Acute Respiratory Distress Syndrome (ARDS) — Phases and Treatment

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Acute Respiratory Distress Syndrome (ARDS) is a severe inflammatory reaction of the lung that is characterized by the presence of pulmonary infiltrates due to alveolar fluid accumulation, without evidence suggestive of a cardiogenic etiology. SIRS and sepsis are the major causes of ARDS. The main finding of ARD is respiratory failure. Chest x-ray usually shows diffuse bilateral lung infiltrates described as "("butterfly opacity"). Management depends mainly on treating the underlying etiology and maintaining adequate oxygenation, which may require intubation and mechanical ventilation.

Introduction to ARDS

ARDS is considered the most common cause of non-cardiogenic pulmonary edema. It is clinically defined by the presence of pulmonary infiltrates due to alveolar fluid
accumulation, without evidence suggestive of a cardiogenic etiology.

Therefore, the main cause of pulmonary edema in ARDS is the damage to the alveolar-capillary membrane, which becomes leaky, allowing fluid rich in protein to exit into the interstitial and alveolar spaces. This leads to reduced diffusing capacity, shortness of breath and hypoxemia.

ARDS can be caused by a variety of etiologies, but the clinical manifestations are the same once the alveolar-capillary membrane has been damaged.

Etiology of ARDS

ARDS is mostly caused by sepsis

ARDS is a type of respiratory failure that can be seen in a variety of clinical disorders that affect the lungs either directly or indirectly. The risk of ARDS increases in a patient with multiple predisposing clinical conditions, e.g., the risk increases from 25% in a patient with severe trauma, to 56% in a patient with severe trauma and sepsis.

Sepsis is considered the most common cause of ARDS and should be suspected in any patient predisposed to severe and serious infections. Other common causes of ARDS are listed in the table below.

<table>
<thead>
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<th>Clinical Disorders Commonly Associated with ARDS</th>
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<td><strong>Direct Lung Injury</strong></td>
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<td>• Pneumonia</td>
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<td>• Aspiration of gastric contents</td>
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<td>• Pulmonary contusion</td>
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<td>• Near-drowning</td>
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<td>• Toxic inhalation injury</td>
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Pathophysiology of ARDS

Discussing the normal physiological basis is fundamental to understanding how the ARDS
causes pulmonary edema.

There are two main extravascular spaces in the lungs:

1. Interstitial space
2. Air spaces that contain the alveoli and connecting airways

The alveolar-capillary membrane prevents the exudation of fluid into these two spaces:

- **Pulmonary capillary endothelium** limits extravasation into the interstitial space
- **Alveolar epithelium** limits extravasation into the air spaces

The alveolar epithelium is impermeable to protein. Therefore, the edema fluid doesn’t enter the alveolar space and causes an osmotic gradient that forces the fluid to accumulate in the interstitium.

**Non-cardiogenic pulmonary edema**, which is referred clinically as **ARDS**, results from injury of the alveolar-capillary membrane. This allows the fluid rich in protein (such as albumin, fibrinogen, and fibrin) to move into the alveolar space. In contrast, the cardiogenic pulmonary edema, in which the alveolar-capillary membrane is intact, results from increased transmural pressure or decreased capillary colloid osmotic pressure.

The high-protein fluid inside the alveoli causes inactivation of the surfactant, resulting in a large increase in the surface tension of the alveoli. This leads to reduced lung compliance, alveolar instability and ultimately, areas of atelectasis. Consequently, intrapulmonary shunting and **hypoxemia** occur, and the work of breathing increases, leading to **dyspnea**.

Alveolar microvascular occlusion results in a reduction of pulmonary arterial blood flow to the ventilated portions of the lung and increasing the dead space, leading to pulmonary hypertension. Increased pulmonary dead space ultimately leads to **hypercapnia**, in addition to the **hypoxemia**.

**Pathology and Clinical Manifestations of ARDS**

The clinical features depend on the pathological changes of ARDS, which encompass three phases: **exudative, proliferative and fibrotic**.

1. **Exudative phase**

   **Duration**

   The respiratory symptoms of ARDS usually start within **6—72 hours** after an eliciting risk factor and progress rapidly.

   The exudative phase usually lasts about **seven days**.

   **Pathology**
The exudative phase is characterized by destruction of alveolar cells type 1 and the capillary endothelial cells. This results in loss of the tight junctions that prevent the movement of fluid and macromolecules into the alveoli. It leads to aggregation of fluid, plasma proteins and cellular debris into the alveoli, together with dysfunction of the pulmonary surfactant. These pathological changes ultimately lead to the formation of **hyaline membrane whorls**.

