Acute Respiratory Distress Syndrome (ARDS) — Phases and Treatment

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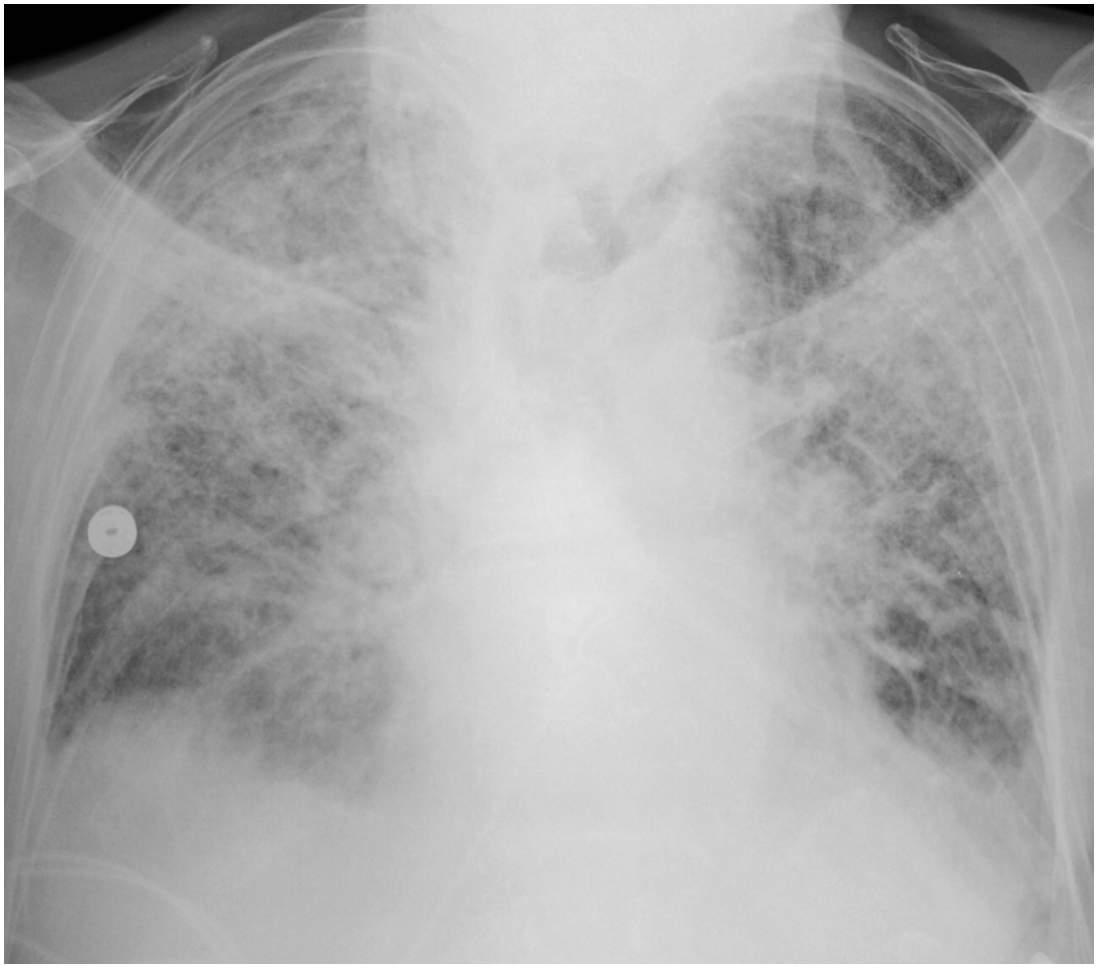
Acute respiratory distress syndrome (ARDS) is a severe inflammatory reaction of the lung that is characterized by the presence of pulmonary infiltrates due to alveolar fluid accumulation, without evidence suggestive of a cardiogenic etiology. SIRS and sepsis are the major causes of ARDS. The main finding 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.

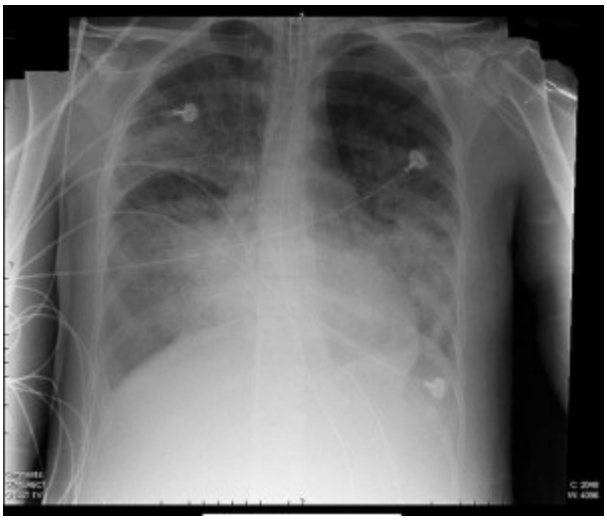


Image: Chest X-ray of a patient with ARDS. By Samir, License: CC BY-SA 3.0

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.

