Acute Respiratory Distress Syndrome (ARDS)

Noor Naif Al-Hakami
Clinical pharmacist intern
2014
OUTLINES:

- Introduction
- Definition
- Etiology
- Epidemiology
- Lung injury prediction score
- Pathophysiology
- Diagnosis
- Clinical presentation
- Management
- Conclusion
During the 1960s, a distinct type of a life threatening respiratory condition characterized by hypoxemia, and stiff lungs was first recognized. Military clinicians in Vietnam called it Shock Lung, while civilian clinicians referred to it as Adult Respiratory Distress Syndrome. Subsequent recognition that individuals of any age could be afflicted led to the current term, Acute Respiratory Distress Syndrome (ARDS).
## Definitions:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>The AECC definition 1994</th>
<th>The Berlin definition 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>≤7 days from the predisposing clinical insult</td>
</tr>
<tr>
<td>Radiographic abnormality</td>
<td>Bilateral infiltrate on frontal chest radiograph</td>
<td>Bilateral opacities on radiograph or computed tomography scan not fully explained by effusion, atelectasis, or nodules</td>
</tr>
<tr>
<td>Noncardiogenic source of pulmonary edema</td>
<td>No clinical evidence of elevated left atrial pressure, or, a pulmonary capillary wedge pressure &lt; 18 mmHg</td>
<td>Respiratory failure not fully explained by cardiogenic pulmonary edema or volume overload</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>PaO₂/FiO₂ ratio</td>
<td>PaO₂/FiO₂ ratio with ≥5 cm H₂O positive end-expiratory pressure (PEEP)</td>
</tr>
<tr>
<td></td>
<td>Acute lung injury: ≤300</td>
<td>Mild ARDS: 201–300</td>
</tr>
<tr>
<td></td>
<td>Acute respiratory distress syndrome: ≤200</td>
<td>Moderate ARDS: 101–200</td>
</tr>
<tr>
<td>Predisposing condition</td>
<td>Not specified</td>
<td>Severe ARDS: &lt;100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If none identified, then need to rule out cardiogenic edema with additional data (eg, echocardiography)</td>
</tr>
</tbody>
</table>
150,000 Americans will be diagnosed with acute respiratory distress syndrome each year.

14,225 Saudis would be diagnosed with acute respiratory distress syndrome each year.

- High mortality rate (ICU: 37%, overall: 42%)
- Only 34% of ARDS survivors are well enough to be discharged directly home.

**Etiology:**

*Direct lung injury*

**Common causes:**
- Aspiration pneumonia
- Pneumonia

**Less common causes:**
- Fat emboli
- Inhalational injury
- Drowning
- Pulmonary injury after lung transplantation or pulmonary embolectomy

*Indirect lung injury*

**Common causes:**
- Sepsis
- Severe trauma or shock with multiple transfusions

**Less common causes:**
- Acute pancreatitis
- Burns
- Cardiopulmonary bypass
- DIC
- Drug overdose
- Head injury
- Transfusion of blood products
- Trauma

The lung injury prediction score (LIPS) identifies patients who are unlikely to develop ARDS. This was demonstrated by a prospective cohort study of 5584 patients. It is the sum of the points assigned for each of the predisposing conditions. The percent of patients with a LIPS <4 who will not develop ARDS is 97 percent. A LIPS >4 predicted ARDS with a sensitivity and specificity of 69 and 78 percent, respectively.

<table>
<thead>
<tr>
<th>Predisposing conditions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>2 points</td>
</tr>
<tr>
<td>Aspiration</td>
<td>2 points</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 point</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Orthopedic spine surgery</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Acute abdominal surgery</td>
<td>2 points</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>2.5 points</td>
</tr>
<tr>
<td>Aortic vascular surgery</td>
<td>3.5 points</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>2 points</td>
</tr>
<tr>
<td>Smoke inhalation</td>
<td>2 points</td>
</tr>
<tr>
<td>Near drowning</td>
<td>2 points</td>
</tr>
<tr>
<td>Lung contusion</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Multiple fractures</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1 point</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30)</td>
<td>1 point</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1 point</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1 point</td>
</tr>
<tr>
<td>Fraction of inspired oxygen &gt;0.35 or &gt;4 L/min</td>
<td>2 points</td>
</tr>
<tr>
<td>Tachypnea &gt;30 breaths/min</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Oxyhemoglobin saturation &lt;95 percent</td>
<td>1 point</td>
</tr>
<tr>
<td>Acidosis (ph &lt;7.35)</td>
<td>1.5 points</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-1 point</td>
</tr>
</tbody>
</table>
Effect of type II diabetes mellitus on outcomes in patients with acute respiratory distress syndrome

