2025 306th KATRD Symposium

Update of ARDS CPG

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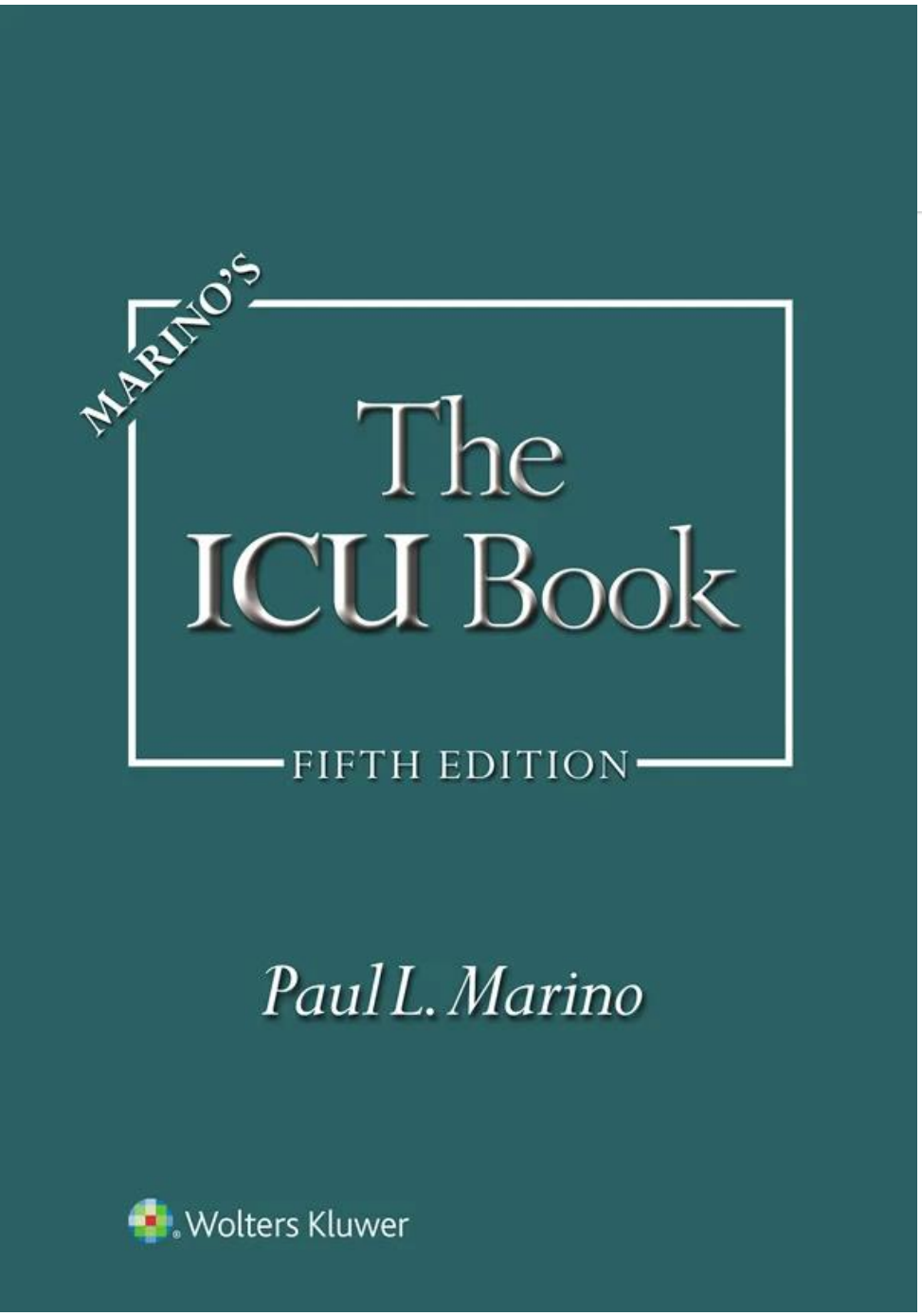

Chapter 24

Acute Respiratory Distress Syndrome

Physicians think they do a lot for a patient when they give his disease a name.

Immanuel Kant

The disease entity described in this chapter has had several names over the years, including shock lung, Da Nang lung (from the Vietnam war), stiff-lung, leaky capillary pulmonary edema, noncardiogenic pulmonary edema, acute lung injury, adult respiratory distress syndrome, and most recently, *acute respiratory distress syndrome*, or *ARDS*. However, none of these names provides any useful information about the disease, which is a diffuse inflammatory injury of the lungs, and one of the leading causes of acute respiratory failure in modern times (1–3).

Acute respiratory distress syndrome

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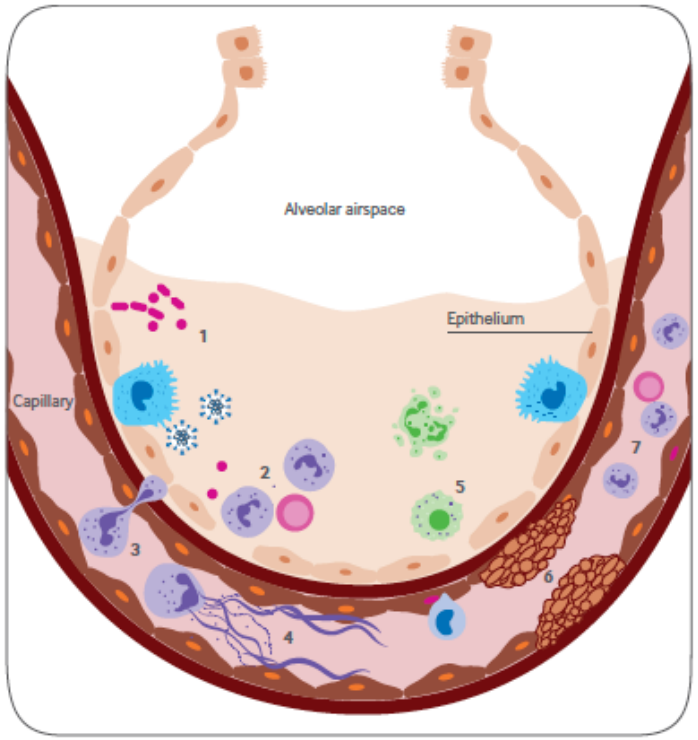
ABSTRACT

The understanding of acute respiratory distress syndrome (ARDS) has evolved greatly since it was first described in a 1967 case series, with several subsequent updates to the definition of the syndrome. Basic science advances and clinical trials have provided insight into the mechanisms of lung injury in ARDS and led to reduced mortality through comprehensive critical care interventions. This review summarizes the current understanding of the epidemiology, pathophysiology, and management of ARDS. Key highlights include a recommended new global definition of ARDS and updated guidelines for managing ARDS on a backbone of established interventions such as low tidal volume ventilation, prone positioning, and a conservative fluid strategy. Future priorities for investigation of ARDS are also highlighted.



Conceptual model: ARDS is an acute diffuse, inflammatory lung injury precipitated by a predisposing risk factor such as pneumonia, non-pulmonary infection, trauma, transfusion, burn, aspiration, or shock. The resulting injury leads to increased pulmonary vascular and epithelial permeability, lung edema, and gravity dependent atelectasis, all of which contribute to loss of aerated lung tissue. The clinical hallmarks are arterial hypoxemia and diffuse radiographic opacities associated with increased shunting, increased alveolar dead space, and decreased lung compliance. The clinical presentation is influenced by medical management (position, sedation, paralysis, and fluid balance). Histological findings vary and may include intra-alveolar edema, inflammation, hyaline membrane formation, and alveolar hemorrhage.

Criteria that apply to all ARDS categories

Risk factors and origin of edema

Precipitated by an acute predisposing risk factor such as pneumonia, non-pulmonary infection, trauma, transfusion, aspiration, or shock. Pulmonary edema is not exclusively or primarily attributable to cardiogenic pulmonary edema/fluid overload, and hypoxemia/gas exchange abnormalities are not primarily attributable to atelectasis. However, ARDS can be diagnosed in the presence of these conditions if a predisposing risk factor for ARDS is also present.

Timing

Acute onset or worsening of hypoxemic respiratory failure within 1 week of the estimated onset of the predisposing risk factor or new or worsening respiratory symptoms.

Chest imaging

Bilateral opacities on chest radiograph, computed tomography, or ultrasonography* not fully explained by effusions, atelectasis, or nodules/masses.

end expiratory pressure; SpO_2=pulse oximetric oxygen saturation. *Ultrasonography operator should be well trained in use of ultrasonography for identifying pulmonary infiltrates. †Blood gas and oximetry measurements should be made when patient is comfortably at rest and ≥30 min

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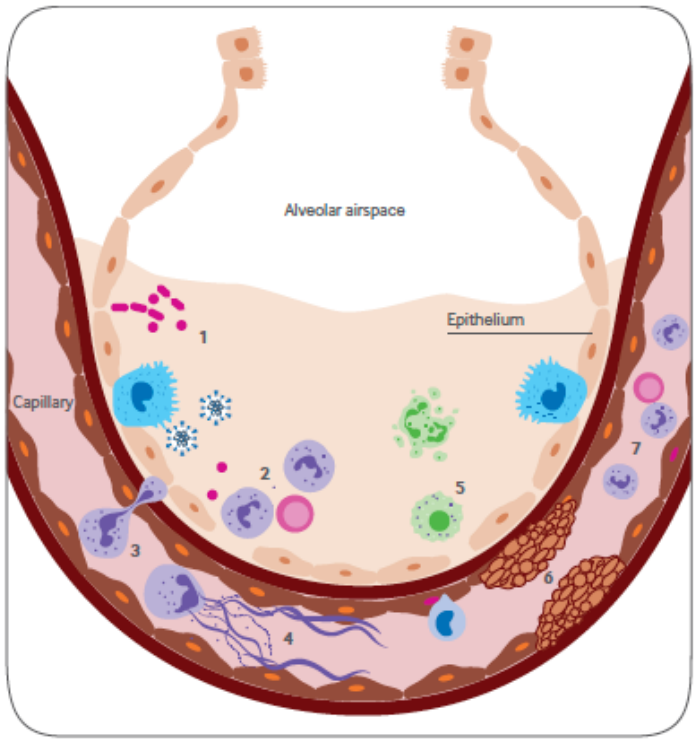

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Criteria that apply to all ARDS categories

Criteria that apply to specific ARDS categories

	Non-intubated ARDS	Intubated ARDS	Modified definition for resource variable settings¶
Oxygenation†‡	$PaO_2/FiO_2 \leq 300$ mm Hg or $SpO_2/FiO_2 \leq 315$ mm Hg (if $SpO_2 \leq 97\%$) on HFNO with a flow of ≥30 L/min or NIV/CPAP with ≥5 cm H_2O expiratory pressure	**Mild§:** $200 < PaO_2/FiO_2 \leq 300$ or $235 \leq SpO_2/FiO_2 \leq 315$ (if $SpO_2 \leq 97\%$) **Moderate:** $100 < PaO_2/FiO_2 \leq 200$ or $148 < SpO_2/FiO_2 \leq 235$ (if $SpO_2 \leq 97\%$) **Severe:** $PaO_2/FiO_2 \leq 100$ or $SpO_2/FiO_2 \leq 148$ (if $SpO_2 \leq 97\%$)	$SpO_2/FiO_2 \leq 315$ (if $SpO_2 \leq 97\%$).** End expiratory pressure or a minimum flow rate of oxygen is not required for diagnosis in resource variable settings

Differences from Berlin definition

- Conceptual model emphasizes the importance of management on the progression of ARDS and histological variability
- New category of "non-intubated ARDS" includes patients supported with HFNO
- SpO_2/FiO_2 may be used to classify hypoxemia severity when $SpO_2 \leq 97\%$
- Lung ultrasonography may be used to diagnose bilateral non-cardiogenic pulmonary edema
- A definition for resource variable settings that does not require a minimum level of respiratory support is formally adopted

course. ¶Modified oxygenation criteria can be applied in settings where arterial blood gas or HFNO, NIV, and mechanical ventilation are not routinely available. **Estimated FiO_2=ambient FiO_2 (eg, 0.21)+0.03×O_2 flow rate (L/min). Adapted with permission from Matthay et al[8]

ARDS epidemiology

1. Before 2016 (AECC)

- ✓ Population based studies since the publication of the AECC definition have varied widely in their estimates of the incidence of ARDS, ranging from 3.65 to 78.9 per 100 000 person years.
- ✓ Hospital based studies similarly vary, with estimated incidence among admissions ranging from as low as 1.3% to as high as 19%.

2. LUNG-SAFE (Berlin)

Incidence

- ✓ 10.4% among patients in ICU
- ✓ 23.4% among mechanically ventilated patients.

Mortality

- ✓ 40% overall;
- ✓ 34.9%, 40.3%, 46.1% mild, moderate, severe

3. COVID-19

Incidence

- ✓10-fold increase in the incidence of ARDS with covid-19 in the US from March 2020 through February 2022
- ✓The incidence of ARDS among patients with covid-19 in ICU was higher than that of the general ICU population, ranging from approximately 50% to 80%.