**Clinical features**

Patients with ARDS typically present with **dyspnea, cyanosis** (i.e., **hypoxemia**) and **diffuse bilateral crackles**. Increased work of breathing and using of accessory muscles may ultimately result in fatigue and respiratory failure.

Clinical findings related to the precipitating factors may also exist, for example, fever and hypotension in the patient with sepsis.

**Images**

*Chest X-ray* is not specific and typically shows **bilateral alveolar infiltrates** at least three-quarters of the lung fields, that are indistinguishable from cardiogenic edema.

*CT Scan* reveals widespread patchy airspace opacities that are more apparent in the dependent lung zones.

**Laboratory Findings**

*Arterial Blood Gas (ABG)* typically shows hypoxemia and may be accompanied with acute respiratory alkalosis due to the associated tachypnea.

### 2. Proliferative phase

**Duration**

It usually lasts from **7—21 days**. Many patients will recover within **3—4 weeks** after the initial lung injury.
Pathology

This phase is characterized by beginning stages of lung repair and resolution of the pathophysiological changes (reparative process). Alveolar cells type 2 start to proliferate along the alveolar basement membranes and produce new pulmonary surfactant.

Clinical features

Although patients start to recover rapidly during this phase, they may still experience dyspnea, tachypnea, and hypoxemia. Some patients develop early progressive fibrosis, which is associated with increased risk of death.

3. Fibrotic phase

Pathology

The inflammatory exudates are converted into an extensive alveolar duct and interstitial fibrosis. Intimal fibrosis of pulmonary vessels leads to progressive vascular occlusion and pulmonary hypertension.

Clinical Features

Many patients will develop lung fibrosis that may require long-term mechanical ventilation and oxygen supply. This phase is associated with appreciable mortality.

Diagnostic Evaluation of ARDS

Acute respiratory distress syndrome (ARDS) is a diagnosis of exclusion, which can be identified once other causes of acute hypoxemic respiratory failure, bilateral diffuse infiltrates and respiratory distress have been excluded.

Therefore, evaluating a patient suspected to have ARDS is aimed at:

1. First, excluding the other similar conditions
2. Identifying the diagnostic criteria of ARDS
3. Identifying specific causes of ARDS, especially those amenable to treatment

1. Excluding other similar conditions

Excluding cardiogenic pulmonary edema

Clinically, it can be excluded by the absence of:

- Cardiac exam abnormalities:
  - S3 or S4 gallop
  - New or changed murmur
- Elevated right-sided filling pressures (elevated JVP)
- Radiographic abnormalities:
  - Pulmonary venous congestion
  - Cardiomegaly
  - Pleural effusions

Diagnostic Evaluation:

- Plasma BNP level < 100 pg/mL favors ARDS, but higher levels neither confirm heart failure nor exclude ARDS.
- **Echocardiography**: reduced left ventricular ejection fraction confirms the cardiogenic cause of pulmonary edema.

**Excluding other causes of hypoxemic respiratory failure**

Once cardiogenic pulmonary edema has been excluded, other less common alternative diagnoses must be considered:

- Diffuse pneumonia
- Diffuse alveolar hemorrhage
- Acute interstitial pneumonitis
- Hypersensitivity pneumonitis
- Toxic injury (e.g., radiation pneumonitis)
- Neurogenic pulmonary edema

**2. Diagnostic Criteria of ARDS**

**The Berlin diagnostic criteria of ARDS:**

1. Characteristic respiratory symptoms of ARDS should have begun within one week of a known clinical insult.
2. Chest X-Ray or CT show characteristic bilateral diffuse opacities that can't be fully explained by other causes.
3. The respiratory failure must not be fully explained by cardiac failure or fluid overload.
4. Moderate to severe impairment of oxygenation must be present:
   - Arterial $PO_2/FIO_2 < 200$ mmHg → is characteristic of ARDS.
   - Arterial $PaO_2/FIO_2$ between 200—300 mmHg → identifies ALI who are more likely to benefit from treatment.

**Identifying the specific cause of ARDS**

Treatable causes of ARDS should be identified once the diagnosis has been established, either by the clinical context or with performing additional diagnostic tests.

**Treatment of ARDS**

Patients with ARDS should be treated in hospitals, usually in the intensive care unit (ICU). Management of ARDS should focus on supportive treatment and improve arterial oxygen saturation.

**Supportive care**

Some patients die from the respiratory failure alone, but more common causes of death are secondary complications such as sepsis or multiorgan system failure. Therefore, patients with ARDS require meticulous supportive care:

1. **Nutritional support:**

   Patients are catabolic and will benefit from enteral feedings.

