Acute Respiratory Distress Syndrome: Pathophysiology and Management

Darius Hartanto
Klinik Pratama Sathya Sai, Jakarta, Indonesia

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

ABSTRAK

Acute respiratory distress syndrome (ARDS) adalah kondisi serius dan fatal yang ditandai dengan kegagalan pernapasan tipe hipoksia berat yang resisten terhadap terapi oksigen dengan infiltrat paru bilateral pada temuan radiologis; pertama kali ditemukan pada tahun 1967 oleh Ashbaugh dan kawan-kawan. Beberapa mekanisme patogenesis yang terlibat dalam ARDS adalah inflamasi berlebih, permeabilitas endotel, permeabilitas epitel, dan gangguan pembersihan cairan alveolar. Kriteria Kigali sebagai hasil modifikasi dari kriteria Berlin, mempertahankan kriteria sebelumnya dengan persyaratan PEEP dihilangkan dan hipoksemia dievaluasi menggunakan rasio saturasi oksigen arteri dengan oksimetri nadi/ fraksi oksigen inspirasi (SpO2/ FiO2). Volume *tidal* dan tekanan ekspirasi akhir positif (PEEP) rendah perlu untuk mencegah kolaps alveolar karena hilangnya surfaktan dan akumulasi cairan di alveoli. Posisi tengkurap terbukti memiliki efek menguntungkan pada pasien kritis. Pengobatan ARDS harus ditujukan untuk mengobati kondisi yang mendasarinya meskipun cedera paru telah terjadi dalam kebanyakan kasus.
Darius Hartanto. *Acute Respiratory Distress Syndrome:* Patofisiologi dan Tatalaksana

Kata kunci: *Acute respiratory distress syndrome*, hipoksia, kriteria Kigali

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

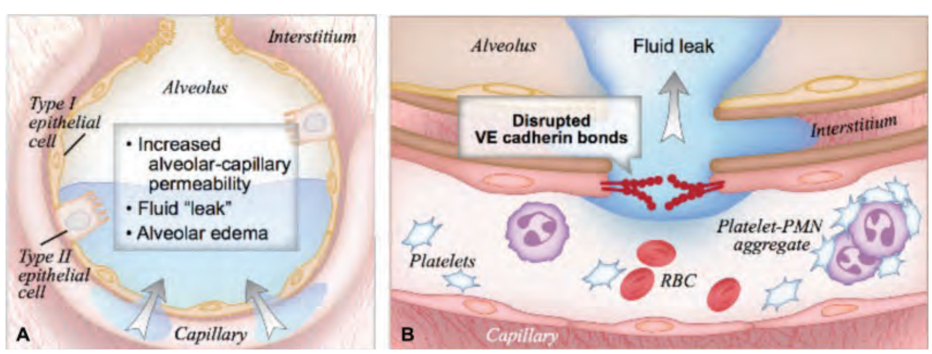

Figure 1. Alveolar damage in acute respiratory distress syndrome[5]

Alamat Korespondensi *email: dariushartanto11@gmail.com*

respiratory failure due to pulmonary and or non-pulmonary insults.[3] 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.[4] Severe sepsis, bacterial pneumonia, aspiration of gastric content, drug overdose, trauma, multiple transfusions are the cause of ARDS in most cases.[5]

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.[5]

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.[5] 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,

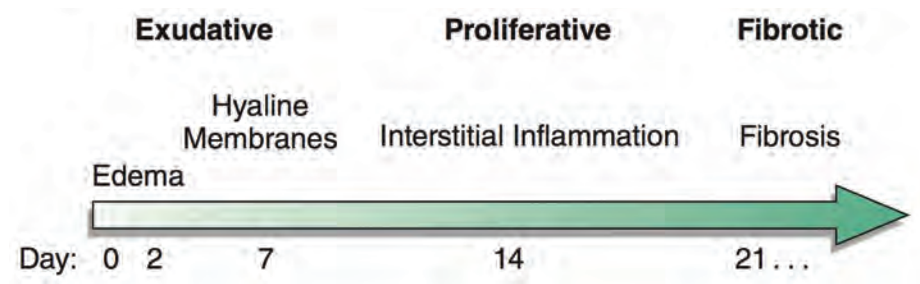

Figure 2. Phases in acute respiratory distress syndrome[6]

Table. Criteria for acute respiratory distress syndrome (ARDS)[8]