Abhishek Singla, MD, Paul Turner, PhD, Madhu Kalyan Pendurthi, MBBS, MPH, Vrinda Agrawal, MBBS, Ariel Modrykaminski, MD, FCCP, FACP

Department of Internal Medicine, Creighton University Medical Center, Omaha, NE, USA
Division of Clinical Research and Evaluative Sciences, Creighton University School of Medicine, Omaha, NE, USA
Division of Endocrinology, Baylor College of Medicine, Houston, TX, USA
Intensive Care Unit and Respiratory Care Services, Pulmonary, Sleep and Critical Care Medicine Division, Creighton University School of Medicine, Omaha, NE, USA

Abstract

Purpose: The acute respiratory distress syndrome (ARDS) is a life-threatening condition, whereas the presence of diabetes has been shown to be protective in its development. We undertook this study to assess the association of type II diabetes mellitus with clinical outcomes in patients with ARDS.

Materials and Methods: We retrospectively examined the medical records of consecutive series of patients with ARDS requiring mechanical ventilation from January 2008 to March 2011. Patients with type I diabetes were excluded from the study. Clinical outcomes such as ventilator-free days, mortality, length of stay in the hospital and intensive care unit (ICU), and reintubations were compared based on the presence of diabetes. Multivariate regression model was used to find if the presence of type II diabetes mellitus predicts ventilator-free days at day 28.

Results: Two hundred forty-nine patients with ARDS were admitted to the ICU during the study period. Fifty (20%) subjects had type II diabetes mellitus. Differences in ventilator-free days, in-hospital mortality, reintubation rate, and length of stay in the hospital or ICU were not statistically significant between diabetic and nondiabetic patients with ARDS. Acute Physiologic and Chronic Health Evaluation II, ICU specialty, use of vasopressors, and the need for reintubation were predictors of ventilator-free days at day 28. The presence of type II diabetes mellitus and its adjustment by body mass index did not show association with ventilator-free days at day 28.

Conclusions: The presence of type II diabetes mellitus is not associated with clinical outcomes in ARDS, even when its presence is adjusted by body mass index.
Neutrophils become activated and release toxic mediators (e.g., reactive oxygen species and proteases). The injury causes release of pro-inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8. In addition, functional surfactant is lost, resulting in alveolar collapse. That damage the capillary endothelium and causes the air spaces to fill with bloody, proteinaceous edema fluid and debris from degenerating cells.
Schematic representation of the time course of the acute respiratory distress syndrome (ARDS). During the early (or exudative) phase, the lesion is characterized by high permeability pulmonary edema followed by the formation of hyaline membranes. After seven to ten days, a proliferative phase may develop, with marked interstitial inflammation, fibrosis, and disordered healing.

• ARDS can be diagnosed once cardiogenic pulmonary edema and alternative causes of acute hypoxemic respiratory failure and bilateral infiltrates have been excluded

• Use the Berlin Definition of ARDS criteria to diagnose ARDS

• Chest X-ray (CXR) and arterial blood gas analysis are required to make the diagnosis

• CT of the chest may give useful information and typically demonstrates the heterogeneous nature of the consolidation seen in ARDS

The clinical features of ARDS usually appear within 6 to 72 hours of an inciting event and worsen rapidly.

Patients typically present with dyspnea, cyanosis (i.e., hypoxemia requiring a moderate to high concentration of inspired oxygen), and diffuse crackles.

Respiratory distress, including tachypnea, tachycardia, diaphoresis, and use of accessory muscles of respiration, cough and chest pain.

Clinical findings related to the precipitant may also exist at presentation. As an example, in patients with ARDS due to sepsis, there may be fever, hypotension, leukocytosis, lactic acidosis, and disseminated intravascular coagulation (DIC).