Clinical Disorders Commonly Associated with ARDS	
Direct Lung Injury	**Indirect Lung Injury**
• Pneumonia • Aspiration of gastric contents • Pulmonary contusion • Near-drowning • Toxic inhalation injury	• Sepsis • Severe trauma: multiple bone fractures, flail chest, head trauma, burn. • Pancreatitis • Multiple transfusions • Drug overdose • Postcardiopulmonary bypass

Pathophysiology of ARDS

Discussing the normal physiological basis is fundamental to understanding how ARDS

causes pulmonary edema.

There are 2 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 2 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 to 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 increase the dead space, leading to pulmonary hypertension. Increased pulmonary dead space ultimately leads to **hypercapnia,** in addition to hypoxemia.

Pathology and Clinical Manifestations of ARDS

The clinical features depend on the pathological changes of ARDS, which encompass 3 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 **7 days**.

Pathology

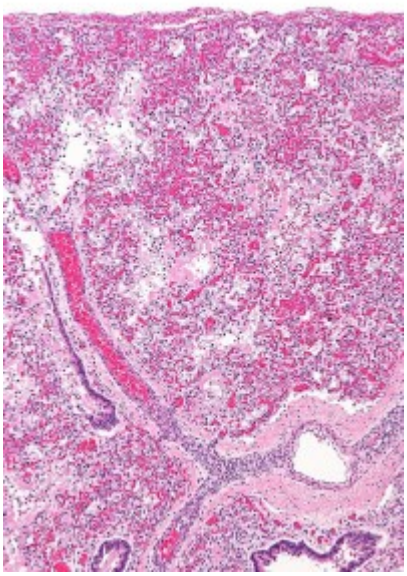


Image: Micrograph of diffuse alveolar damage, the histological correlation of ARDS. H&E stain. By Nephron, License: CC BY-SA 3.0

The exudative phase is characterized by the destruction of type 1 alveolar cells and the capillary endothelial cells. This results in the 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 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 3/4ths of the lung fields, that are indistinguishable from cardiogenic edema.

Computed tomography (**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 by 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 the 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 an 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 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 jugular venous pressure (JVP))
- Radiographic abnormalities:
    - Pulmonary venous congestion
    - Cardiomegaly
    - Pleural effusions

Diagnostic evaluation:

- **Plasma brain natriuretic peptide (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 1 week of a known clinical insult or become worse over the past week.
2. Chest X-ray or CT shows characteristic bilateral diffuse opacities that cannot be fully explained by other causes.
3. Respiratory failure must not be fully explained by cardiac failure or fluid overload.
4. Impaired oxygenation based on **arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FIO_2):**
    - Mild: **201 – 300** mm Hg
    - Moderate: **101 – 200**mm Hg
    - Severe: **≤ 100** mm Hg

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 by performing additional diagnostic tests.

Treatment of ARDS

Patients with ARDS are treated in the hospital, preferably in an intensive care unit (ICU). The management of ARDS is supportive, focused on improvement of oxygenation and directed at the underlying cause.

Mechanical ventilation: Almost all patients with a diagnosis of ARDS require endotracheal intubation and mechanical ventilation. Very few patients with mild ARDS may not have any indications for invasive ventialtion and may be managed noninvasively. However, they would still require close monitoring for any signs of disease progression.

- Low tidal volume ventilation: This is a lung protective mode of ventilation, delivering 4-8 mL/kg predicted body weight per breath. It is implemented through the assist (or volume) control ventilation mode and is intended to avoid alveolar overdistension.
- Positive end-expiratory pressure (PEEP): This is applied to maximize alveolar recruitment and improve oxygenation. Typically, PEEP is set at 5 cm H2O and adjusted further based on patient response and inspired oxygen (FiO2).

Treating underlying disorder: Failure to respond to the treatment of ARDS is often the result of failure to control the underlying disease. Intensification of therapy (e.g. steroids and bronchodilators in patients with exacerbation of chronic obstructive pulmonary disease) may improve response to the treatment of ARDS.

Supportive care: Some patients die from 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. **Conservative 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.

2. **Nutritional support:**

Patients are catabolic and will benefit from enteral feedings.

3. **Glucocorticoids:**

Current evidence does not support the routine use of glucocorticoids in the treatment of ARDS.

4. **Treatment of nosocomial pneumonia:**

Nosocomial pneumonia frequently complicates ARDS and can be associated with 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 the gastrointestinal tract (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.

Options for refractory patients

- **Prone ventilation:** Studies have shown improved 28-day mortality with this maneuver. Prone positioning requires an experienced team.
- **Maximizing alveolar recruitment:** a high PEEP strategy may be used by some physicians to maximize alveolar recruitment and improve oxygenation. However, evidence to support high PEEP ventilation is lacking. If high PEEP is used, its effectiveness should be assessed through close monitoring of oxygenation.
- **Neuromuscular blockers (NMB):** Application of NMB for patient ventilator synchrony in severe cases of ARDS and in the early hours of ventilation has increased survival and ventilator-free days.
- **Ectracorporeal membrane oxygenation (ECMO):** Patients who fail to respond to other means of therapy, ECMO has been shown to improve mortality.

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 26–44%, the majority of patients recover the maximum function of their lungs within 6 months.

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

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

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

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