	AECC definition	Berlin criteria	Kigali modification of Berlin criteria
Timing	Acute onset	Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	PaO2/FiO2 ≤200mmHg(defined as acute lung injury if ≤300 mmHg)	Mild: PaO2/FiO2 >200 mmHg but ≤300 mmHg Moderate: PaO2/FiO2 >100 mmHg but ≤200 mmHg Severe:PaO2/FiO2 ≤100mmHg	SpO2/FiO2 ≤315
PEEP requirement	None	Minimum 5 cmH2O PEEP required byinvasive mechanical ventilation (noninvasive acceptable for mild ARDS)	No PEEP requirement, consistent with AECC definition
Chest imaging	Bilateral infiltrates seen on frontal chest radiograph	Bilateral opacities not fully explained byeffusions, lobar/ lung collapse or nodules by chest radiograph or CT	Bilateral opacities not fully explained by effusions, lobar/ lung collapse or nodules by chest radiograph or ultrasound
Origin of oedema	Pulmonary artery wedge pressure <18 mmHg when measured or no evidence of left atrial hypertension	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)	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)

PEEP: positive end-expiratory pressure; PaO2: arterial oxygen tension; FiO2: inspiratory oxygen fraction; SpO2: arterial oxygen saturation measured by pulse oximetry; CT: computed tomography.

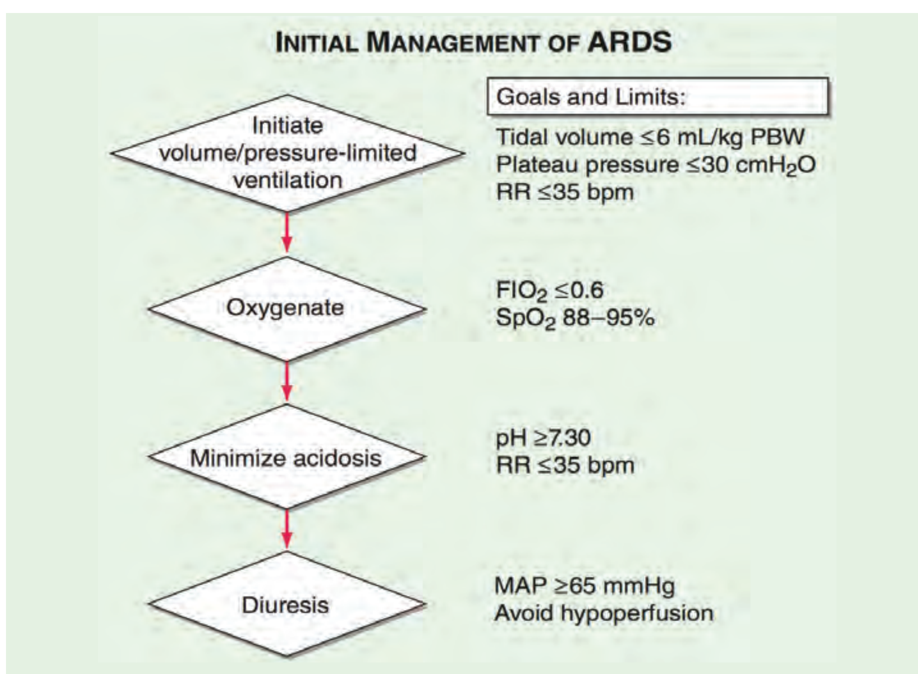

Figure 3. Initial management in acute respiratory distress syndrome[8]


active and passive smoking have an impact on the occurrence and severity of ARDS.[5]

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.[5] 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.[5] 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-β1. These cytokines cause alveolar damage and decreased AFC in ARDS patients.[5]