Treatment of ARDS is mainly supportive and has three cornerstones:

1) Recognizing patients with acute lung injury and ruling out other causes of acute hypoxemia

2) Identifying and treating the underlying disease

3) Mechanical ventilation to secure oxygenation and ventilation whilst protecting the lung from ventilation-induced lung injury

- Many other adjunctive therapies and procedures have been assessed over the last two decades attempting to improve ARDS clinical outcomes, with scarcely any success

• Lung protective ventilation strategies:

• Low tidal volume ventilation (LTVV) is referred to as lung protective ventilation.

• The rationale for this approach is that smaller tidal volumes are less likely to generate alveolar overdistension, one of the principal causes of ventilator-associated lung injury.

• In a multicenter study of patients with ARDS, patients randomized to receive a lower tidal volume (Vt) [4-6 mL/kg predicted body weight (PBW), and maintenance of plateau pressure between 25 and 30 cmH2O] had a survival benefit. Mortality was reduced from 40% in the conventional arm to 31% in the low Vt arm.

• In addition to lung over-distention, cyclic opening and closing of small airways and alveolar units (so called atelectrauma) can also lead to lung injury

• Several clinical trials have been conducted in ARDS patients to examine the effects of an “open lung” approach in which the application of recruitment maneuvers and higher levels of positive end expiratory pressure (PEEP) may limit atelectrauma

• A recent meta-analysis that incorporated trials (from 1996 to January 2010) comparing higher vs. lower levels of PEEP concluded that there is no difference in mortality applying lower vs. higher levels of PEEP in patients with mild ARDS. However, in the subgroup of patients with severe ARDS, as defined by a PaO2/FiO2 <200, there was be a benefit from higher levels of PEEP

Non conventional therapies in severe ARDS:

1. Prone positioning
2. High frequency oscillatory ventilation (HFOV)
3. Extracorporeal membrane oxygenation (ECLS)

Although all these strategies have demonstrated to improve oxygenation, their impact on mortality is controversial.

• Other supportive care and oxygenation strategies including:

1. Intelligent use of sedatives and neuromuscular blockade
2. Fluid management
3. Nutritional support
4. Control of blood glucose levels
5. Expeditious evaluation and treatment of nosocomial pneumonia
6. Prophylaxis against deep venous thrombosis (DVT) and gastrointestinal (GI) bleeding

What about pharmacological therapies?
• Neuromuscular blockade

• Initial small studies eliminating patient effort via skeletal muscle inhibition with neuromuscular blockade (NMB) improved patient-ventilator synchrony, as evidenced by reduced airway pressures and improved chest wall compliance.

• These beneficial effects led to a multi-center, randomized, placebo-controlled trial showed that infusion with cisatracurium besylate within 48 hours of mechanical ventilation in patients with moderate ARDS improved 90-day survival. However, no difference was noted between the intervention and placebo groups until Day 20.

• While promising, the protective effect of neuromuscular blockade needs to be confirmed.

Nitric oxide & Prostacyclin:

- Routine inhaled nitric oxide (NO) and prostacyclin have not become routine therapy for adults with ARDS because, although they improve oxygenation, they have not been shown to reduce morbidity or mortality.

- They should be reserved for patients with intractable, life-threatening hypoxemia despite conventional management.

- The major advantage of inhaled prostacyclin compared with inhaled NO is that inhaled prostacyclin does not require sophisticated equipment for administration.

- Further studies are required to fully evaluate the safety and efficacy of these medications as therapy for patients with ARDS.
- **Corticosteroids:**
  - The role of glucocorticoids in the management of ARDS is a source of ongoing controversy.
  - The uncertain effect of glucocorticoids on mortality is exemplified by four meta-analyses that compared systemic glucocorticoid therapy to placebo in patients with ARDS.
  - It has been suggested by some clinical trials that the effects of systemic glucocorticoids vary according to when they are initiated.
  - Taken together, these data indicate that systemic glucocorticoid therapy should NOT be initiated 14 days or longer after the onset of ARDS and the impact of earlier therapy on mortality is uncertain.
  - Larger trials are indicated to resolve the uncertainty regarding the effect of early systemic glucocorticoid therapy in ARDS.

Statins:

- The original idea that statin therapy might be beneficial to patients with ARDS was based upon studies that found that statins reduced the concentration of proinflammatory cytokines, reduced the inflammatory infiltrate in the interstitium, and improved survival in animal models.

