator-induced lung injury in several animal models of ARDS. However, low pH and, in particular, metabolic acidosis have been associated with increased risk of ARDS. Obesity is also an independent risk factor for the development of ARDS. Although the effects of body position and compression atelectasis may in part explain the observed association, additional mechanisms have been proposed. These include an imbalance between proinflammatory and anti-inflammatory cytokines, which increases lung inflammation and injury through the tumor necrosis factor-α and interleukin-6 pathways.

Diabetes mellitus seems to be associated with a lower risk of ARDS in septic shock. Indeed, a meta-analysis that included a total of 12,794 adult patients suggested that diabetes protected against ARDS. Although the exact mechanism is not known, one possible explanation is that diabetic patients...
ARDS pathogens: “Multiple hit” hypothesis

**Patient at risk (1st hit):**
- Pneumonia
- Toxic inhalation
- Pancreatitis
- Aspiration
- Trauma
- Sepsis
- Shock
- Age
- SNPs
- Alcohol
- Tobacco
- Thoracic and vascular surgery
- Preexisting lung disease
- Vasculitis
- Radiation
- Chemotherapy

**Risk modifiers that may risk ↑ of ALI (2nd hit):**
- High tidal volume, transfusion, delayed resuscitation, inappropriate antibiotics, aspiration, high FiO₂

**Risk modifiers that may risk ↓ of ALI:**
- PEEP, modulators of oxidative stress, inflammation, coagulation

**Oxidative stress**
- Inflammation
- Coagulation

**Capillary permeability**
- Apoptosis
- Alveolar clearance

**Hospital admission**
- ICU admission

**Fig. 15.1** Illustration of Interaction between Risk factors and Risk Modifiers in the Development of Acute respiratory Distress Syndrome. ALI, acute lung injury; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; PEEP, positive end-expiratory pressure; SNP, single nucleotide polymorphism.

**% ALI development according to predisposing conditions**

**Fig. 15.2** Predisposing Factors for Development of Acute Respiratory Distress Syndrome. ALI, acute lung injury. (From Gajic et al.31.)
have impaired activation of the inflammatory cascade in the lungs.40

An alternative hypothesis for ARDS pathogenesis has been proposed, suggesting that surfactant dysfunction may be a critical step in ARDS progression.41 Both spontaneous and mechanical hyperventilation can induce surfactant dysfunction, leading to higher surface tension and atelectasis. This injury is augmented by supine position and sedation, and this effect can be particularly pronounced in obese patients.2 However, trials administering surfactant in ARDS patients did not show an outcome benefit.42

**RISK PREDICTION MODELS**

The Lung Injury Prediction Score (LIPS) was created in 2011 with the intent to facilitate the design and conduct of ARDS prevention studies.43 The model includes risk factors and risk modifiers present at the time of hospital admission, before ARDS occurs. It was later validated31 and refined (Table 15.1). A simplified model, the Early Acute Lung Injury Score, predicts ARDS on the basis of oxygen requirement, respiratory rate, and presence of immunosuppression in patients with bilateral infiltrates on chest imaging.44

### TABLE 15.1 LIPS Calculation Table.

| **LIPS Points** | **Examples** |
|-----------------|--------------|
| **Predisposing Conditions** | | |
| Shock | 2 | (1) Patient with history of alcohol abuse with septic shock from pneumonia requiring FiO2 > 0.35 in the emergency room: sepsis + shock + pneumonia + alcohol abuse + FiO2 > 0.35 1 + 2 + 1.5 + 1 + 2 = 7.5 |
| Aspiration | 2 | |
| Sepsis | 1 | |
| Pneumonia | 1.5 | |
| **High-Risk Surgery** | | |
| Orthopedic spine | 1 | |
| Acute abdomen | 2 | |
| Cardiac | 2.5 | |
| Aortic vascular | 3.5 | |
| **High-Risk Trauma** | | |
| Traumatic brain injury | 2 | (2) Motor vehicle accident with traumatic brain injury, lung contusion, and shock requiring FiO2 > 0.35 2 + 1.5 + 2 + 2 = 7.5 |
| Smoke inhalation | 2 | |
| Near drowning | 2 | |
| Lung contusion | 1.5 | |
| Multiple fractures | 1.5 | |
| **Risk Modifiers** | | |
| Alcohol abuse | 1 | |
| Obesity (BMI > 30) | 1 | |
| Hypoalbuminemia | 1 | |
| Chemotherapy | 1 | |
| FiO2 > 0.35 (> 4 L/min) | 2 | |
| Tachypnea (RR > 30) | 1.5 | |
| SpO2 < 95% | 1 | |
| Acidosis (pH < 7.35) | 1.5 | |
| Diabetes mellitus | -1 | |
| **BMI**, body mass index; **FiO2**, fraction of inspired oxygen; **LIPS**, Lung Injury Prediction Score; **RR**, respiratory rate; **SpO2**, oxygen saturation by pulse oximetry. |
| From Gajic et al.31 | |

**HOSPITAL-ACQUIRED EXPOSURES**

Hospitalized patients are frequently exposed to various potentially harmful factors that may modify their risk of ARDS development. Compared with patients who died of other causes, ARDS decedents have a markedly higher incidence of potentially preventable adverse events (medical or surgical misadventures).45 High tidal volume ventilation,46–48 high oxygen concentration,49 and plasma transfusion from multiparous female donors50 each have been implicated as iatrogenic contributors to ARDS. In septic patients, delays in fluid resuscitation and in the initiation of antimicrobial treatment have also been associated with ARDS.51 Although lung-protective mechanical ventilation is considered a standard of care for patients with established ARDS, a series of studies suggest that its application to all mechanically ventilated patients may be safe and beneficial.56–48

A large case-control study found iatrogenic risk factors to be significantly greater in patients with ARDS than in matched controls and deemed most of these factors to be preventable.52 Multiple potential strategies directed at preventing ARDS have been proposed. These include early identification of “at-risk” patients, standardization of clinical
practice to prevent iatrogenic injury, and early treatment of predisposing conditions.\textsuperscript{52,53} The Checklist for Lung Injury Prevention (CLIP) has been developed to ensure compliance with evidence-based practice that may affect ARDS occurrence and is currently used in clinical trials of ARDS prevention.\textsuperscript{54} CLIP items include lung-protective mechanical ventilation, aspiration precautions, early adequate antimicrobial therapy, restrictive fluid and transfusion management, and early assessment for extubation with daily awakening and breathing trials.