Mortality

- ✓39% a global pooled;
- ✓Similar to that of non-covid ARDS

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Table 1 | Landmark trials informing critical care management of patients with acute respiratory distress syndrome (ARDS)

Trial	Publication year	Intervention	Principal findings	Implications for management
Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (ARMA)[6]	2000	Tidal volume of 12 mL/kg PBW and plateau pressure of ≤50 cm H_2O *v* 6 mL/kg PBW and plateau pressure of ≤30 cm H_2O	8.8% lower mortality before discharge in lower tidal volume group than in higher tidal volume group	LTV ventilation should be applied for all patients with ARDS
Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome (ALVEOLI)[189]	2004	Higher PEEP *v* lower PEEP titrated on basis of Fi_02	No difference in primary outcome of proportion discharged alive and breathing without assistance or any secondary outcome	Patients can be managed with use of higher or lower PEEP strategy
Comparison of Two Fluid Management Strategies in Acute Lung Injury (FACTT)[190]	2006	Factorial assignment to central venous or pulmonary artery catheter and conservative or liberal fluid strategy	No difference in primary outcome of 60 day mortality, but more ventilator-free days and ICU-free days to day 28	Patients likely benefit from even-to-negative fluid balance after initial resuscitation
Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome (ACURASYS)[191]	2010	Cisatracurium besylate *v* placebo within 48 h of onset of severe (PaO_2/FiO_2 <150 mm Hg) ARDS	Higher adjusted 90 day survival (HR 0.68, 95% CI 0.48 to 0.98) in intervention arm	Neuromuscular blockade was recommended before publication of ROSE trial (below)
Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA)[192]	2013	Prone positioning for ≥16 h/day in moderate to severe (PaO_2/FiO_2 <150 mm Hg) ARDS until improvement in oxygenation *v* remaining supine	16.8% lower 28 day mortality (primary outcome) and 17.4% lower 90 day mortality (secondary outcome) in intervention arm	Prone positioning is recommended for ARDS with PaO_2/FiO_2 <150
High-Flow Nasal Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure (FLORALI)[193]	2015	HFNO *v* standard oxygen therapy *v* NIPPV for non-hypercapnic patients with PaO_2/FiO_2 ≤300 mm Hg; 79% had bilateral infiltrates	Lower mortality at 90 days in HFNO group compared with both NIPPV and standard oxygen. Lower rate of intubation in HFNO group compared with either NIPPV or standard oxygen when PaO_2/FiO_2 ≤200 mm Hg	HFNO is a safe way to manage patients with hypoxemic respiratory failure/non-intubated ARDS

(Continued)

Table 1 | (Continued)

Trial	Publication year	Intervention	Principal findings	Implications for management
Effect of Noninvasive Ventilation versus Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure (IVNICTUS)[194]	2015	NIPPV *v* standard oxygen therapy for non-hypercapnic, immunocompromised patients with respiratory failure (PaO_2 <60 mm Hg on room air, or tachypnea >30/min, or labored breathing or respiratory distress or dyspnea at rest)	No statistical difference in primary endpoint of 28 day mortality or secondary outcomes, including intubation rate	NIV is not different from standard oxygen therapy for immunocompromised patients with hypoxemic respiratory failure with respect to clinical outcomes
Effect of High-Flow Nasal Oxygen versus Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure (HIGH)[195]	2018	HFNO *v* standard oxygen therapy for non-hypercapnic, immunocompromised patients with respiratory failure (PaO_2 <60 mm Hg or SpO_2 <90% on room air, or tachypnea >30/min or labored breathing or respiratory distress, and need for oxygen ≥6 L/min)	No statistical difference in primary endpoint of 28 day mortality or any secondary outcomes	HFNO is not different from standard oxygen therapy for immunocompromised patients with hypoxemic respiratory failure with respect to clinical outcomes
Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA)[196]	2018	ECMO *v* conventional treatment for very severe ARDS (PaO_2/FiO_2 <60 mm Hg for 3 h or <80 mm Hg for 6 h or arterial blood pH <7.25 with $PaCO_2$ ≥60 for 6 h). Crossover permitted for rescue therapy	No statistical difference in primary endpoint of 60 day mortality (35% in ECMO group *v* 46% in control group; P=0.09). High rate of crossover (28%) in conventional therapy group	ECMO remains an important option for rescue therapy in refractory cases of ARDS
Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome (ROSE)[190]	2019	Cisatracurium infusion with deep sedation for 48 h *v* usual care with light sedation targets. High PEEP strategy used for all patients	No between group differences for primary endpoint of 90 day hospital mortality or any secondary outcome. 17% crossover rate and low use of prone positioning (15.8%). Higher rate of serious cardiovascular events in NMB group	NMB recommendations differ, but certainty of evidence is low. Other routine supportive measures, including prone positioning, should be prioritized. NMB might provide benefit in early severe ARDS

(Continued)

Table 1 | (Continued)

Trial	Publication year	Intervention	Principal findings	Implications for management
Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome ($LOCO_2$)[197]	2020	PaO_2 target of 90-100 mm Hg *v* 55-70 mm Hg	Trial stopped early by DSMB because of possibility of harm in conservative oxygen group. No difference in primary outcome of 28 day mortality but significantly higher 90 day mortality in conservative group (44.4% *v* 30.4%) and higher rate of mesenteric ischemia in conservative group (5 *v* 0 events)	A conservative arterial PaO_2 target of 55-70 mm Hg is not beneficial and may be harmful in ARDS
Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal versus Standard Care Ventilation on 90-day Mortality in Patients with Acute Hypoxemic Respiratory Failure (REST)[198]	2021	Target tidal volume of 3 ml/kg PBW facilitated by $ECCO_2R$ *v* standard LTV ventilation in patients with $PaO_2/FiO_2 \leq 150$ mm Hg not caused by cardiogenic pulmonary edema. Approximately 60% had ARDS at enrollment	Trial stopped early by DSMB for futility and lack of feasibility to continue trial. Increased rate of severe adverse events including intracranial hemorrhage in intervention group, though this was not cited as reason for stopping trial. Results similar in ARDS subgroup	There is no benefit to and possible harm from extra-LTV ventilation facilitated by $ECCO_2R$ compared with standard LTV ventilation
Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure (HOT-ICU)[199]	2021	Target PaO_2 of 60 mm Hg *v* 90 mm Hg among hypoxemic patients receiving ≥10 L/min oxygen in open system or FiO_2 of 0.50 in closed system	No difference in primary outcome of 90 day mortality or in secondary outcomes. No difference in adverse events including mesenteric ischemia. Median achieved arterial oxygenation in lower target group was 70 mm Hg *v* 93.3 mm Hg in higher target group	A second trial confirming no benefit of a lower oxygen target compared with higher
High-flow nasal oxygen alone or alternating with non-invasive ventilation in critically ill immunocompromised patients with acute respiratory failure (FLORALI-IM)[200]	2022	HFNO alone *v* HFNO alternating with NIV for non-hypercapnic, immunocompromised patients with respiratory failure (respiratory rate of ≥25 breaths/min and PaO_2/FiO_2 ≤300 mm Hg)	No difference in primary outcome of 28 day mortality or any secondary outcomes except for comfort (less discomfort in HFNO group)	HFNO among immunocompromised patients with hypoxemic respiratory failure does not differ from alternating HFNO and NIV in terms of clinical outcomes and can be favored for patient comfort

(Continued)

Table 2 | Select trials of pharmacologic interventions for acute respiratory distress syndrome (ARDS) and severe pneumonia

Trial	Publication year	Intervention	Principal findings	Implications for management and further research
Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome (SAILS)[235]	2014	40 mg loading dose followed by 20 mg daily rosuvastatin for up to 28 days *v* placebo in patients with Berlin defined ARDS	No difference in primary outcome of 60 day mortality. Fewer hepatic/renal failure-free days in rosuvastatin group	Rosuvastatin does not provide benefit in sepsis associated ARDS and might contribute to liver and kidney injury
Simvastatin in the Acute Respiratory Distress Syndrome (HARP-2)[236]	2014	80 mg simvastatin or placebo for up to 28 days in patients with Berlin defined ARDS	No difference in primary outcome of ventilator-free days. More treatment related adverse events in simvastatin group but similar number of serious adverse events	Simvastatin does not provide benefit in all cause ARDS
Randomized Clinical Trial of a Combination of an Inhaled Corticosteroid and Beta Agonist in Patients at Risk of Developing the Acute Respiratory Distress Syndrome (LIPS-B)[237]	2015	Nebulized budesonide/formoterol *v* placebo among hypoxemic patients in the emergency department with at least one risk factor for ARDS	Greater improvement in SaO_2/FiO_2 in intervention arm. No progression to ARDS in intervention group	Inhaled ICS/LABA warrants further investigation for prevention of ARDS
Dexamethasone Treatment for the Acute Respiratory Distress Syndrome (DEXA-ARDS)[238]	2020	20 mg dexamethasone daily on days 1-5 followed by 10 mg dexamethasone daily on days 6-10 in patients with established (after 24 h) moderate-to-severe ARDS compared with standard care	4.8 (95% CI 2.57 to 7.03) more ventilator-free days (primary outcome) in intervention group. Lower 60 day mortality in intervention group and no difference in adverse events	Early treatment with dexamethasone might benefit patients with established moderate-to-severe ARDS
Dexamethasone in Hospitalized Patients with COVID-19 (RECOVERY Dexamethasone)[239]	2021	6 mg dexamethasone daily for up to 10 days *v* usual care alone in patients admitted to hospital with covid-19	Lower 28 day mortality (primary outcome) in patients with any oxygen requirement, including mechanical ventilation (RR 0.64, 95% CI 0.51 to 0.81). No benefit in patients not requiring oxygen	Dexamethasone is beneficial and should be administered to patients with covid-19 ARDS
Hydrocortisone in Severe Community Acquired Pneumonia (CAPECOD)[240]	2023	Continuous infusion of 200 mg hydrocortisone/day for 4 days for followed by taper for total course of 8-14 days *v* placebo in patients with severe CAP. Patients with septic shock were excluded	Terminated early because of feasibility during covid-19 pandemic and evidence of benefit after second interim analysis. 5.4% lower 90 day mortality (primary outcome) and lower rates of endotracheal intubation and vasopressor initiation in hydrocortisone group	Although not specific to ARDS, some of the patients in CAPECOD met criteria for ARDS. Consider steroids in patients with non-covid ARDS due to severe CAP
Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery (ASTER)[150]	2024	After closure of vitamin C arm, 1:1 randomization of patients with sepsis and hypotension or respiratory failure to 1 g paracetamol or placebo every 6 h for up to 5 days	Lower rate of ARDS development in paracetamol arm. Ascorbate arm closed because of evidence of harm in another large RCT of vitamin C in sepsis	Paracetamol may prevent development of ARDS in critically ill patients with sepsis. A larger trial is needed
Arrest Respiratory Failure from Pneumonia (ARREST PNEUMONIA)	Recruiting	Inhaled budesonide and formoterol *v* placebo every 12 h for 10 doses	Study recruiting	Study recruiting

Current vs Future

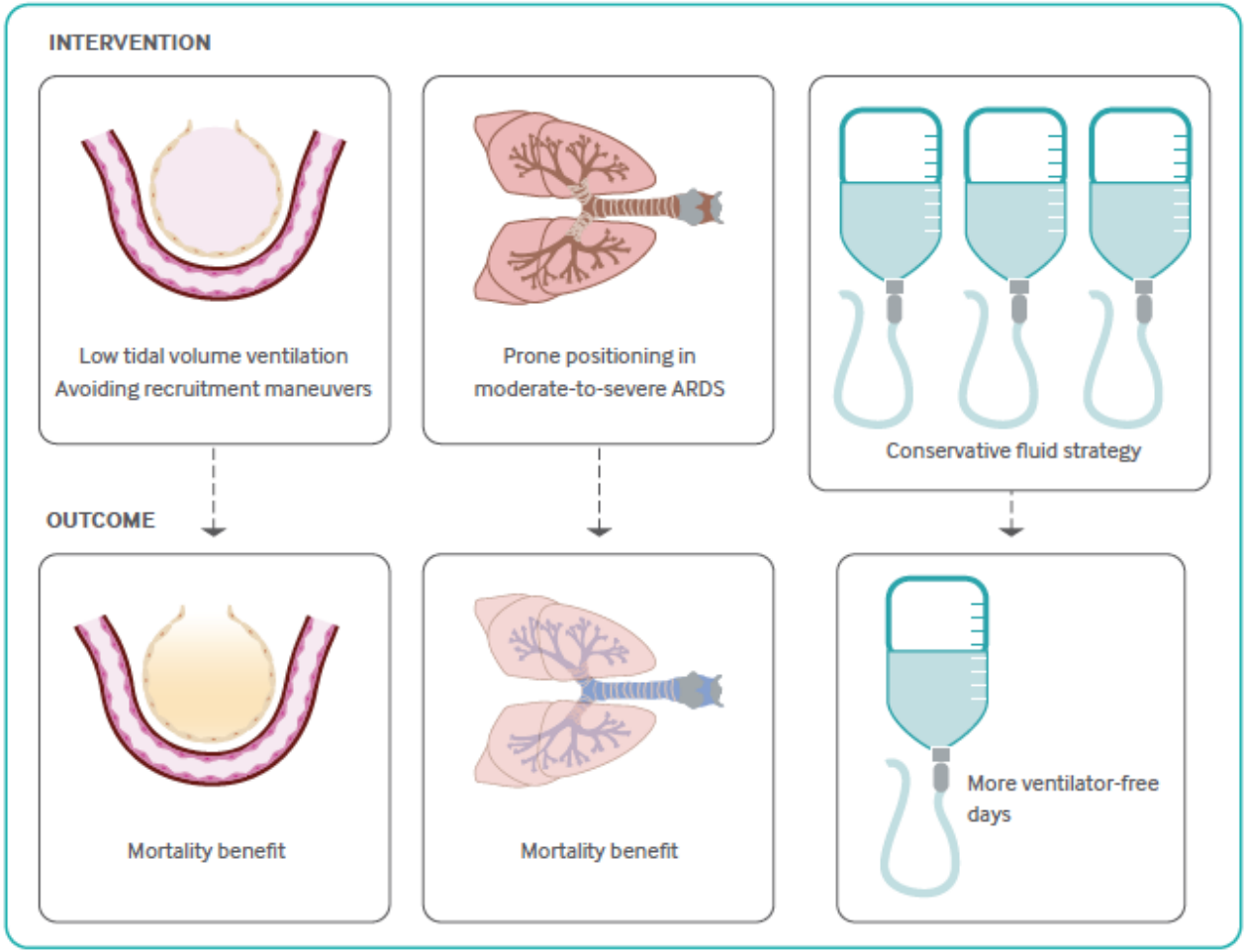

Fig 3 | Interventions to improve outcomes in acute respiratory distress syndrome (ARDS). Interventions that have