2. **Fluid management:**

   Left atrial filling pressure should be reduced with fluid restriction and diuretics to decrease the pulmonary edema and prevent further decrements in arterial oxygenation.
3. **Glucocorticoids:**

Few studies have shown benefits of treating a patient with ARDS using glucocorticoids since the lungs are rich in inflammatory mediators and leukocytes.

4. **Treatment of nosocomial pneumonia:**

Nosocomial pneumonia frequently complicates ARDS and can be associated with an increased morbidity in these patients.

Microbiological assessment of the offending organisms is important in order to choose an initial antibiotic regimen since delayed or inappropriate treatment is associated with a poor outcome.

5. **GIT prophylaxis:**

Patients with prolonged mechanical ventilation are at risk of GIT bleeding, and prophylaxis against stress ulcers should be provided.

6. **DVT prophylaxis:**

The risk of DVT and pulmonary embolism is high in patients with ARDS due to prolonged immobility.

**Management**

Patients with ARDS are severely hypoxemic and require immediate measures to improve arterial oxygen saturation ($\text{SaO}_2$). **Those include:**

1. **Oxygen supplementation:**

   Since most patients require a high FiO$_2$, high flow oxygen should be provided through a facemask or an endotracheal tube.

2. **Mechanical Ventilation:**

   Almost all patients with ARDS require intubation and mechanical ventilation because oxygen supply through a facemask can hardly provide more than about 70 % of the needed oxygen due to the environmental air being entrained.

   **Ventilator-induced lung injury** can be associated with poor outcome in patients with ARDS. Therefore, mechanical ventilatory strategies should be provided to decrease the incidence of ventilator-induced lung injury. **Those include:**

   A. **Low tidal volume ventilation:**

      Patients with ALI or ARDS should be ventilated with low tidal volume ($V_T$) ventilation (6 mL/kg predicted body weight) to protect against ventilator-induced lung injury, which occurs with high ($V_T$) ventilation and may lead to overdistension and injury to the healthy areas of the lung.

   B. **Open Lung ventilation:**

      It’s a strategy that provides a combination of:

      a. Low tidal volume ventilation $\rightarrow$ to avoid alveolar overdistention.

      b. Positive end-expiratory pressure (PEEP) $\rightarrow$ to minimize atelectasis.

   C. **High Positive end-expiratory pressure (high PEEP):**

      It is a type of open lung ventilation, which opens the collapsed alveoli and reduces theirs overdistention. It’s set to minimize FiO$_2$ and maximize PaO$_2$. 
Prognosis and Outcome of ARDS

ARDS is a serious condition that is usually associated with high mortality and morbidity. Although the mortality rate of patients with ARDS is high and ranges from 26 % to 44 %, the majority of patients recover the maximum function of their lungs within six months.

It has been demonstrated that non-pulmonary causes of ARDS, such as sepsis and non-pulmonary organ failure, account for more than 80 % of death cases.

**Several risk factors** have been identified to estimate the prognosis in a patient with ARDS:

- **Advanced age**: the older age, the higher the mortality rate.
- **Preexisting organ dysfunction from chronic diseases**, such as chronic liver disease, chronic renal disease, immunosuppression.
- **ARDS from direct lung injury** have twice the mortality of those with indirect causes of lung injury.

Review Questions

The answers are below the references.

1. **Acute respiratory distress syndrome (ARDS) is characterized by arterial PO_{2}/FIO_{2}:**

   A. Arterial PO_{2}/FIO_{2} < 200 mmHg
   B. Arterial PO_{2}/FIO_{2} > 200 mmHg
   C. Arterial PO_{2}/FIO_{2} 200—300 mmHg
   D. Arterial PO_{2}/FIO_{2} > 300 mmHg

2. A 50-year-old patient with NO chronic illnesses is diagnosed with pancreatitis and admitted in the ICU for supportive treatment. A few days later, the patient starts to breathe rapidly, his arterial PO_{2}/FIO_{2} is < 200 mmHg and chest x-ray shows bilateral diffuse pulmonary infiltrates. The most probable diagnosis is:

   A. Cardiogenic pulmonary edema.
   B. Diffuse alveolar hemorrhage.
   C. Acute respiratory distress syndrome.
   D. Interstitial pneumonia.

3. A 62-year-old patient diagnosed with ARDS is on mechanical ventilation. The patient requires prophylactic measures against:

   A. Nosocomial pneumonia.
   B. Gastrointestinal bleeding.
   C. Deep venous thrombosis and pulmonary embolism.
   D. All of the above.
References


Correct answers: 1A, 2C, 3D

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