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# Current diagnostic criteria, therapeutic approaches, and long-term outcomes in acute respiratory distress syndrome

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## ABSTRACT

Acute respiratory distress syndrome (ARDS) is a common condition in intensive care units, characterized by severe hypoxemic respiratory failure. It typically develops following triggering factors such as pneumonia or sepsis. Diagnosis is based on clinical and radiological findings in conjunction with oxygenation parameters, and the syndrome is classified as mild, moderate, or severe. Key management strategies include low tidal volume ventilation, appropriate positive end-expiratory pressure, prone positioning, and extracorporeal membrane oxygenation in selected cases. Corticosteroids and neuromuscular blocking agents should be used with caution in specific patient groups. Since survivors of ARDS are at risk for long-term physical, cognitive, and psychological impairments, rehabilitation and long-term follow-up are of paramount importance. This article provides an updated overview of the diagnosis, differential diagnosis, treatment strategies, and long-term management of ARDS.

**Keywords**: ARDS, alveolar damage, hypoxemia, intensive care

## DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a severe clinical condition characterized by hypoxemic respiratory failure affecting both lungs, and it was first described in the 1960s. Initially referred to as "shock lung" or "adult respiratory distress syndrome," the terminology later evolved to "ARDS" upon recognition that the condition can affect individuals of all age groups.[1] Technological advancements such as high-flow nasal oxygen (HFNO), pulse oximetry, and thoracic ultrasonography have prompted the need for revisions in the definition of ARDS.

ARDS is an acute, widespread inflammatory lung injury that develops following triggers such as pneumonia, sepsis, trauma, or aspiration.[2] Clinically, it presents within the first 7 days with dyspnea and hypoxemia; tachypnea, bilateral crackles, and, in advanced cases, cyanosis and confusion may also be observed. The hallmark of pathogenesis is diffuse alveolar damage.[3] Elevated pro-inflammatory cytokines activate neutrophils, and the released mediators injure the capillary endothelium and alveolar epithelium.[4] This damage leads to the leakage of protein-rich fluid into the alveolar spaces, surfactant depletion, and atelectasis. Consequently, arterial hypoxemia, increased shunt fraction, dead space ventilation, and reduced lung compliance occur; hypercapnia may develop in the later stages.[5,6]

## LABORATORY TESTS

Although there is no specific laboratory test diagnostic for ARDS, certain abnormalities can provide guidance in identifying the underlying cause and assessing disease severity. Complete blood count may reveal leukocytosis or leukopenia. Biochemical tests may indicate renal or hepatic dysfunction secondary to hypoxemia or shock. In cases of severe inflammation, coagulation abnormalities such as prothrombin time, activated partial thromboplastin time, and elevated D-dimer levels may be observed. While arterial blood gas (ABG) analysis usually shows hypoxemia and respiratory alkalosis, hypercapnic acidosis may develop in advanced stages and this may be an indicator of poor prognosis.

## IMAGING FINDINGS

Radiologic imaging plays a crucial supportive role in the diagnosis of ARDS. The most common finding on chest radiographs is the presence of diffuse alveolar opacities affecting both lungs. These opacities are typically centrally located and predominantly involve the lower lobes, rather than being peripheral. More detailed findings can be identified through thoracic ultrasonography or chest computed tomography (CT). These modalities often reveal diffuse and patchy opacities, interstitial thickening, and an increase in B-lines.

## DEFINITION AND CLASSIFICATION OF ARDS ACCORDING TO BRITISH THORACIC SOCIETY (BTS) GUIDELINES

The guidelines supported by the BTS adopt the Berlin Definition for the characterization of ARDS. ARDS is defined as a condition marked by acute onset hypoxemia, bilateral pulmonary infiltrates, and non-cardiogenic pulmonary involvement.[7] To confirm the diagnosis, imaging studies must demonstrate bilateral widespread infiltrates, and cardiac etiologies must be excluded. The BTS guidelines particularly recommend chest radiography or thoracic CT for diagnostic confirmation.

The Berlin Definition classifies ARDS into three categories based on the severity of hypoxemia: mild, moderate, and severe. This classification is grounded in oxygenation parameters and serves as a crucial guide in determining clinical management strategies.