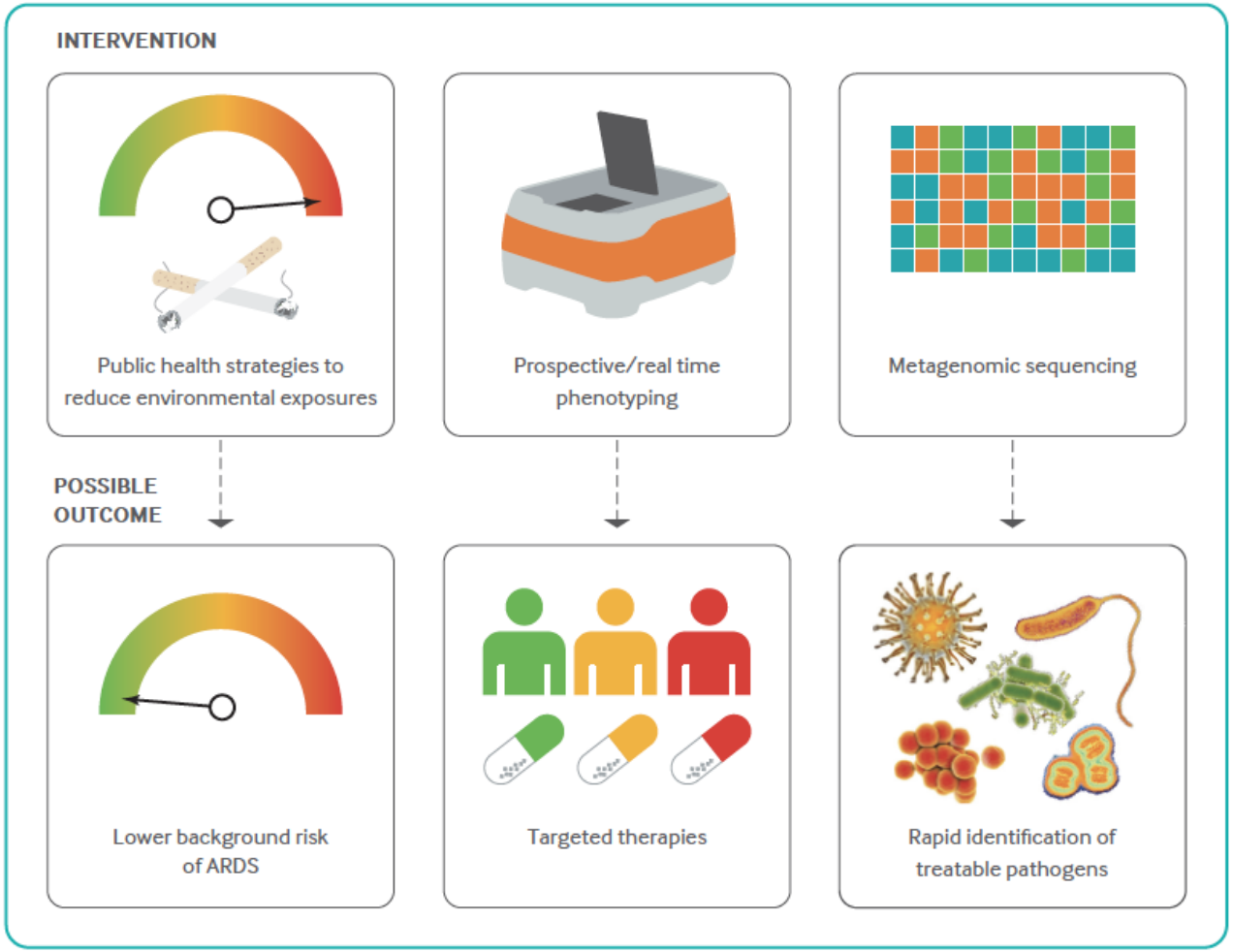

Fig 4 | Investigational interventions to improve outcomes of acute respiratory distress syndrome (ARDS)

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2023 ARDS CPG: ESICM

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

Table 3 Comparison between 2017 and 2023 ARDS guidelines

	2017	2023	CHANGE IN RECOMMENDATION	COMMENTS
Definition			★	No comparison available as the **2017** guidelines did not include a Definition domain.
Phenotypes			★	No comparison available as the **2017** guidelines did not include an ARDS Phenotype domain.
High flow nasal oxygen			★	No comparison available as the **2017** guidelines did not include recommendations on high flow nasal oxygen.
Non-invasive ventilation			★	No comparison available as the **2017** guideline did not include recommendations on non-invasive ventilation.
Tidal volume			⊘	In agreement with the use of low tidal volume strategies. **2023** guidelines extend this recommendation to patients with COVID-19.
Positive end-expiratory pressure			◉	**2017:** suggest that adult patients with moderate or severe ARDS receive higher rather than lower levels of PEEP. **2023:** analysis of data does not allow to make a recommendation for or against higher PEEP strategy.
Recruitment maneuvers			◉	**2017:** suggest that adult patients with ARDS receive RMs. **2023:** recommend against RMs due to increased mortality and risks.
Oscillatory ventilation				**2017:** recommend that HFOV not be used routinely in patients with moderate or severe ARDS. **2023:** not examined given the absence of studies since 2017 and the lack of use of HFVO in adults.
Prone position			⊘	Agreement with the use of prone position in ARDS. Additions in **2023** are the use of awake proning and the use in COVID-19.
Neuromuscular blockade			★	No comparison available as the **2017** guidelines did not include recommendations on neuromuscular blockade.
Extracorporeal membrane oxygenation			◉	**2017:** additional evidence is necessary to make a definitive recommendation. **2023:** recommend ECMO in patients with severe ARDS.
Extracorporeal CO_2 removal			★	No comparison available as the **2017** guidelines did not include recommendations on extracorporeal CO_2 removal. **2023** guidelines recommend against $ECCO_2R$ in ARDS.

AVAILABLE · NOT AVAILABLE · NEW RECOMMENDATION /DOMAIN SINCE 2017 · CHANGE IN RECOMMENDATION · NO CHANGE · NOT CONSIDERED

LOW TIDAL VOLUME VENTILATION

Q1 **In adult patients with ARDS and COVID-19-related ARDS, does low tidal volume ventilation alone compared with more traditional approaches to ventilation decrease mortality?**

1 We **recommend** the use of low tidal volume ventilation strategies (i.e., 4-8 ml/kg PBW), compared to larger tidal volumes (traditionally used to normalize blood gases), to reduce mortality in patients with ARDS not due to COVID-19. — HIGH LEVEL OF EVIDENCE

2 This recommendation applies also to ARDS from COVID-19. — MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE: NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION · STRONG RECOMMENDATION · WEAK RECOMMENDATION

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CONFERENCE REPORTS AND EXPERT PANEL

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

Check for updates

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POSITIVE END-EXPIRATORY PRESSURE AND RECRUITMENT MANEUVERS

Q1 **In patients with ARDS undergoing invasive mechanical ventilation, does routine positive end-expiratory pressure (PEEP) titration using a higher PEEP/FiO_2 strategy compared to a lower PEEP/FiO_2 strategy reduce mortality?**

1 We are **unable to make a recommendation** for or against routine PEEP titration with a higher PEEP/FiO_2 strategy versus a lower PEEP/FiO_2 strategy to reduce mortality in patients with ARDS. — ? HIGH LEVEL OF EVIDENCE

2 This statement applies also to ARDS from COVID-19. — ? MODERATE LEVEL OF EVIDENCE

Q2 **In patients with ARDS undergoing invasive mechanical ventilation, does routine PEEP titration based principally on respiratory mechanics compared to PEEP titration based principally on a standardized PEEP/FiO_2 table reduce mortality?**

1 We are **unable to make a recommendation** for or against PEEP titration guided principally by respiratory mechanics, compared to PEEP titration based principally on PEEP/FiO_2 strategy, to reduce mortality in patients with ARDS. — ? HIGH LEVEL OF EVIDENCE

2 This statement applies also to ARDS from COVID-19. — ? MODERATE LEVEL OF EVIDENCE

Q3 **In patients with ARDS undergoing invasive mechanical ventilation, does use of prolonged high-pressure recruitment maneuvers (RMs), compared to not using prolonged high-pressure RMs, reduce mortality?**

1 We **recommend against** use of prolonged high-pressure RMs (defined as airway pressure maintained ≥ 35 cmH_2O for at least one minute) to reduce mortality of patients with ARDS. — !! MODERATE LEVEL OF EVIDENCE

2 This recommendation applies also to ARDS from COVID-19. — !! LOW LEVEL OF EVIDENCE

Q4 **In patients with ARDS undergoing invasive mechanical ventilation, does *routine* use of brief high-pressure RMs, compared to no use of brief high-pressure RMs, reduce mortality?**

1 We **suggest against** *routine* use of brief high-pressure RMs (defined as airway pressure maintained ≥ 35 cmH_2O for less than one minute) to reduce mortality in patients with ARDS. — ! HIGH LEVEL OF EVIDENCE

2 This suggestion applies also to ARDS from COVID-19. — ! MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE: NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

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2023 ARDS CPG: ESICM

CONFERENCE REPORTS AND EXPERT PANEL

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

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Recruitment maneuvers			◉	**2017:** suggest that adult patients with ARDS receive RMs. **2023:** recommend against RMs due to increased mortality and risks.
Oscillatory ventilation				**2017:** recommend that HFOV not be used routinely in patients with moderate or severe ARDS. **2023:** not examined given the absence of studies since 2017 and the lack of use of HFVO in adults.
Prone position			⊘	Agreement with the use of prone position in ARDS. Additions in **2023** are the use of awake proning and the use in COVID-19.
Neuromuscular blockade			★	No comparison available as the **2017** guidelines did not include recommendations on neuromuscular blockade.
Extracorporeal membrane oxygenation			◉	**2017:** additional evidence is necessary to make a definitive recommendation. **2023:** recommend ECMO in patients with severe ARDS.
Extracorporeal CO_2 removal			★	No comparison available as the **2017** guidelines did not include recommendations on extracorporeal CO_2 removal. **2023** guidelines recommend against $ECCO_2R$ in ARDS.

AVAILABLE · NOT AVAILABLE · NEW RECOMMENDATION /DOMAIN SINCE 2017 · CHANGE IN RECOMMENDATION · NO CHANGE · NOT CONSIDERED

PRONE POSITIONING

Q1 In intubated patients with ARDS, does prone position compared to supine position reduce mortality?

1 We **recommend** using prone position as compared to supine position for patients with moderate-severe ARDS (defined as PaO_2/FiO_2<150 mmHg and PEEP≥5 cmH_2O, despite optimization of ventilation settings) to reduce mortality. — HIGH LEVEL OF EVIDENCE

2 This recommendation applies also to ARDS from COVID-19. — MODERATE LEVEL OF EVIDENCE

Q2 In patients with moderate-severe ARDS, when should prone positioning be started to reduce mortality?

