Acute Respiratory Distress Syndrome: Pathophysiology and Management

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ABSTRACT
Acute respiratory distress syndrome (ARDS) is a severe and fatal condition characterized by severe hypoxic respiratory failure resistant to oxygen therapy with bilateral lung infiltrates in radiological findings, first described in 1967 by Ashbaugh and colleagues. Several pathogenesis mechanisms were involved in ARDS, such as excess inflammation, endothelial permeability, epithelial permeability, and impaired alveolar fluid clearance. Kigali criteria as modified Berlin criteria typically maintain the previous criteria with removed PEEP requirement and hypoxemia evaluated using the ratio of arterial oxygen saturation by pulse oximetry/inspiratory oxygen fraction (SpO2/FiO2). Low tidal volumes and positive end-expiratory pressure (PEEP) were needed to prevent alveolar collapse due to loss of surfactant and fluid accumulation in alveoli. The prone position was shown to have a beneficial effect on a critically ill patient. Treatment should be aimed at the underlying condition even though lung injury has occurred in many cases.

Keywords: Acute respiratory distress syndrome, hypoxia, Kigali criteria

INTRODUCTION
Acute respiratory distress syndrome (ARDS) is a severe and fatal condition characterized by severe hypoxic respiratory failure resistant to oxygen therapy, with bilateral lung infiltrates in radiological examination. ARDS was first described in 1967 by Ashbaugh and colleagues.1 Latent period between insult and development of symptoms is usually 18 – 36 hours.2 ARDS is a clinical condition with acute

Figure 1. Alveolar damage in acute respiratory distress syndrome3

TINJAUAN PUSTAKA
respiratory failure due to pulmonary and or non-pulmonary insults. A study involving 50 countries showed that the incidence of ARDS was 10.4% among intensive care unit (ICU) patients, and the mortality rates for mild, moderate, severe ARDS were 34.9%, 40.3%, and 46.1%, respectively. Severe sepsis, bacterial pneumonia, aspiration of gastric content, drug overdose, trauma, multiple transfusions are the cause of ARDS in most cases.

PATHOGENESIS

Excess Inflammation
Acute lung injury (ALI) is preceded by dysregulation of inflammation. Antigen products from microbes will bind to Toll-like receptors (TLR) and activate the natural immune system (innate immune system). The immune system will work through the formation of neutrophil extracellular traps and the release of histones. Both of these mechanisms are useful for capturing pathogens but can exacerbate alveolar damage. The formation of reactive oxygen species (ROS), proteases, chemokines, and cytokines can also exacerbate lung damage despite having positive effects against pathogens. There is a fragile balance between activation of the immune system to fight infection and overactivation or dysregulation of the immune system, causing alveolar damage.

Endothelial Permeability
Vascular endothelial cadherin (VE-cadherin) helps maintain endothelial integrity in healthy individuals. The increase in thrombin, tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), and leukocyte activation due to lung injury cause disruption of VE-cadherin binding. This mechanism causes increased endothelial permeability and the accumulation of alveolar fluid. Figure 1 shows the illustration of the mechanism.

Epithelial Permeability
The pulmonary epithelium also has epithelial-cadherin (E-cadherin) bonds useful for maintaining endothelial permeability. The permeability of E-cadherin is lower than that of VE-cadherin. Neutrophil migration causes apoptosis and breakdown of intracellular junctions leading to destruction and increased epithelial permeability. Several genetic and environmental factors such as air pollution, Table:

<table>
<thead>
<tr>
<th>AECC definition</th>
<th>Berlin criteria</th>
<th>Kigali modification of Berlin criteria</th>
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<tr>
<td><strong>Timing</strong></td>
<td>Acute onset</td>
<td>Within 1 week of a known clinical insult or new or worsening respiratory symptoms</td>
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<td><strong>Oxygenation</strong></td>
<td>PaO2/FiO2 ≤200 mmHg (defined as acute lung injury if ≤300 mmHg)</td>
<td>Mild: PaO2/FiO2 &gt;200 mmHg but ≤300 mmHg Moderate: PaO2/FiO2 &gt;100 mmHg but ≤200 mmHg Severe: PaO2/FiO2 ≤100 mmHg</td>
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<tr>
<td><strong>PEEP requirement</strong></td>
<td>None</td>
<td>Minimum 5 cmH2O PEEP required by invasive mechanical ventilation (noninvasive acceptable for mild ARDS)</td>
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<tr>
<td><strong>Chest imaging</strong></td>
<td>Bilateral infiltrates seen on frontal chest radiograph</td>
<td>Bilateral opacities not fully explained by effusions, lobar lung collapse or nodules by chest radiograph or CT</td>
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<tr>
<td><strong>Origin of oedema</strong></td>
<td>Pulmonary artery wedge pressure ≤18 mmHg when measured or no evidence of left atrial hypertension</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)</td>
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PEEP: positive end-expiratory pressure; PaO2: arterial oxygen tension; FiO2: inspiratory oxygen fraction; SpO2: arterial oxygen saturation measured by pulse oximetry; CT: computed tomography.
active and passive smoking have an impact on the occurrence and severity of ARDS.  