## CORE DIAGNOSTIC CRITERIA FOR ARDS APPLICABLE ACROSS ALL SUBGROUPS

The diagnosis of ARDS relies on the comprehensive evaluation of clinical, radiologic, and pathophysiologic findings. Several fundamental criteria have been established to define the condition across all subcategories:

### Risk Factors

ARDS is typically triggered by acute-onset predisposing conditions such as pneumonia, sepsis, extrapulmonary systemic infections, trauma, massive transfusion, aspiration, or shock. Differentiating pulmonary involvement from cardiogenic pulmonary edema is essential; therefore, cardiogenic causes such as congestive heart failure or left ventricular dysfunction must be excluded. Moreover, the primary cause of hypoxemia and impaired ventilation should not be solely attributed to atelectasis.

### Timing

The onset of ARDS usually occurs within one week of exposure to an identifiable risk factor or is characterized by a significant worsening of existing respiratory symptoms. In some cases, such as viral infections like COVID-19, the onset may be more gradual, making this temporal criterion particularly relevant.

### Imaging Findings

Radiological assessment is a cornerstone in the diagnostic process. Chest radiography, CT, or thoracic ultrasonography typically reveal newly developed bilateral consolidations. These findings must not be fully explained by alternative causes such as massive pleural effusion, unilateral atelectasis, or progressive nodular/mass lesions. Particularly in settings where radiography or CT is unavailable, thoracic ultrasonography serves as a viable alternative diagnostic modality and has been incorporated into the diagnostic criteria.

## ASSESSMENT OF ARDS SEVERITY

After confirming the clinical, radiological, and temporal criteria for ARDS, the diagnosis is finalized based on the presence of refractory hypoxemia. Recent guidelines have re-evaluated the oxygenation parameters used to classify the severity of the syndrome.[8]

Traditionally, the $PaO_2/FiO_2$ ratio obtained via ABG has been used as the standard parameter in ARDS diagnosis and staging. However, in settings where ABG is not available or is costly, the $SpO_2/FiO_2$ ratio, based on pulse oximetry, offers a practical alternative.

HFNO has become an accepted respiratory support strategy for non-intubated ARDS patients and is now included in diagnostic criteria. Severity is determined by the level of positive end-expiratory pressure (PEEP) applied during: HFNO at ≥30 L/min flow, noninvasive ventilation (NIV) at ≥5 L/min, or continuous positive airway pressure. The classification is summarized in the following **Table.**

**Table.** Classification of ARDS severity based on oxygenation parameters

| ARDS severity | $PaO_2/FiO_2$ ratio (with PEEP ≥5 cm $H_2O$) | $SpO_2/FiO_2$ ratio (when $SpO_2$ ≤97%) |
|---|---|---|
| Mild | 200-300 mmHg | 235-315 mmHg |
| Moderate | 100-200 mmHg | 148-235 mmHg |
| Severe | ≤100 mmHg | ≤148 mmHg |

ARDS: Acute respiratory distress syndrome

## EXCLUSION OF ACUTE CARDIOGENIC PULMONARY EDEMA IN THE DIFFERENTIAL DIAGNOSIS

Before confirming a diagnosis of ARDS, it is essential to exclude acute cardiogenic pulmonary edema, particularly in intensive care and emergency settings.[9] Common causes include left ventricular dysfunction, valvular heart disease, malignant hypertension, and advanced renal failure. Differential diagnosis should involve transthoracic echocardiography and measurement of BNP or NT-proBNP levels. Chest radiographs showing cardiomegaly, pleural effusion, or Kerley B lines support a cardiac origin. Additional clinical signs such as an S3/S4 gallop, jugular venous distention, and peripheral edema can aid in differentiation. A rapid response to diuretic therapy may further confirm a cardiogenic cause retrospectively.

## PRIMARY CAUSES OF ARDS

ARDS may develop as a result of various pulmonary and extrapulmonary triggers. Although its pathophysiology varies depending on the etiology, the clinical and radiological manifestations are often similar across different causes. Below are the primary causes of ARDS: Sepsis, aspiration, pneumonia, severe trauma, massive transfusion, substance and alcohol use.