1 We **recommend** starting prone position in patients with ARDS receiving invasive mechanical ventilation early after intubation, after a period of stabilization during which low tidal volume is applied and PEEP adjusted and at the end of which the PaO_2/FiO_2 remains <150 mmHg; and proning should be applied for prolonged sessions (16 consecutive hours or more) to reduce mortality. — HIGH LEVEL OF EVIDENCE

2 This recommendation applies also to ARDS from COVID-19. — MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE: NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION · STRONG RECOMMENDATION · WEAK RECOMMENDATION

2023 ARDS CPG: ESICM

SNUBH IMRCCM

CONFERENCE REPORTS AND EXPERT PANEL

ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

Check for updates

Table 3 Comparison between 2017 and 2023 ARDS guidelines

	2017	2023	CHANGE IN RECOMMENDATION	COMMENTS
Definition			★	No comparison available as the **2017** guidelines did not include a Definition domain.
Phenotypes			★	No comparison available as the **2017** guidelines did not include an ARDS Phenotype domain.
High flow nasal oxygen			★	No comparison available as the **2017** guidelines did not include recommendations on high flow nasal oxygen.
Non-invasive ventilation			★	No comparison available as the **2017** guideline did not include recommendations on non-invasive ventilation.
Tidal volume			⊘	In agreement with the use of low tidal volume strategies. **2023** guidelines extend this recommendation to patients with COVID-19.
Positive end-expiratory pressure			◉	**2017:** suggest that adult patients with moderate or severe ARDS receive higher rather than lower levels of PEEP. **2023:** analysis of data does not allow to make a recommendation for or against higher PEEP strategy.
Recruitment maneuvers			◉	**2017:** suggest that adult patients with ARDS receive RMs. **2023:** recommend against RMs due to increased mortality and risks.
Oscillatory ventilation				**2017:** recommend that HFOV not be used routinely in patients with moderate or severe ARDS. **2023:** not examined given the absence of studies since 2017 and the lack of use of HFVO in adults.
Prone position			⊘	Agreement with the use of prone position in ARDS. Additions in **2023** are the use of awake proning and the use in COVID-19.
Neuromuscular blockade			★	No comparison available as the **2017** guidelines did not include recommendations on neuromuscular blockade.
Extracorporeal membrane oxygenation			◉	**2017:** additional evidence is necessary to make a definitive recommendation. **2023:** recommend ECMO in patients with severe ARDS.
Extracorporeal CO_2 removal			★	No comparison available as the **2017** guidelines did not include recommendations on extracorporeal CO_2 removal. **2023** guidelines recommend against $ECCO_2R$ in ARDS.

AVAILABLE · NOT AVAILABLE · NEW RECOMMENDATION /DOMAIN SINCE 2017 · CHANGE IN RECOMMENDATION · NO CHANGE · NOT CONSIDERED

NEUROMUSCULAR BLOCKING AGENTS

Q1 **Does the *routine* use of a continuous infusion of neuromuscular blocking agents (NMBA) in patients with moderate to severe ARDS not due to COVID-19 or moderate to severe ARDS due to COVID-19 reduce mortality?**

1 We **recommend against** the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS not due to COVID-19. — MODERATE LEVEL OF EVIDENCE

2 We are **unable to make a recommendation** for or against the *routine* use of continuous infusions of NMBA to reduce mortality in patients with moderate to severe ARDS due to COVID-19. — NO EVIDENCE

EXTRACORPOREAL LIFE SUPPORT

Q1 **In adult patients with severe ARDS or COVID-19 does veno-venous extracorporeal membrane oxygenation (VV-ECMO) compared with conventional ventilation improve outcomes?**

1 We **recommend** that patients with severe ARDS not due to COVID-19 as defined by the EOLIA trial eligibility criteria, should be treated with ECMO in an ECMO centre which meets defined organisational standards, adhering to a management strategy similar to that used in the EOLIA trial. — MODERATE LEVEL OF EVIDENCE

2 This recommendation applies also to severe ARDS from COVID-19. — LOW LEVEL OF EVIDENCE

Q2 **In adult patients with ARDS, does extracorporeal carbon dioxide removal ($ECCO_2R$) compared with conventional ventilation improve outcomes?**

1 We **recommend against** the use of $ECCO_2R$ for the treatment of ARDS not due to COVID-19 to prevent mortality outside of randomized controlled trials. — HIGH LEVEL OF EVIDENCE

2 This recommendation applies also to severe ARDS from COVID-19. — MODERATE LEVEL OF EVIDENCE

LEVELS OF EVIDENCE: NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION · STRONG RECOMMENDATION · WEAK RECOMMENDATION

2023 ARDS CPG: ESICM (not in Korea)

SNUBH IMRCCM

HIGH FLOW NASAL OXYGEN

Q1 **In non-mechanically ventilated patients with acute hypoxemic respiratory failure (AHRF) not due to cardiogenic pulmonary edema or acute exacerbation of chronic obstructive pulmonary disease (COPD), does high flow nasal oxygen (HFNO) compared to conventional oxygen therapy (COT) reduce mortality or intubation?**

1. We **recommend** that non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD receive HFNO as compared to COT to reduce the risk of intubation. — MODERATE LEVEL OF EVIDENCE
2. This recommendation applies also to AHRF from coronavirus 2019 (COVID-19) — LOW LEVEL OF EVIDENCE
3. We are **unable to make a recommendation** for or against the use of HFNO over COT to reduce mortality. — HIGH LEVEL OF EVIDENCE
4. This recommendation applies also to AHRF from COVID-19. — MODERATE LEVEL OF EVIDENCE

Q2 **In non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD, does HFNO compared to non-invasive ventilation (NIV) reduce mortality or intubation?**

1. We are **unable to make a recommendation** for or against the use of HFNO compared to continuous positive airway pressure (CPAP)/NIV to reduce intubation or mortality in the treatment of unselected patients with AHRF not due to cardiogenic pulmonary edema or acute exacerbation of COPD. — MODERATE LEVEL OF EVIDENCE FOR MORTALITY; LOW LEVEL OF EVIDENCE FOR INTUBATION
2. We **suggest** that CPAP/NIV can be considered instead of HFNO to reduce the risk of intubation in AHRF due to COVID-19. — HIGH LEVEL OF EVIDENCE
3. **No recommendation** can be made for whether CPAP/NIV can decrease mortality compared to HFNO in COVID-19. — HIGH LEVEL OF EVIDENCE

LEVELS OF EVIDENCE: NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION · STRONG RECOMMENDATION · WEAK RECOMMENDATION

CONTINUOUS POSITIVE AIRWAY PRESSURE / NON-INVASIVE VENTILATION

Q1 **In non-mechanically ventilated patients with AHRF not due to cardiogenic pulmonary edema, obesity hypoventilation or acute exacerbation of COPD, does CPAP/NIV, as compared to COT reduce mortality or intubation?**

1. We are **unable to make a recommendation** for or against the use of CPAP/NIV compared to COT for the treatment of AHRF (not related to cardiogenic pulmonary edema or acute exacerbation of COPD) to reduce mortality or to prevent intubation. — HIGH LEVEL OF EVIDENCE FOR MORTALITY; MODERATE LEVEL OF EVIDENCE FOR INTUBATION
2. We **suggest** the use of CPAP over COT to reduce the risk of intubation in patients with AHRF due to COVID-19. — LOW LEVEL OF EVIDENCE
3. We are **unable to make a recommendation** for or against the use of CPAP over COT to reduce mortality in AHRF due to COVID-19. — MODERATE LEVEL OF EVIDENCE

Q2 **In patients being treated with CPAP/NIV for AHRF, does the use of a helmet interface as compared to face mask reduce intubation or mortality?**

1. We are **unable to make a recommendation** for or against the use of helmet interface for CPAP/NIV as compared to face mask to prevent intubation or reduce mortality in patients with AHRF. — VERY LOW LEVEL OF EVIDENCE

Q3 **In patients with AHRF, does NIV as compared to CPAP reduce mortality or intubation?**

1. We are **unable to make a recommendation** for or against the use of NIV compared to CPAP for the treatment of AHRF. — NO EVIDENCE

PRONE POSITIONING

Q3 **In non intubated patients with AHRF, does awake prone positioning (APP) as compared to supine positioning reduce intubation or mortality?**

1. We **suggest** awake prone positioning as compared to supine positioning for non-intubated patients with COVID-19-related AHRF to reduce intubation. — LOW LEVEL OF EVIDENCE
2. We are **unable to make a recommendation** for or against APP for non-intubated patients with COVID-19-related AHRF to reduce mortality. — MODERATE LEVEL OF EVIDENCE
3. We are **unable to make a recommendation** for patients with AHRF failure not due to COVID-19. — NO EVIDENCE

LEVELS OF EVIDENCE: NO EVIDENCE / VERY LOW LEVEL / LOW LEVEL / MODERATE LEVEL / HIGH LEVEL

NO RECOMMENDATION · STRONG RECOMMENDATION · WEAK RECOMMENDATION

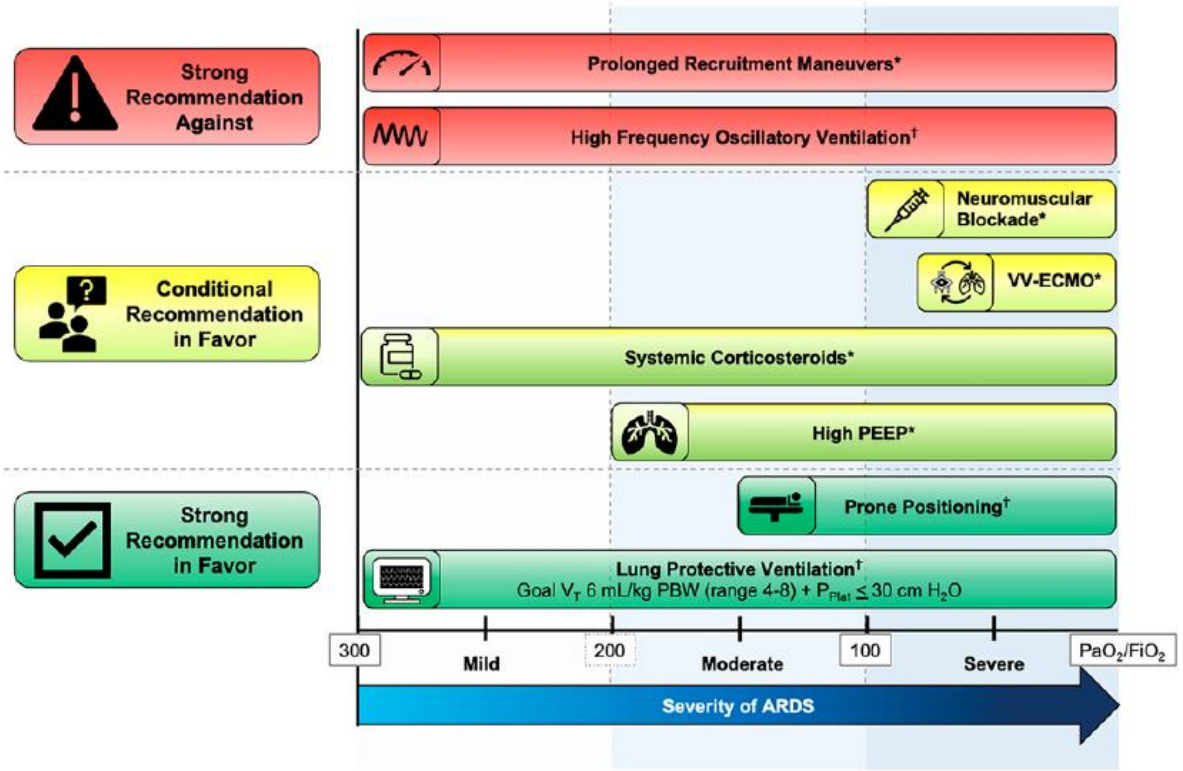
2023 ARDS CPG: ATS

SNUBH IMRCCM

AMERICAN THORACIC SOCIETY DOCUMENTS

An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome

An Official American Thoracic Society Clinical Practice Guideline



Overview

This guideline updates and adds to recommendations for the management of patients with acute respiratory distress syndrome (ARDS) (Figure 1). New recommendations in this guideline include:

- We suggest using corticosteroids for patients with ARDS (conditional recommendation, moderate certainty of evidence).
- We suggest using venovenous extracorporeal membrane oxygenation (VV-ECMO) in selected patients with severe ARDS (conditional recommendation, low certainty of evidence).
- We suggest using neuromuscular blockers in patients with early severe ARDS (conditional recommendation, low certainty of evidence).
- With regard to positive end-expiratory pressure (PEEP):
  - We suggest using higher PEEP without lung recruitment maneuvers (LRMs) as opposed to lower PEEP in patients with moderate to severe ARDS (conditional recommendation, low to moderate certainty).
  - We recommend against using prolonged LRMs in patients with moderate to severe ARDS (strong recommendation, moderate certainty).

Recommendations from the 2017 guideline that remain in place include:

- We recommend using mechanical ventilation strategies that limit tidal volume (4–8 mL/kg predicted body weight) and inspiratory pressures (plateau pressure <30 cm H_2O) in patients with ARDS (strong recommendation, moderate certainty of evidence).
- We recommend prone positioning for >12 hours per day in patients with severe ARDS (strong recommendation, moderate certainty of evidence).
- We recommend against the routine use of high-frequency oscillatory ventilation in patients with moderate or severe ARDS (strong recommendation, high certainty of evidence).