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

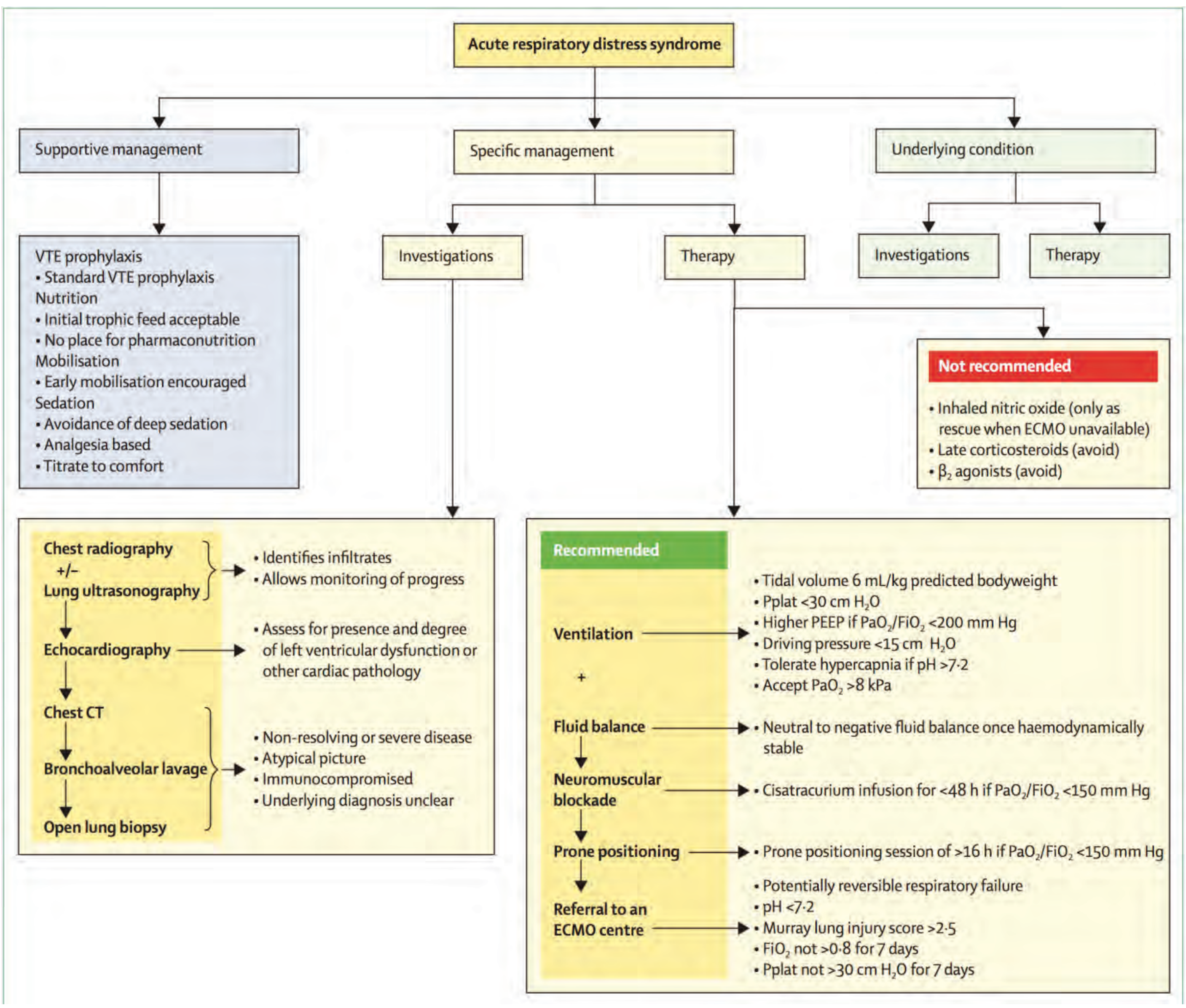

Figure 4. Algorithm in acute respiratory distress syndrome management[9]

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.[7] 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.[7]

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.[7]

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.[7,8]

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

1. Eworuke E, Major JM, McClain LIG. National incidence rates for acute respiratory distress syndrome (ARDS) and ARDS cause-specific factors in the United States (2006–2014). J Crit Care 2018;47:192–7
2. Villar J, Blanco J, Kacmarek RM. Current incidence and outcome of the acute respiratory distress syndrome. Curr Opin Crit Care 2016;22:1-6.
3. Confalonieri M, Salton F, Fabiano F. Acute respiratory distress syndrome. Eur Respir Rev. 2017;26:160.
4. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2017;315(8):788-800.
5. Huppert LA, Matthay MA, Ware LB. Pathogenesis of acute respiratory distress syndrome. Semin Respir Crit Care Med. 2019;40:31–9.
6. Levy BD, Choi AMK. Acute respiratory distress syndrome. In: Kasper DL, Hauser SL, Jameson JL, et al. Harrison's principles of internal medicine 19th ed. McGraw Hill Education: 2015.p. 1763-40.
7. Jameson JL, Fauci AS, Kasper DL, Longo D, Loscalzo J, Hauser SL. Harrison's manual of medicine. 20th ed. McGraw Hill; 2020 .p. 72-5.
8. Bradley J, Gurnell M, Wood D. Clinical medicine lecture notes 7th ed. Wiley-Blackwell; 2012. p.110-27.
9. Sweeney RM, McAuley DF. Acute respiratory distress syndrome. Lancet 2016;388:2416-30.