**Impaired Alveolar Fluid Clearance**

Damages caused by increased endothelial and epithelial permeability cause non-cardiogenic pulmonary edema, as seen in Figure 1. Under normal circumstances, ion transport through the epithelial layer will form an osmotic gradient causing fluid movement from the alveolar to the interstitial space. Interstitial fluid will be absorbed by the lymphatics or enter the bloodstream via Starling’s law mechanism. Sodium is transported through the epithelial sodium channel (ENaC) on the apical surface of alveolar types I and II cells; sodium - through Na/K-ATPase - will penetrate the basolateral area. Once the ion gradient is formed, aquaporin will facilitate the movement of fluid across the epithelial surface.

In the ARDS condition, the ability to remove edema fluid in the alveoli is reduced, and alveolar fluid clearance (AFC) disruption. Hypoxic and hypercapnia conditions directly interfere with AFC. Low oxygen and high carbon dioxide levels can decrease ENaC transcription and the function of Na/K-ATPase. ROS also causes endocytosis and necrosis of cells. Oxygen therapy and improving hypercapnia conditions can help cure alveolar edema by keeping sodium transport active through the pulmonary epithelium. Edema fluid contains large amounts of the proinflammatory cytokine interleukin-1β (IL-1β), IL-8, TNF-α, and transforming growth factor (β). These cytokines cause alveolar damage and decreased AFC in ARDS patients.

**PATHOPHYSIOLOGY**

There are three phases in the course of ARDS (Figure 2).

**Exudative Phase**

This phase is marked with pulmonary edema and inflammation of the neutrophils. Damage to the alveolar causes the formation of the...
hyaline membrane. Pulmonary edema can lead to atelectasis and decreased pulmonary compliance. Hypercapnia occurs as a result of hypoxemia, tachypnea, dyspnea, and increased alveolar dead space. Respiratory failure events are common during this phase. On radiological examination, bilateral opacities that lead to pulmonary edema can be found.

**Proliferative Phase**

This phase usually occurs on days 7 to 21. Some patients are recovered, but some will experience progressive lung damage and even pulmonary fibrosis.

**Fibrotic Phase**

Most patients will experience recovery in 3-4 weeks. Some patients develop progressive fibrosis, which requires prolonged ventilatory support with or without oxygen supplementation. Decreased lung compliance, pneumothorax, and increased pulmonary dead space can be found in this phase.

**DIAGNOSIS**

Several criteria have been used for ARDS diagnosis (Table). Berlin criteria are not suitable in all settings, especially with the constrained resource with difficult access for arterial blood gas measurement and mechanical ventilation. Kigali criteria as modified Berlin criteria typically maintain the previous measures with removed PEEP requirement. Hypoxemia is evaluated with the ratio of arterial oxygen saturation by pulse oximetry/inspiratory oxygen fraction (SpO2/FiO2).8

**TREATMENT**

Figure 3 summarized the initial management for patients with ARDS. Hypoxemia and increased breathing effort need ventilatory support. The recommended ventilation treatment is to limit alveolar distension by maintaining adequate tissue oxygenation. Supportive management, specific management, and treating the underlying condition are essential in managing ARDS patients (Detailed algorithm in Figure 4). Low tidal volume (≤6-mL/kg predicted body weight) was shown to have a lower mortality rate than higher tidal volumes. Low tidal volumes and positive end-expiratory pressure (PEEP) were needed to prevent alveolar collapse due to loss of surfactant and fluid accumulation in alveoli. Prone position was shown to have a beneficial effect in critically ill patients. ARDS treatment should be aimed at treating the underlying condition even though lung injury has occurred.7

**SUMMARY**

Acute respiratory distress syndrome (ARDS) is a severe and fatal condition characterized by severe hypoxic respiratory failure resistant to oxygen therapy, with bilateral lung infiltrates in radiological examination. Three phases in ARDS disease progression are exudative, proliferative, and fibrotic phases. Kigali criteria can be used for ARDS diagnosis without PEEP requirement. Low tidal volume (≤6-mL/kg predicted body weight) was shown to result in lower mortality rates than higher tidal volumes, and prone position can be beneficial for critically ill patients.

**REFERENCES**