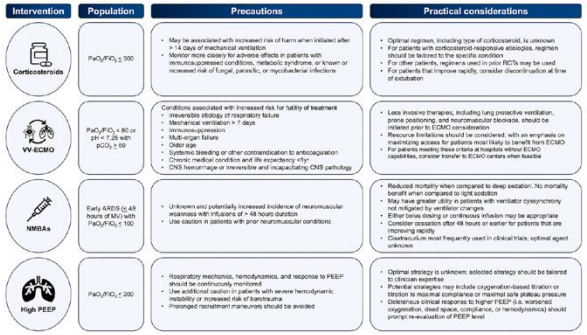


Figure 2. Precautions and practical considerations for the use of corticosteroids, venovenous extracorporeal membrane oxygenation, neuromuscular blocking agents, and positive end-expiratory pressure. ARDS = acute respiratory distress syndrome; CNS = central nervous

Korean ARDS CPG, the 2nd Edition

"compared with ATS/ESICM"

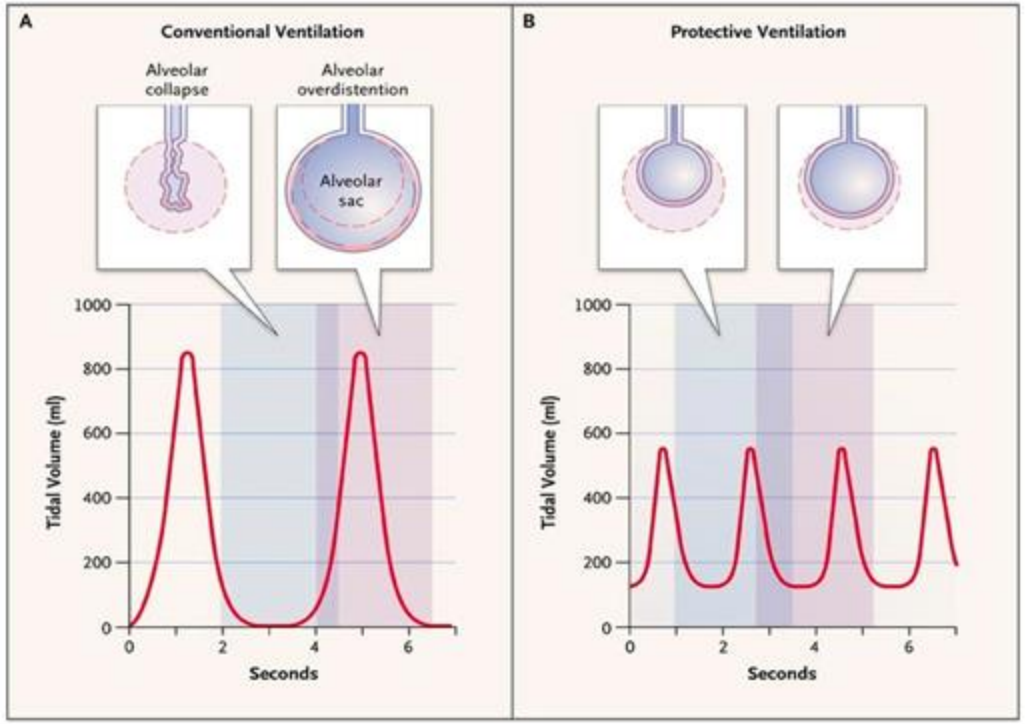
KATRD Study Group of Intensive Care
KSCCM Study Group of Respiratory Failure

비약물적 치료 – 기계환기 (1)

- KQ 1.

  급성호흡곤란증후군 환자에서 저일회호흡량 (6mL/kg 예측체중 미만) 적용을 권고한다.

  (권고등급: 강함, 근거수준: 높음)

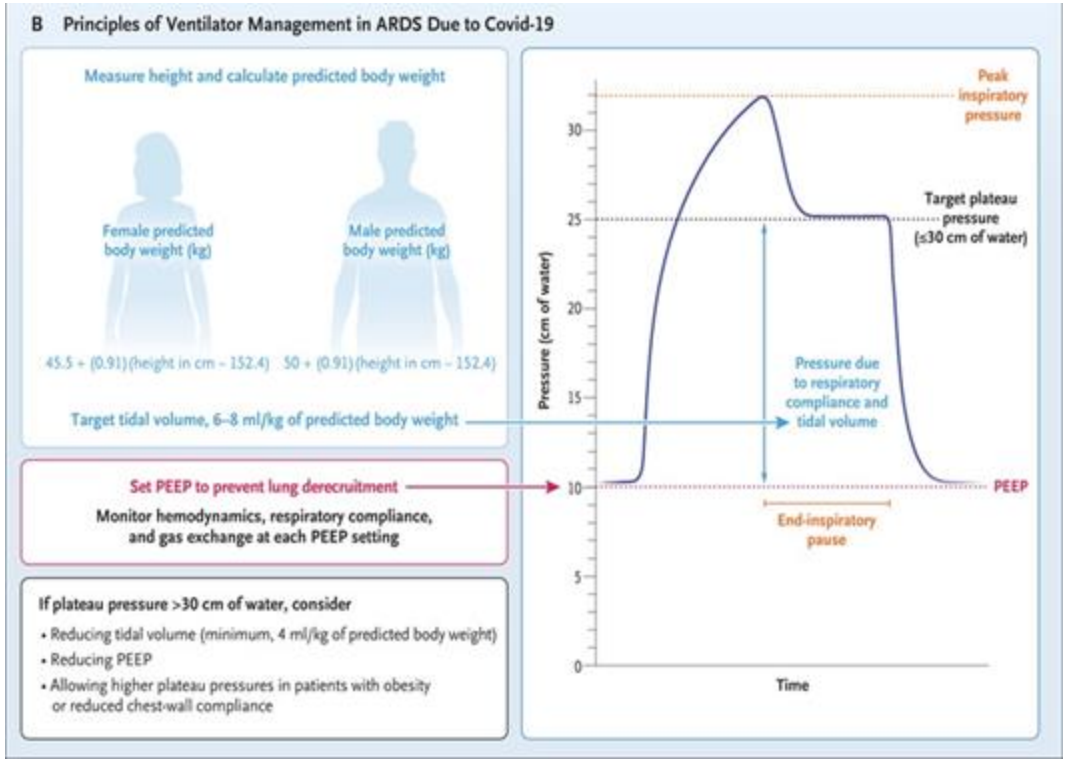


비약물적 치료 – 기계환기 (2)

- KQ 2.

  급성호흡곤란증후군 환자에서 고원부기도압(plateau pressure)은 30 cmH2O 이하를 권고한다.

  (권고등급: 강함, 근거수준: 낮음)

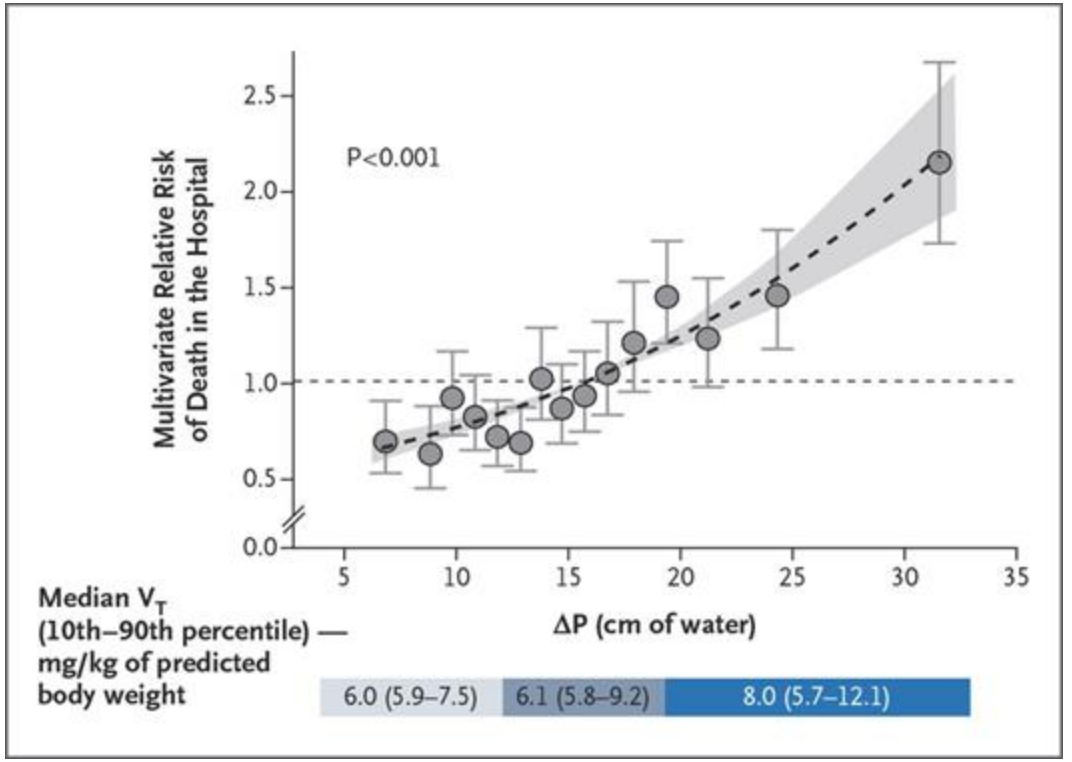


비약물적 치료 – 기계환기 (3)

- KQ 3.

  급성호흡곤란증후군 환자에서 **구동압력(driving pressure) 제한**을 제안한다.

  (권고등급: 조건부, 근거수준: 낮음)



Lung Protective Ventilation

TABLE 24.5	Protocol for Lung Protective Ventilation in ARDS
First Stage	1. Calculate patient's predicted body weight (PBW)†. Males: PBW = 50 + [2.3 x (height in inches – 60)] Females: PBW = 45.5 + [2.3 x (height in inches – 60)] 2. Set initial tidal volume (V_T) at 8 mL/kg PBW. 3. Add positive end-expiratory pressure (PEEP) of 5 cm H_2O. 4. Select the lowest FIO_2 that achieves an SpO_2 of 88–95%. 5. Reduce V_T by 1 mL/kg every 2 hrs until V_T = 6 mL/kg.
Second Stage	1. When V_T = 6 mL/kg, measure plateau pressure (Ppl). 2. If Ppl >30 cm H_2O decrease V_T in 1 mL/kg increments until Ppl <30 cm H_2O or V_T. = 4 mL/kg.
Third Stage	1. Monitor blood gases for respiratory acidosis. 2. If pH = 7.15–7.30, increase respiratory rate (RR) until pH >7.30 or RR = 35 bpm. 3. If pH <7.15, increase RR to 35 bpm. If pH is still <7.15, increase V_T in 1 mL/kg increments until pH >7.15.
Optimal Goals	V_T = 6 mL/kg, Ppl ≤30 cm H_2O, SpO_2 = 88–95%, pH = 7.30–7.45.

Still not included about "Driving Pressure"

Adapted from the protocol developed by the ARDS Network, available at www.ardsnet.org.

†Predicted body weight is the weight associated with normal lung volumes.

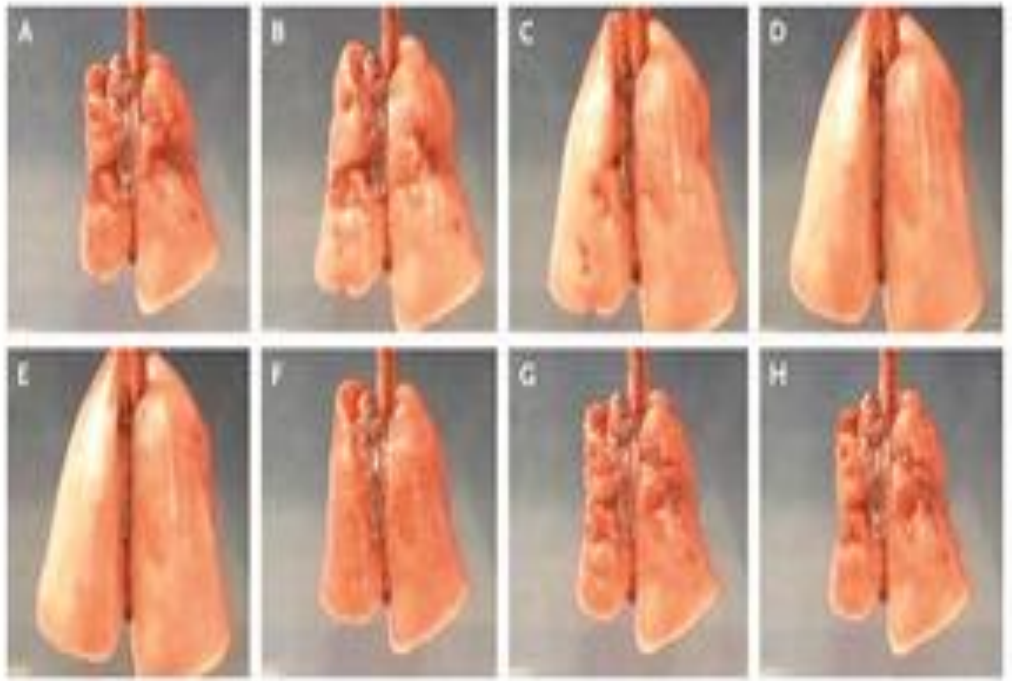
Marino's The ICU Book, 5th Edit

비약물적 치료 – 날숨끝양압 (1)

- KQ 4.