## COVID-19-ASSOCIATED ARDS

COVID-19 is one of the major viral infections that can lead to the development of ARDS. SARS-CoV-2 infection results in diffuse alveolar damage, interstitial edema, and microthrombosis within the lungs. The pathophysiology of COVID-19-associated ARDS differs in certain aspects

from classical ARDS, most notably with more pronounced vascular pathology, widespread endothelial injury, capillary dilation, and in-situ microthrombosis.[10]

Additionally, a distinctive feature of COVID-19 ARDS is "silent hypoxemia," where patients experience severe hypoxemia without noticeable respiratory distress.[11] Imaging findings typically begin with peripheral and basilar ground-glass opacities, progressing to characteristic consolidations as the disease advances.

In terms of clinical management, low tidal volume ventilation, prone positioning, and moderate levels of PEEP are recommended. Furthermore, due to the hypercoagulable state specific to COVID-19, anticoagulant therapy has become an integral component of the management strategy.[12]

## MANAGEMENT OF ARDS AND PHARMACOTHERAPEUTIC APPROACH

Due to its complex pathophysiology, ARDS is a severe clinical condition that necessitates a multidisciplinary approach. The primary therapeutic goals include improving oxygenation, supporting ventilation, maintaining hemodynamic stability, and addressing the underlying cause. As there is no disease-specific pharmacological treatment proven to be effective, management largely relies on supportive care strategies. Given the high risk of non-cardiogenic pulmonary edema resulting from increased capillary permeability and hydrostatic imbalance, meticulous fluid management is essential.[13]

## ROLE OF NEUROMUSCULAR BLOCKERS IN THE MANAGEMENT OF ARDS

Neuromuscular blockers (NMBs) may be used as an adjunctive therapy in severe ARDS cases to improve patient-ventilator synchrony and reduce ventilator-induced lung injury (VILI).[14] Despite potential benefits such as reducing oxygen consumption and systemic inflammation, current clinical guidelines do not recommend the routine use of NMBs, as meta-analyses have failed to demonstrate significant improvements in mortality or duration of mechanical ventilation. Contemporary recommendations support the short-term use of NMBs (up to 48 hours) only in the early phase of disease and in severe cases; however, this recommendation is based on low-quality evidence.[15] Furthermore, the therapeutic benefit of NMBs has predominantly been observed when used in conjunction with deep sedation; comparable outcomes have not been demonstrated with light sedation. Therefore, the use of NMBs should be restricted to carefully selected patients.

## SYSTEMIC GLUCOCORTICOID THERAPY IN ARDS

Systemic glucocorticoids exert anti-inflammatory effects by inhibiting the synthesis of proinflammatory mediators involved in the pathogenesis of ARDS. Traditionally used in the treatment of secondary conditions such as refractory septic shock or pneumonia, these agents have recently gained attention for their mortality-reducing effects, particularly in COVID-19–related ARDS.[16] In line with this, the 2024 ATS guidelines conditionally recommend the use of systemic corticosteroids in all patients diagnosed with ARDS. The duration of glucocorticoid therapy should not exceed 14 days. Recommended dosing regimens include dexamethasone at 20 mg/day for the first 5 days followed by 10 mg/day for the next 5 days, and methylprednisolone initiated at 1 mg/kg/day with gradual tapering.[16,17] Close monitoring for potential adverse effects such as infection, hyperglycemia, and muscle weakness is essential throughout the treatment course.

## USE OF INHALED PULMONARY VASODILATORS IN ARDS

In cases of ARDS with persistent refractory hypoxemia despite standard ventilation strategies, case series and small-scale studies have reported on the use of inhaled pulmonary vasodilators, such as nitric oxide or prostacyclin. These agents have been shown to temporarily improve oxygenation, particularly in patients with right ventricular dysfunction or concomitant pulmonary arterial hypertension.[18] The primary mechanism of action of inhaled vasodilators is enhancing ventilation-perfusion matching by promoting vascular dilation in ventilated alveoli. This selective pulmonary vasodilation occurs with minimal impact on the systemic circulation.

However, there is no robust clinical evidence demonstrating a significant improvement in morbidity or mortality with the use of these agents. The therapeutic response is generally assessed within the first 24 hours following administration. If no clinical benefit is observed, continuation of the therapy is not recommended. Prior to initiation, it is essential to carefully evaluate the potential benefits, as well as the cost and risk of adverse effects.