- They have not become routine therapy for adults with ARDS because they have not been shown to improve patient-important outcomes.

- Two larger trials are presently recruiting in the UK and Ireland (HARP-2) and in the USA (SAILS, NCT00979121), investigating simvastatin and rosuvastatin, respectively.

• Macrolide antibiotics

• Macrolide antibiotics have both antimicrobial and anti-inflammatory effects, and animal models suggest that these agents may have a beneficial effect in ARDS

• To evaluate the effects of macrolide antibiotics in humans with ARDS, an observational study was conducted

• This preliminary evidence warrants further evaluation with a controlled clinical trial

• Heparin:

• During the inflammatory process of ARDS fibrin is deposited throughout the alveolus, both intra- and extravascularly, impairing oxygenation.

• Experimental data show that, among other effects, heparin can reduce fibrin deposition, this led to a small study investigating the efficacy of nebulized heparin in patients at risk for ARDS.

• Although there was no significant effect on the P/F ratio, this study suggested heparin may increase the number of ventilator-free days (VFD) and have prompted further studies investigating the long-term impact of nebulized heparin in patients at risk of ARDS.

• Aspirin:

• During ARDS, platelets become activated and play an important role in disease progression by sequestering within the lung, forming micro-thrombi and attracting inflammatory cells to injured tissue.

• The potent anti-platelet effect of aspirin may offer a therapeutic approach to this pathological process.

• Observational data associated pre-hospital anti-platelet use with a reduction in subsequent ARDS incidence.

• Clinical trials are planned to investigate the effect of aspirin on reducing inflammation in a human model of ARDS while others are ongoing to assess the impact of aspirin in the prevention of ARDS.

• β-adrenergic agonists:

• Experimental data suggest β-adrenergic agonists could accelerate alveolar fluid clearance, as well as provide cytoprotection, increased surfactant secretion and decreased endothelial permeability

• The β-Agonist Lung Injury Trial (BALTI) showed that salbutamol therapy significantly reduced extravascular lung water at Day 7 compared with placebo

• Subsequently, two large multi-center, randomized placebo-controlled trials were initiated:
  – The first American study, ALTA (Albuterol Treatment for Acute Lung Injury) failed to demonstrate a difference in ventilator-free days between those receiving inhaled β-agonist therapy and those given placebo
  – BALTI-2 was a concurrent UK multi-center study which was terminated early due to excess mortality in the group receiving IV salbutamol

• On the basis of these larger trials, β-agonists should be avoided in patients with ARDS. It is hypothesized that β-agonists may have a harmful cardiac effect, stimulating tachyarrhythmias and cardiac ischemia, resulting in a poorer outcome

• Ineffective or harmful therapies:

• A number of potential therapies for ARDS were once regarded as promising, but have since proven to be either ineffective or harmful. They include the following:

• N-acetylcysteine
• Procysteine (L-2-oxothiazolidine-4-carboxylate)
• Glutamine
• Antioxidant preparations (selenium, beta carotene, zinc, vitamin E and C)
• Lisophylline
• Intravenous prostaglandin E1
• Neutrophil elastase inhibitors
• Ibuprofen
• Activated protein C
• Ketoconazole

• Regenerative medicine is an emerging field, using stem cells or growth factors to aid the repair of damaged tissue and organs.

• Stem cells exhibit anti-inflammatory, immunomodulatory and reparative effects, largely mediated through secreted growth factors, although cell to cell contact between stem cells and alveoli also mediates important effects.

• This prompts questions regarding the optimal delivery of stem cell therapy, as animal models of ARDS have shown survival to increase when treatment was delivered directly to the bronchial tree.

• In addition, recent evidence in ex-vivo human lung models of ALI support the investigation of delivering stem cells directly to the lung.

• Clinical trials are awaited in this promising area.

Despite recent advances, ARDS is still associated with significant morbidity and mortality.

Basic management should include good supportive care and treatment of the underlying cause.

The only specific management strategy shown to have a survival benefit is restrictive ventilation with a tidal volume of 6 ml kg and a plateau pressure of 30 cm H2O.

Other measures may be considered in ARDS individual cases, but there is insufficient evidence to recommend their widespread use for all patients.