  급성호흡곤란증후군 환자에서 높은 날숨끝양압의 적용은 낮은 날숨끝양압과 비교하여 병원내 사망률을 낮추지 못하므로 **권고를 보류한다.**

  (권고등급: 없음, 근거수준: 중등)



Additional recommendation

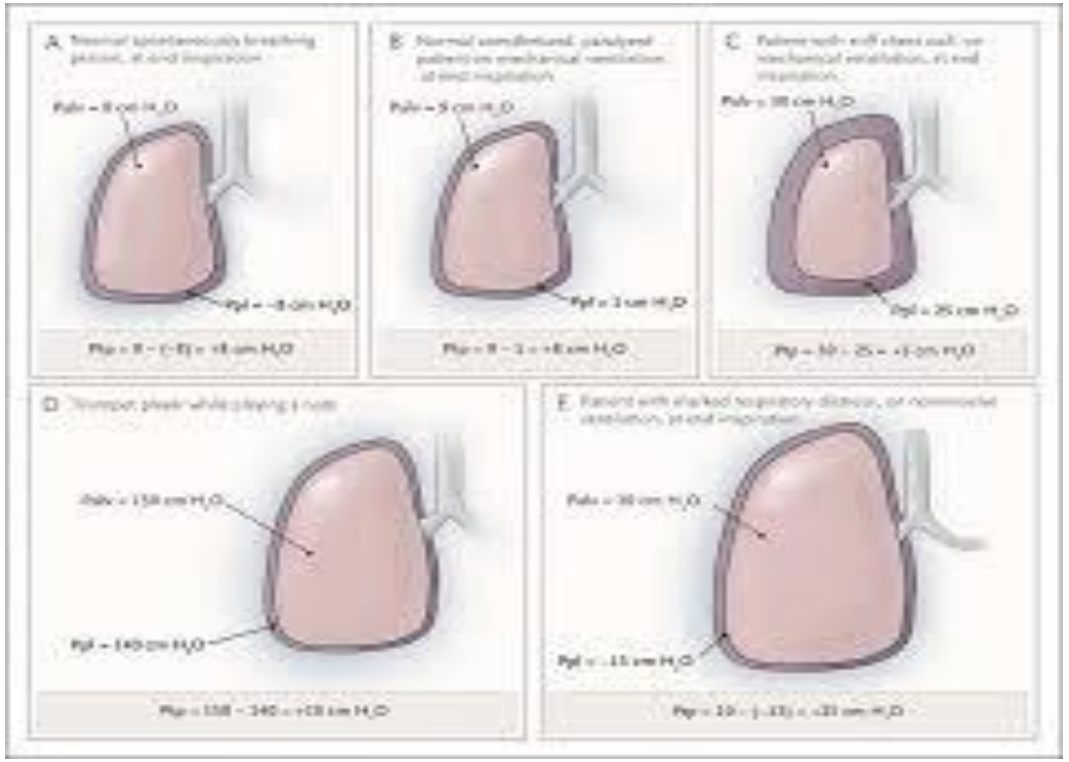
- 높은 날숨끝양압의 적용이 낮은 날숨끝양압군에 비해, 28일동안 기계환기이탈일수(ventilator-free days)의 개선과, 1일, 3일째 산소화비(PaO2/FiO2)가 호전될 수 있어서, 산소화비 (PaO2/FiO2)가 200mmHg 이하인 **중등증 성인 급성호흡곤란증후군 환자에서 적용해 볼 수는 있다.**
(권고등급: 약함, 근거수준: 중등)

비약물적 치료 – 날숨끝양압 (2)

- KQ 5.

  급성호흡곤란증후군 환자에서 식도내압측정 혹은 전기임피던스단층촬영법을 통한 호기말양압조절은 **권고를 보류한다.**

  (권고등급: 없음, 근거수준: 낮음)

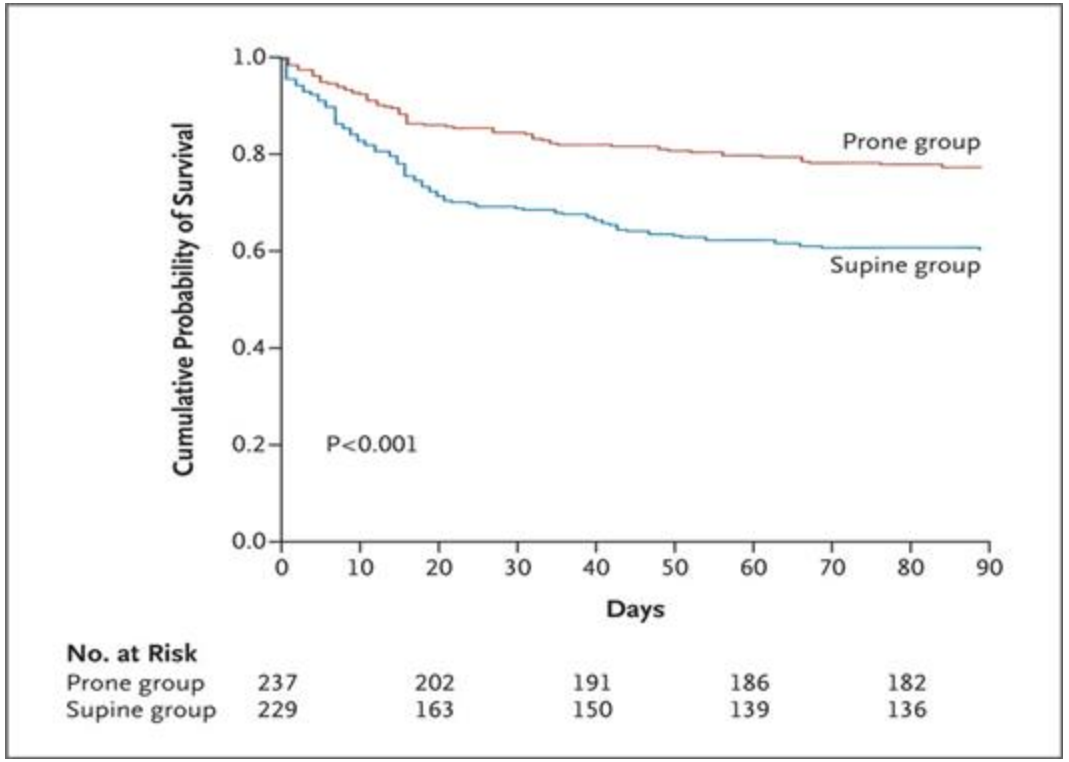


비약물적 치료 – 복와위

- KQ 6.

  중등도 이상의 급성호흡곤란증후군 환자에서 복와위 적용을 권고한다.

  (권고등급: 강함, **근거수준: 중등**)



Additional recommendations

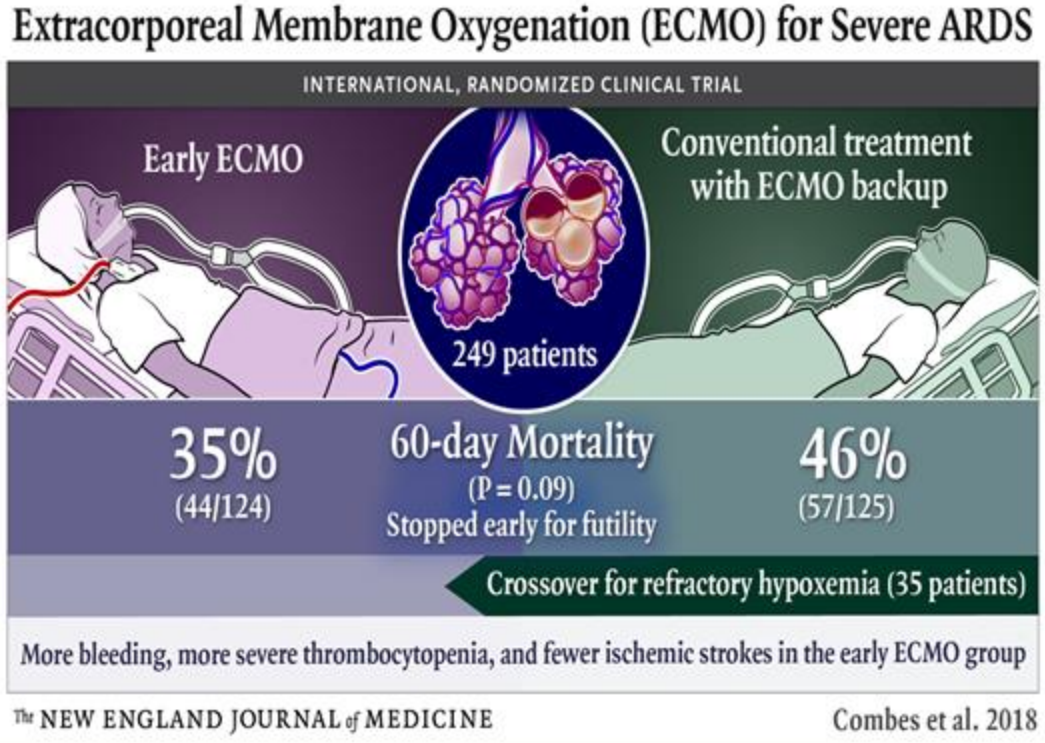
- 기계환기를 시행함에도 불구하고 산소화의 호전이 없는 경우 (P/F ratio <150)
- 최소한 12시간 이상 적용 권장
- 폐 보호 환기를 적용할 것을 권장

비약물적 치료 – 체외막산소요법

- KQ 7.

  중등도 이상의 급성호흡곤란증후군 환자에서 체외막산소요법을 **고려할 수 있다**.

  (권고등급: 조건부, 근거수준: 중등)



Additional recommendations

- 적절한 기계환기 적용*에도 불구하고, 3시간 이상 P/F ration <50mmHg 또는 6시간 이상 PaO_2 <80mmHg
- 고원부압 ≤32 cmH_2O 로 유지하기 위해 6시간 동맥혈 pH <7.25 이면서 $PaCO_2$ ≥60 mmHg 인 경우 (호흡수 ≤35/min)

* FiO_2 ≥80%, VT ≤6ml/kg, PEEP ≥10 cmH_2O

약물적 치료 – 전신 스테로이드

- KQ 8.

  급성호흡곤란증후군 환자에서 전신 스테로이드의 사용을 권고할 수 있다.

  (권고등급: 조건부, 근거수준: 중등)

	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12·3 (9·9)	7·5 (9·0)	4·8 (2·57 to 7·03)	<0·0001
All-cause mortality at day 60	29 (21%)	50 (36%)	−15·3% (−25·9 to −4·9)	0·0047
ICU mortality	26 (19%)	43 (31%)	−12·5% (−22·4 to −2·3)	0·0166
Hospital mortality	33 (24%)	50 (36%)	−12·5% (−22·9 to −1·7)	0·0235
Actual duration of mechanical ventilation in ICU survivors, days	14·2 (13·2)	19·5 (13·2)	−5·3 (−8·4 to −2·2)	0·0009
Actual duration of mechanical ventilation in survivors at day 60, days	14·3 (13·3)	20·2 (14·0)	−5·9 (−9·1 to −2·7)	0·0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5·2% (−5·2 to 15·6)	0·33
New infections in ICU	33 (24%)	35 (25%)	1·6% (−8·5 to 11·7)	0·75
Barotrauma	14 (10%)	10 (7%)	2·8% (−4·0 to 9·8)	0·41

Data are n (%) or mean (SD). ICU=intensive care unit. *Data included the period from randomisation to day 10 (for hyperglycaemia) and from randomisation to ICU discharge (for new infections and barotrauma).

Table 2: **Outcomes, adverse events, and complications**

기타 의견

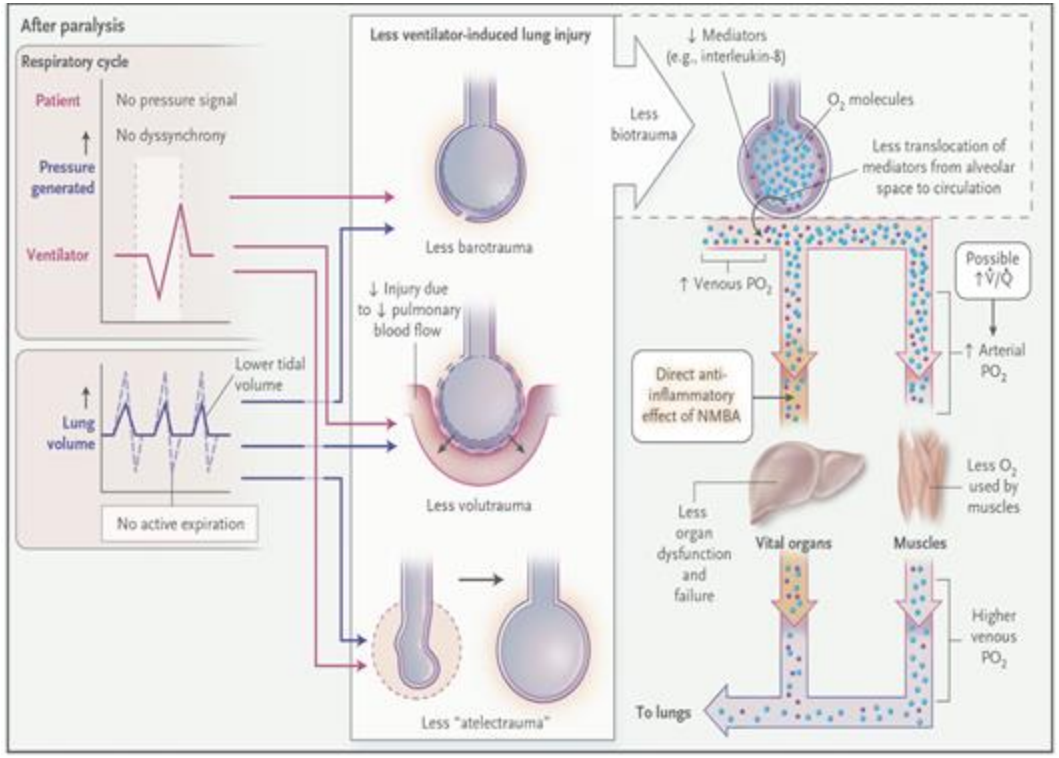
- 감염 원인 별로 구분하는 것은 생략

약물적 치료 - 신경근육차단제

- KQ 9.