## SUPPORTIVE CARE APPROACHES IN ARDS

Mortality in ARDS is not solely attributable to respiratory failure but also results from multiple organ dysfunction and secondary complications. Therefore, supportive care strategies are critical components of management.

Supportive care in ARDS includes careful fluid management with hemodynamic monitoring, targeting a central venous pressure (CVP) of less than 4 $cmH_2O$. Early initiation of enteral nutrition is recommended to meet metabolic demands and support immune function.[19] Blood glucose levels should be closely regulated to prevent hyperglycemia-related complications. Infection control measures are crucial to prevent nosocomial and ventilator-associated pneumonia (VAP).[20] Routine pharmacologic prophylaxis should be implemented to reduce the risk of venous thromboembolism (VTE) associated with immobility and mechanical ventilation. Additionally, proton pump inhibitors or $H_2$ receptor blockers should be used for stress ulcer prophylaxis.

## VENTILATION STRATEGIES AND RESPIRATORY SUPPORT IN ARDS

The choice of ventilation mode in patients with ARDS varies depending on the underlying pathology and individual respiratory mechanics.[21] In most clinical scenarios, volume-

controlled ventilation is preferred due to its ability to guarantee a consistent tidal volume and ensure adequate ventilation. However, due to the commonly observed decreased lung compliance in ARDS, even low tidal volumes may exceed inspiratory capacity, leading to elevated airway pressures. This can increase the risk of VILI. Therefore, pressure-controlled volume-guaranteed ventilation-which incorporates pressure-limiting features while maintaining volume targets-is frequently recommended as a safer and more protective mode of ventilation in ARDS management.[22]

In patients with severe ARDS, invasive mechanical ventilation is frequently required.[8] In contrast, for patients with non-severe ARDS, the use of HFNO has been suggested, as it may reduce the need for intubation. However, it is also emphasized that HFNO has not demonstrated a significant impact on mortality outcomes.[15]

In patients with acute hypoxemic respiratory failure (AHRF) who are not receiving invasive mechanical ventilation, and after excluding specific conditions such as cardiogenic pulmonary edema, obesity hypoventilation syndrome, or acute exacerbation of COPD, there is no conclusive evidence that NIV reduces intubation rates or mortality. Nevertheless, particularly in AHRF cases associated with COVID-19, NIV has been shown to reduce the need for intubation compared to conventional oxygen therapy, and its use has been recommended in this context.[15]

## LOW TIDAL VOLUME VENTILATION IN ARDS

Low tidal volume ventilation (LTVV), also known as lung-protective ventilation, is a key strategy in the management of ARDS. Its main aim is to provide effective respiratory support while reducing alveolar overdistension and preventing VILI.

Guidelines recommend setting the tidal volume between 4-8 ml/kg of predicted body weight (PBW), with 6 ml/kg PBW being the usual starting point in clinical practice.[23]

Because lung compliance is reduced in ARDS, even low tidal volumes may result in high airway pressures. For this reason, plateau pressure should be kept below 30 $cmH_2O$. The respiratory rate is usually set between 14–22 breaths per minute, and should not exceed 35 breaths per minute.[24]

## ROLE OF POSITIVE END-EXPIRATORY PRESSURE AND RECRUITMENT MANEUVERS IN THE MANAGEMENT OF ARDS

PEEP is a fundamental ventilatory parameter used in ARDS to prevent alveolar collapse and improve oxygenation. The 2017 guidelines recommend the use of high PEEP and recruitment maneuvers in moderate to severe ARDS cases; however, there is no standardized algorithm for determining the optimal PEEP-$FiO_2$ combination.[16] High PEEP may enhance gas exchange by reducing intrapulmonary shunting and may offer protection against oxygen toxicity. On the other hand, it may also increase plateau pressure, leading to potential adverse effects such as barotrauma and decreased cardiac output. Considering these risks, meta-analyses have not demonstrated a significant difference in mortality between high and low PEEP strategies.[25] Current guidelines support the use of high PEEP in moderate to severe ARDS cases without routine recruitment maneuvers, while no definitive recommendation is provided for mild ARDS. Although LTVV is generally well tolerated, it may result in permissive hypercapnia, which should be carefully managed, especially in patients with elevated intracranial pressure.