A population-based cohort study conducted in Olmsted County, Minnesota, reported a decrease in the incidence of ARDS from 82.4 cases per 100,000 person-years in 2001 to 38.9 cases per 100,000 person-years in 2008.\textsuperscript{55} This decrease in ARDS incidence was observed despite a stable incidence of community-acquired ARDS and an increase in the population’s severity of illness, comorbidity burden, and predisposing conditions for ARDS over the same time period. This decrease was attributed to the prevention strategies described above, including lung-protective ventilation strategies in all mechanically ventilated patients, restrictive transfusion practice, male-donor-predominant plasma, improved sepsis treatment, and more conservative fluid management.\textsuperscript{50,55,56}

Although several potential pharmacologic therapies have emerged to target specific components of the underlying pathogenetic pathway of ARDS, to date, none has been proven to be effective in the prevention of ARDS. Most recently, a phase IIa double-blind multicenter randomized controlled trial (RCT) studying the feasibility of the combination of an inhaled corticosteroid and inhaled long-acting beta-adrenergic agonist in patients at an increased risk of ARDS (LIPS score > 4) showed an improvement in oxygenation when compared with placebo and, although not intended to study the effect on prevention of ARDS, there was a lower incidence of ARDS in the treatment group that became nonsignificant after adjustment for shock. Although this was only a pilot study and limited by sample size, this trial will help to inform future studies.\textsuperscript{57}

The use of inhaled beta-adrenergic agonists only have also been formally evaluated in a phase II RCT. In 362 patients undergoing esophagectomy, intraoperative administration of inhaled salmeterol reduced several biomarkers of alveolar inflammation and injury and was associated with a decreased incidence of postoperative adverse events (predominantly pneumonia); however, the incidence of ARDS did not differ between the groups.\textsuperscript{58}

The administration of aspirin was thought to be protective in earlier observational studies;\textsuperscript{59,60} however, in a phase II RCT comparing aspirin and placebo in patients at an increased risk of ARDS (LIPS score > 4), there was no difference in the incidence of ARDS or other important outcomes.\textsuperscript{61} However, an ancillary mechanistic study demonstrated the important role of biomarkers for intravascular monocyte activation and a potential preventive effect of aspirin on ARDS development in per-protocol analysis.\textsuperscript{62}

Animal studies had suggested that statins may be beneficial in modulating hyperinflammatory ARDS. However, the HARP-2 clinical trial of 540 patients failed to demonstrate benefit.\textsuperscript{63} A systematic review of observational studies and other RCTs have shown no beneficial effect for statins in the prevention of ARDS in high-risk patients.\textsuperscript{64,65}

Several other pharmacologic therapies for prevention of ARDS in patients at risk are being evaluated in clinical studies. These include\textsuperscript{58} inhaled heparin,\textsuperscript{66} inhaled steroids,\textsuperscript{67} peroxisome proliferator receptor antagonist, angiotensin inhibitors, curcumin, and vitamin D.\textsuperscript{68,69}

In conclusion, although sepsis, pneumonia, and shock commonly predispose patients to ARDS, many risk factors are potentially modifiable and early identification of those at risk is important. Ongoing clinical studies are evaluating various promising preventive strategies. Meanwhile, attention to best practices and avoidance of iatrogenic exposures is a simple and powerful strategy for reducing the burden of this important complication of critical illness.

AUTHORS’ RECOMMENDATIONS

- Sepsis, pneumonia, and shock are the most common conditions predisposing to ARDS.
- Certain host genetic variants have been associated with development of sepsis and ARDS.
- Abuse of alcohol and tobacco predispose to ARDS, as does malnutrition and obesity.
- The LIPS and the simplified Early Acute Lung Injury Score predict ARDS based on clinical and investigational criteria.
- Hospital-acquired ARDS may result from a medley factors, of which high tidal volume ventilation, high oxygen concentration, and plasma transfusion are most commonly implicated.
- The Checklist for Lung Injury Prevention (CLIP) has been developed to ensure compliance with evidence-based practice that may affect ARDS occurrence.
- To date, no pharmacologic intervention has been shown to prevent ARDS.

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Abstract: Sepsis, pneumonia, and shock are the most common conditions predisposing to acute respiratory distress syndrome (ARDS) and certain host genetic variants have been associated with the development of ARDS. Risk modifiers include abuse of alcohol and tobacco, malnutrition, and obesity. The Lung Injury Prediction Score (LIPS) and the simplified Early Acute Lung Injury Score predict ARDS based on clinical and investigational criteria. Hospital-acquired ARDS may result from a medley factors of which high tidal volume ventilation, high oxygen concentration, and plasma transfusion are most commonly implicated. The Checklist for Lung Injury Prevention (CLIP) has been developed to ensure compliance with evidence-based practice that may affect ARDS occurrence. To date, no pharmacologic intervention has been shown to prevent ARDS

Keywords: prevention, ARDS, risk factors, genetics, LIPS, CLIP