  급성호흡곤란증후군 환자에서 기계 환기 시작 후 48시간 동안 신경근육차단제의 사용을 권고할 수 있다.

  (권고등급: 조건부, 근거수준: 중등)



Additional recommendations

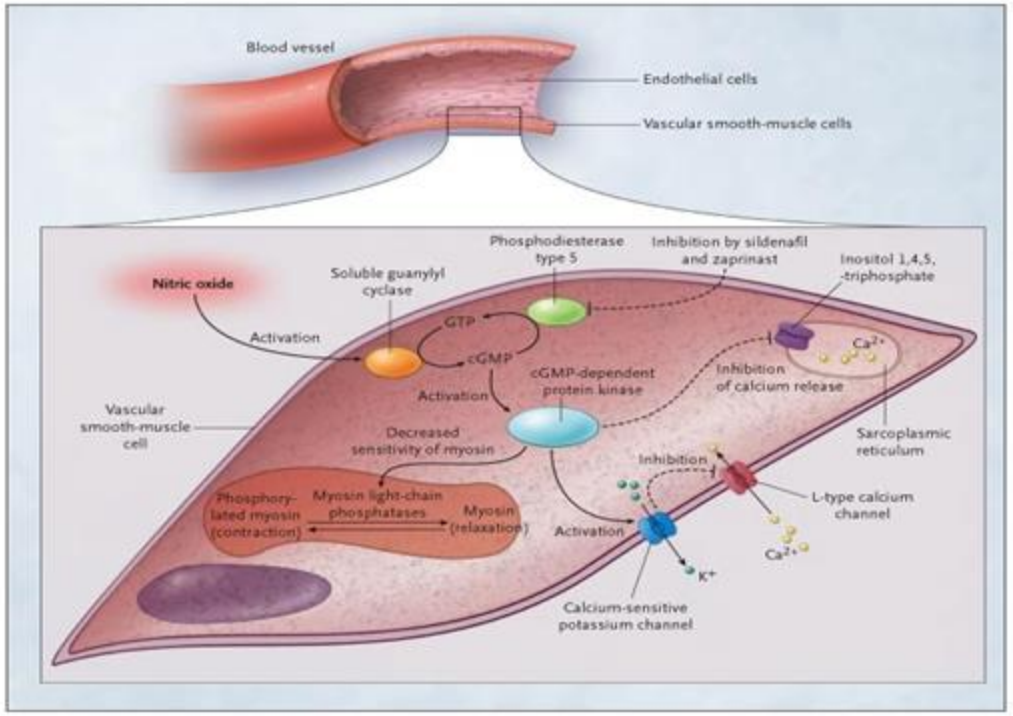
- 급성호흡곤란증후군 환자에서 신경근육차단제의 사용은 인공호흡기 사용 기간 및 사망률을 감소시키지 못함.
- 첫 48시간 동안 저산소혈증의 호전 효과가 있음.
- 압력 손상을 줄일 수 있음.

약물적 치료 – 흡입 일산화질소

- KQ 10.

  급성호흡곤란증후군 환자에서 흡입 일산화질소가스는 통상적인 치료법으로 **사용하지 않을 것을 권고**한다.

  (권고등급: 조건부, 근거수준: 중등)



Additional recommendations

- 인공호흡기 사용 기간 및 사망률을 감소시키지 못함.
- 신장 기능 손상의 위험을 증가시킬 수 있음.

2023 ARDS CPG: ATS vs ESICM vs Korea

Aspect	ATS Guideline (2024)	ESICM Guideline (2023)	KATRD-KSCCM Guideline (2025)
Scope	Adult ARDS patients, focus on non-pharmacological respiratory support strategies	Adult ARDS and acute hypoxemic respiratory failure patients, includes definition and phenotypes	Adult ARDS patients, focus on non-pharmacological and pharmacological treatments
ARDS Definition	Maintains existing Berlin definition	Discusses limitations of Berlin definition and suggests future improvements	Maintain existing Berlin definition
Phenotypes	Not mentioned	Detailed discussion of ARDS phenotypes	Not mentioned
HFNO	No recommendation	Strong recommendation over conventional oxygen therapy	No recommendation
NIV	No recommendation	No recommendation compared to HFNO	No recommendation
Tidal Volume	4-8 mL/kg PBW strongly recommended	6 mL/kg PBW strongly recommended	6 mL/kg PBW strongly recommended
PEEP	Conditional recommendation for higher PEEP in moderate-severe ARDS	No recommendation for higher PEEP in moderate-severe ARDS	No recommendation for higher PEEP in moderate-severe ARDS
Prone Positioning	Strongly recommended in severe ARDS	Strongly recommended in moderate-severe ARDS	Strongly recommended in moderate-severe ARDS
Neuromuscular Blockade	Conditional recommendation in early severe ARDS	No recommendation in moderate-severe ARDS	Conditional recommendation in early (<48 hrs) ARDS
ECMO	Conditional recommendation in selected severe ARDS patients	Strongly recommended in selected severe ARDS patients	Conditional recommendation in selected moderate-severe ARDS

Corticosteroids Conditional recommendation No recommendation Conditional recommendation

2023 ARDS CPG: ~~ATS vs ESICM~~ vs Korea

Aspect	ATS Guideline (2024)	ESICM Guideline (2023)
Scope	Adult ARDS patients, focus on non-pharmacological respiratory support strategies	Adult ARDS and acute hypoxemic respiratory failure patients, includes definition and phenotypes
ARDS Definition	Maintains existing Berlin definition	Dis sses limitations of Berlin n and suggests future ovements
Phenotypes	ntioned	Detailed discussion of ARDS phenotypes
HFNO	No	Strong recommendation over conventional oxygen therapy
NIV	No recom	No recommendation compared to HFNO
Tidal Volume	g PBW str mended	6 mL/kg PBW strongly ecommended
PEEP	onditional recommendati for higher PEEP in moderate-severe ARDS	recommendation for EEP in moderate- re ARDS
Prone Positioning	Strongly recommended in severe ARDS	Strongly recommended in moderate-severe ARDS
Neuromuscular Blockade	Conditional recommendation in early severe ARDS	Weak recommendation in moderate-severe ARDS
ECMO	Conditional recommendation in selected severe ARDS patients	Weak recommendation in severe ARDS

KATRD-KSCCM Guideline (2025)
Adult ARDS patients, focus on non-pharmacological and pharmacological treatments
Maintain existing Berlin definition
Driving Pressure : Conditional recommended
Inhaled NO : Against recommended

Corticosteroids in SCCM

ONLINE SPECIAL ARTICLE

2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

Population, Intervention, Control, and Outcomes Questions

Population	Intervention	Comparison	Outcomes
Should corticosteroids be administered to hospitalized patients with sepsis?			
All adult and pediatric patients with sepsis	Corticosteroids	Placebo or no corticosteroids	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
If patients with sepsis are administered corticosteroids, should high dose/short duration or low dose/long duration be used?			
All adult and pediatric patients with sepsis	High dose/short duration	Low dose/long duration	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
Should corticosteroids compared with no corticosteroids be used in patients with ARDS?			
All adult and pediatric patients with ARDS	Corticosteroids	Placebo or no corticosteroids	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
Should methylprednisolone be used over other corticosteroids in patients with ARDS?			
All adult and pediatric patients with ARDS	Methylprednisolone	Dexamethasone, hydrocortisone	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
Should corticosteroids be administered to hospitalized patients with CAP?			
All adult and pediatric patients with CAP	Corticosteroids	Placebo or no corticosteroids	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)

ARDS = Acute Respiratory Distress Syndrome, CAP = community-acquired pneumonia.

Summary of Recommendations[a]

Recommendation 2024	Recommendation Strength, Quality of Evidence	Comparison to 2017 Recommendations
Acute respiratory distress syndrome		
2A. We "suggest" administering corticosteroids to adult hospitalized patients with acute respiratory distress syndrome	Conditional recommendation, moderate certainty evidence	We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (Pao_2/Fio_2 of < 200 and within 14 d of onset) (conditional recommendation, moderate quality of evidence)

Corticosteroid Dosing Regimens

Disease State	Common Corticosteroid Regimens
ARDS	Early ARDS (within 24 hr) Dexamethasone 20 mg IV daily for 5 d, then 10 mg IV daily for 5 d until extubation (64) Early ARDS (within 72 hr) (65) Methylprednisolone 1 mg/kg IV bolus, then • Days 1–14: 1 mg/kg/d continuous infusion • Days 15–21: 0.5 mg/kg/d • Days 22–25: 0.25 mg/kg/d • Days 26–28: 0.125 mg/kg/d • If extubated between days 1 and 15 then advance to day 15 of regimen Unresolving ARDS (7–21 d) (26) Methylprednisolone 2 mg/kg IV bolus, then • Days 1–14: 2 mg/kg/d divided every 6 hr • Days 15–21: 1 mg/kg/d • Days 22–28: 0.5 mg/kg/d • Days 29–30: 0.25 mg/kg/d • Days 31–32: 0.125 mg/kg/d • If extubated before day 14, then advance to day 15 of regimen drug therapy

Summary of Recommendations[a]

Recommendation 2024	Recommendation Strength, Quality of Evidence	Comparison to 2017 Recommendations
Acute respiratory distress syndrome		
2A. We "suggest" administering corticosteroids to adult hospitalized patients with acute respiratory distress syndrome	Conditional recommendation, moderate certainty evidence	We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (Pao_2/Fio_2 of < 200 and within 14 d of onset) (conditional recommendation, moderate quality of evidence)

Corticosteroid Dosing Regimens

TABLE 24.3 Recommendations for Corticosteroid Therapy in ARDS

Condition	Drug Regimen
COVID-19 that requires any of the following: a. Oxygen therapy b. Noninvasive ventilation c. Mechanical ventilation	Dexamethasone: 6 mg (IV or PO) once daily for up to 10 days.
Moderate-to-Severe ARDS in the first 72 hrs after onset.	Methylprednisolone: 1 mg/kg/day (IBW) by continuous infusion, and taper slowly over 14 days. Can eventually switch to PO therapy using once daily dosing.
Moderate-to-Severe ARDS that persists 7–14 days after onset	Same regimen as above, except the methylprednisolone dose is 2 mg/kg/day (IBW).

From References 27,29. IBW = ideal body weight.

Corticosteroids in Korea

Summary of Recommendations[a]

Recommendation 2024	Recommendation Strength, Quality of Evidence	Comparison to 2017 Recommendations
Acute respiratory distress syndrome		
2A. We "suggest" administering corticosteroids to adult hospitalized patients with acute respiratory distress syndrome	Conditional recommendation, moderate certainty evidence	We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (Pao_2/Fio_2 of < 200 and within 14 d of onset) (conditional recommendation, moderate quality of evidence)

KATRD-KSCCM Guideline (2025)

Conditional recommendation in ARDS

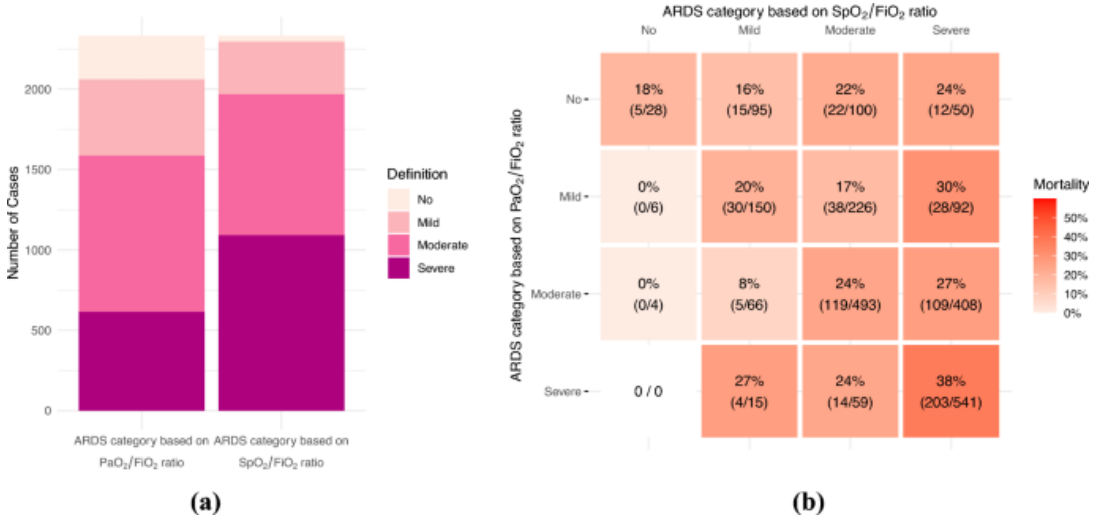
No mention about sub-etiology or severity
No mention about which medications, dosing, timing, schedule

ARDS What's Next?