## PERMISSIVE HYPERCAPNIA AND VENTILATION STRATEGIES

Permissive hypercapnia is a foreseeable and generally tolerable consequence of LTVV. While LTVV aims to reduce alveolar overdistension and ventilator-associated lung injury (VILI), it can lead to arterial hypercapnia due to alveolar hypoventilation.[26] In efforts to maintain adequate minute ventilation, increasing the respiratory rate may shorten the expiratory phase, potentially resulting in the development of auto-PEEP. This complication can be avoided through careful adjustment of ventilatory parameters. Moreover, high-frequency ventilation has not demonstrated a significant impact on mortality in patients with moderate to severe ARDS, and thus its routine use is not recommended.[15]

## OXYGENATION-SUPPORTIVE THERAPIES IN ARDS

In moderate to severe ARDS, especially when LTVV fails to provide adequate oxygenation, additional oxygen support strategies become critical. The main goals are to enhance oxygen delivery and reduce systemic oxygen consumption.

### Supportive Measures to Reduce Oxygen Consumption

Fever, anxiety, pain, and increased work of breathing can elevate oxygen demand. The use of antipyretics, sedatives, and analgesics is recommended to help maintain the balance between ventilation and oxygenation, particularly in patients with high oxygen requirements.

### Prone Ventilation

Prone positioning enhances perfusion and ventilation-perfusion matching in the dorsal regions of the lungs by reducing both cardiac and diaphragmatic compression. This intervention can lead to a significant improvement in oxygenation levels. It is particularly recommended for patients with moderate to severe ARDS who exhibit inadequate oxygenation despite LTVV, provided there are no contraindications, such as spinal instability.

The optimal period for prone positioning is within the first seven days of disease onset. It is advised to implement prone positioning early and maintain it for at least 16 consecutive hours. This duration and timing are crucial for not only improving oxygenation but also potentially reducing mortality rates.

### Extracorporeal Membrane Oxygenation (ECMO)

In ARDS patients where adequate oxygenation cannot be achieved through conventional ventilation strategies, ECMO emerges as a therapeutic option. Specifically, venovenous ECMO can be utilized to support oxygenation in cases of severe ARDS. Current guidelines classify the use of

venovenous ECMO as a "conditional recommendation" with a low level of evidence.[15]

For optimal effectiveness, early initiation of ECMO is crucial, ideally within the first seven days following symptom onset. The highest success rates are typically observed when ECMO is commenced during this early phase. Therefore, it is recommended that patients in centers without ECMO capabilities be transferred promptly to specialized reference centers where this intervention is available.

## LONG-TERM MORBIDITY ASSOCIATED WITH ARDS

ARDS poses not only a significant risk of acute mortality but also represents a major clinical concern due to the long-term morbidity observed in survivors. These individuals frequently experience cognitive impairments (including deficits in attention, memory, and executive function), psychological disorders (such as anxiety, depression, and post-traumatic stress disorder), and physical complications (including muscle weakness, exercise intolerance, and neuromuscular dysfunction).[27,28] These sequelae are collectively described under the term post-intensive care syndrome and are known to substantially impair quality of life. Additionally, the post-ARDS period is often associated with reduced rates of return to work, income loss, and social isolation, further exacerbating the burden of illness. Therefore, the implementation of multidisciplinary and long-term rehabilitation programs for ARDS survivors is of critical importance for improving both clinical outcomes and overall quality of life.

## ETHICAL DECLARATIONS

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

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### Author Contributions

The author declares that they solely conducted the design, execution, analysis, and writing of the manuscript, and approved the final version.

## REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet.* 1967;2(7511):319-323. doi:10.1016/s0140-6736(67)90168-7
2. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med.* 2012;38(10):1573-1582. doi:10.1007/s00134-012-2682-1
3. Hughes KT, Beasley MB. Pulmonary manifestations of acute lung injury: more than just diffuse alveolar damage. *Arch Pathol Lab Med.* 2017;141(7):916-922. doi:10.5858/arpa.2016-0342-RA
4. Wilson JG, Liu KD, Zhuo H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *Lancet Respir Med.* 2015;3(1):24-32. doi:10.1016/S2213-2600(14)70291-7
5. Kiiski R, Takala J, Kari A, Milic-Emili J. Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1992;146(5 Pt 1):1131-1135. doi:10.1164/ajrccm/146.5_Pt_1.1131
6. Roupie E, Dambrosio M, Servillo G, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;152(1):121-128. doi:10.1164/ajrccm.152.1.7599810
7. Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res.* 2019;6(1):e000420. doi:10.1136/bmjresp-2019-000420
8. Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med.* 2023;49(7):727-759. doi:10.1007/s00134-023-07050-7
9. Schwarz MI, Albert RK. "Imitators" of the ARDS: implications for diagnosis and treatment. *Chest.* 2004;125(4):1530-1535. doi:10.1378/chest.125.4.1530
10. Dorward DA, Russell CD, Um IH, et al. Tissue-specific immunopathology in fatal COVID-19. *Am J Respir Crit Care Med.* 2021;203(2):192-201. doi:10.1164/rccm.202008-3265OC
11. Swenson KE, Swenson ER. Pathophysiology of acute respiratory distress syndrome and COVID-19 lung injury. *Crit Care Clin.* 2021;37(4):749-776. doi:10.1016/j.ccc.2021.05.003
12. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med.* 2020;383(2):120-128. doi:10.1056/NEJMoa2015432
13. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med.* 2017;43(2):155-170. doi:10.1007/s00134-016-4573-3
14. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010;363(12):1107-1116. doi:10.1056/NEJMoa1005372
15. Qadir N, Sahetya S, Munshi L, et al. An update on management of adult patients with acute respiratory distress syndrome: an official American thoracic society clinical practice guideline. *Am J Respir Crit Care Med.* 2024;209(1):24-36. doi:10.1164/rccm.202311-2011ST
16. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med.* 2017;43(12):1751-1763. doi:10.1007/s00134-017-4919-5
17. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med.* 2020;8(3):267-276. doi:10.1016/S2213-2600(19)30417-5
18. Karam O, Gebistorf F, Wetterslev J, Afshari A. The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a cochrane systematic review with trial sequential analysis. *Anaesthesia.* 2017;72(1):106-117. doi:10.1111/anae.13628
19. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine and american society for parenteral and enteral nutrition: executive summary. *Crit Care Med.* 2009;37(5):175. doi:10.1097/CCM.0b013e3181a40116
20. Zampieri FG, Póvoa P, Salluh JI, et al. Lower respiratory tract infection and short-term outcome in patients with acute respiratory distress syndrome. *J Intensive Care Med.* 2020;35(6):588-594. doi:10.1177/0885066618772498
21. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA.* 2016;315(8):788-800. doi:10.1001/jama.2016.0291
22. Umoh NJ, Fan E, Mendez-Tellez PA, et al. Patient and intensive care unit organizational factors associated with low tidal volume ventilation in acute lung injury. *Crit Care Med.* 2008;36(5):1463-1468. doi:10.1097/CCM.0b013e31816fc3d0
23. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1301-1308. doi:10.1056/NEJM200005043421801

24. de Durante G, del Turco M, Rustichini L, et al. Lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2002;165(9):1271-1274. doi:10.1164/rccm.2105050
25. Santa Cruz R, Villarejo F, Irrazabal C, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev.* 2021;3(3):CD009098. doi:10.1002/14651858.CD009098.pub3
26. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER. Hypercapnic acidosis and mortality in acute lung injury. *Crit Care Med*. 2006;34(1):1-7. doi:10.1097/01.ccm.0000194533.75481.03
27. Hiser SL, Fatima A, Ali M, Needham DM. Post-intensive care syndrome (PICS): recent updates. *J Intensive Care.* 2023;11(1):23. doi:10.1186/s40560-023-00670-7
28. Ilias I, Mantziou V, Vamvakas E, et al. Post-traumatic stress disorder and burnout in healthcare professionals during the sars-cov-2 pandemic: a cross-sectional study. *J Crit Care Med (Targu Mures).* 2021;7(1):14-20. doi:10.2478/jccm-2020-0042