Controversies in new definitions : "A chromatic advice"

Key Changes in the 2023 Global Definition vs. Berlin Criteria

Aspect	Berlin Definition (2012)	New Global Definition (2023)
Oxygenation Metrics	PaO_2/FiO_2 only	PaO_2/FiO_2 **or** SpO_2/FiO_2 ($SpO_2 \leq 97\%$)
Imaging Criteria	Chest X-ray/CT required	Lung ultrasound (B-lines/consolidation) added
Ventilation Support	Invasive/NIV (PEEP ≥5 cmH_2O)	Includes HFNO (flow ≥30 L/min)
Resource Adaptation	Not addressed	Integrates Kigali modification ($SpO_2/FiO_2 \leq 315$ for low-resource settings)



(a)

(b)

1. Diagnostic Reliability

- ✓ Overinclusivity : New definition doubles severe ARDS diagnoses, contradicting claims of early-stage detection.
- ✓ SpO_2/FiO_2 Limitations : Affected by hypoperfusion (e.g., lactate >4mmol/L reduces SpO_2/FiO_2 by 20% vs. PaO_2/FiO_2).
- ✓ Predictive Validity Failure : Mortality trends misalign between SpO_2/FiO_2 andPaO_2/FiO_2 severity categories.

→ Hypoperfusion statistically impacts SpO_2/FiO_2 but does not fully explain misalignment.

→ SpO_2/FiO_2 remains critical for resource-limited settings despite limitations.

2. Clinical applicability

- ✓ High-income settings : Overdiagnosis risks diluting research cohorts.
- ✓ Low-resource settings : Misdiagnosis (e.g., CHF vs. ARDS) due to limited imaging/ultrasound expertise.

→ Kigali modification improves ARDS recognition in low-resource areas by 34%.

→ Training programs can mitigate ultrasound misinterpretation.

3. Physiological Validity

<SpO_2/FiO_2 vs. PaO_2/FiO_2>

- ✓ SpO_2/FiO_2 : Reflects oxygenation and perfusion status (confounding factor).
- ✓ PaO_2/FiO_2 : Pure lung function metric.

→ "SpO_2/FiO_2 conflates respiratory/circulatory failure.

→ Misalignment persists even after adjusting for perfusion (lactate).

Intensive Care Med (2024) 50:608-609, 1001–1002, 1003-1005

ARDS New Definition

Controversies in new definitions : Proposed Solutions

1. Berlin Definition Updates

- ✓ Incorporate respiratory mechanics (compliance, driving pressure)
- ✓ Biomarkers (sRAGE, IL-6).
- ✓ Leverage automated radiomics for imaging standardization.

2. New Global Definition Refinements

- ✓ Mandate perfusion assessment (lactate, capillary refill) with SpO_2/FiO_2.
- ✓ Require lung recruitability testing (CT/ultrasound) for HFNO patients.

Implications for Clinical Practice

Setting	Recommendations
High-Resource	Prioritize PaO_2/FiO_2; reserve SpO_2/FiO_2 for early screening.
Low-Resource	Use SpO_2/FiO_2 + ultrasound; adopt Kigali criteria ($SpO_2/FiO_2 \leq 315$).
HFNO Patients	Confirm recruitability via imaging before ARDS diagnosis.

Future Directions

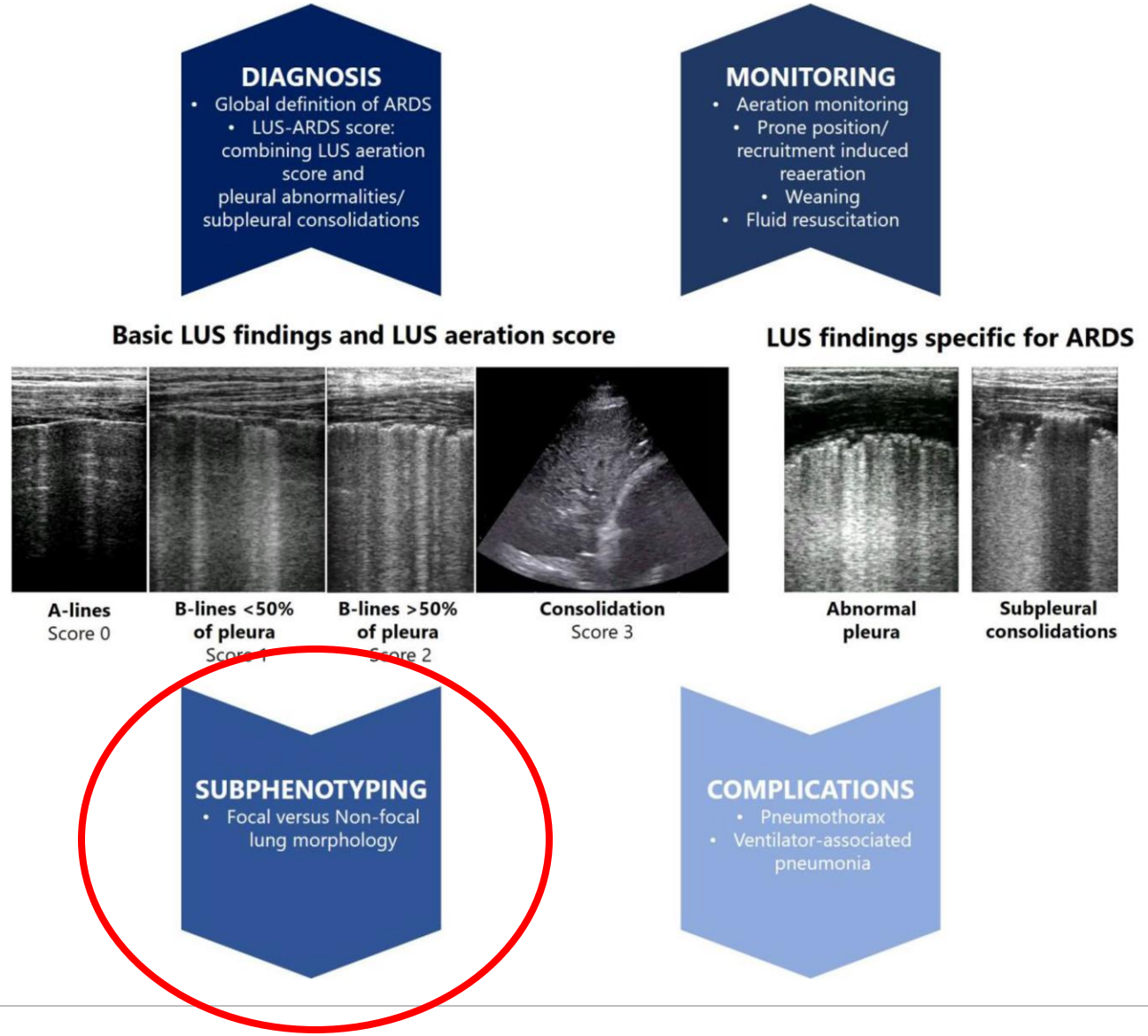
- **Validation Studies**:
  - ✓ **PRoVENT-ARDS 2.0** (NCT05249452):Prospective validation across 45 ICUs.
  - ✓ Develop **AI-driven SpO_2/PaO_2 correction algorithms** for real-time adjustments.
- **Consensus Building**:
  - ✓ Address etiology-specific definitions (e.g., COVID-19 vs. bacterial ARDS).
  - ✓ Standardize lung ultrasound training globally.

Intensive Care Med (2024) 50:608-609, 1001–1002, 1003-1005

ARDS Lung ultrasound

New Diagnostic Device:

“Lung Ultrasound”



Intensive Care Med (2024) 50:1143-1145

ARDS Prone +- ECMO

New Combinations: Prone Positioning +- ECMO

EDITORIAL

Prone positioning during extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Pro

Marco Giani[1,2*], Laurent Papazian[3,4] and Giacomo Grasselli[5,6]

EDITORIAL

Prone positioning during extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Con

Matthieu Schmidt[1,2,3,5*], Antoine Kimmoun[4] and Alain Combes[1,2,3]

EDITORIAL

Prone positioning during extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Not sure

Darryl Abrams[1,2*], Christophe Guervilly[3] and Daniel Brodie[4]

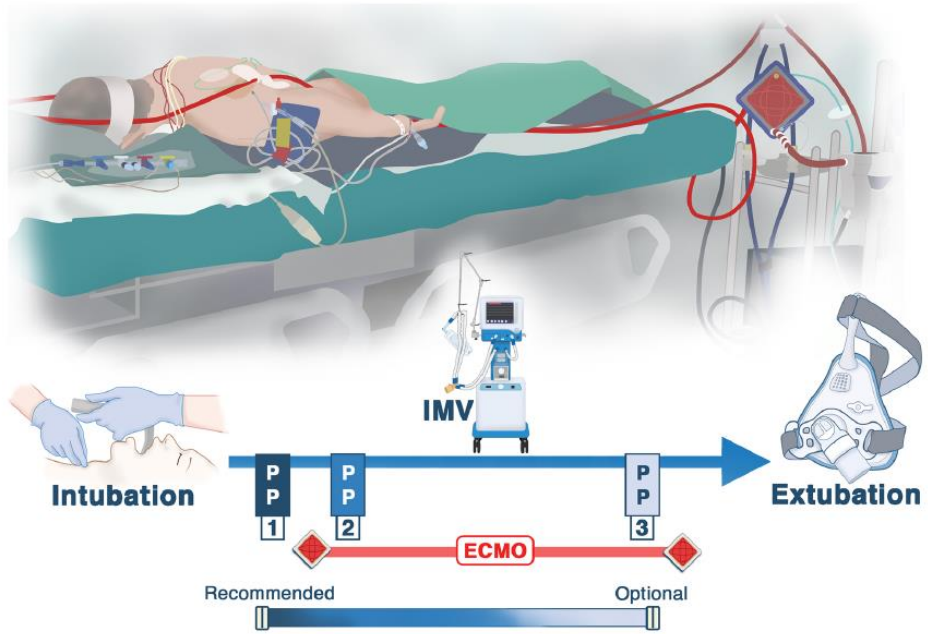


Fig. 1 Prone position in mechanically ventilated patients with severe ARDS with ECMO support. *PP* prone position; *IMV* invasive mechanical ventilation; *ECMO* extracorporeal membrane oxygenation. Timepoints of PP in severe ARDS patients: (1) before ECMO; (2) early PP during ECMO; (3) late PP during ECMO

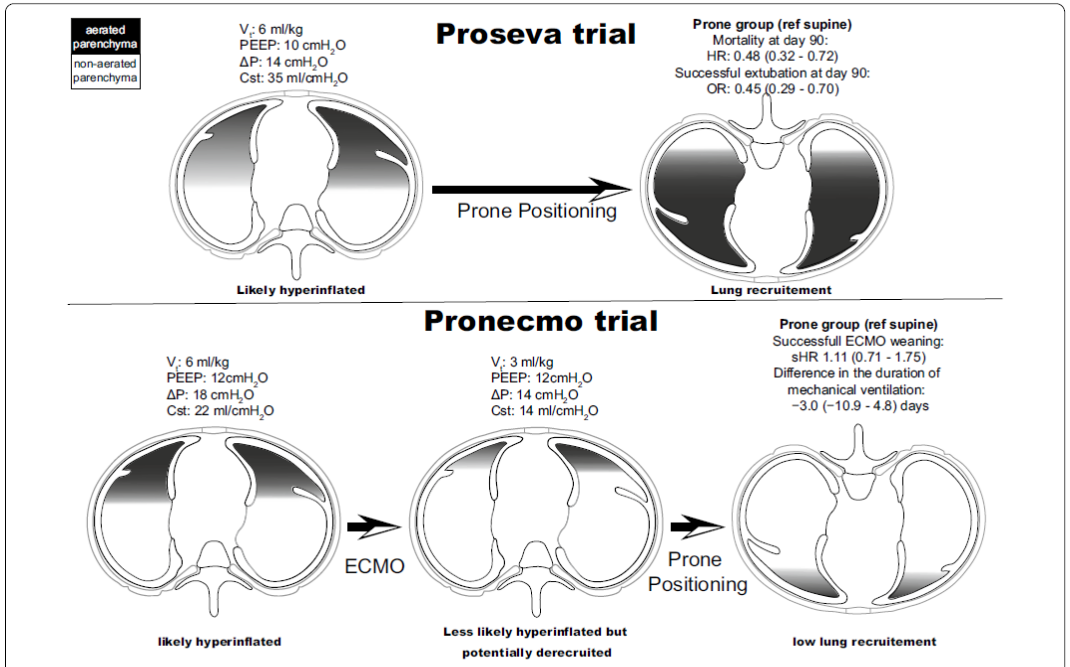


Fig. 1 PROSEVA [7] and PRONECMO trials' [1] respiratory parameters, cross-sectional thoracic computed tomography scan schemes, and clinical endpoints before and after prone positioning. *Cst* static compliance; *ECMO* extracorporeal membrane oxygenation; *HR* hazard ratio; *OR* odds ratio; *PEEP* positive end-expiratory pressure; *sHR* subdistribution hazard ratio; V_t tidal volume; *ΔP* driving pressure

Intensive Care Med (2024) 50:944–946, 947-949, 950-952

ARDS Prone +- ECMO

Aspect	Pro	Con	Not Sure
Physiological Basis	- Redistributes ventilation to reduce VILI in dorsal lung regions [Pro]	- No benefit when ultra-lung-protective ventilation is used [Con]	- Uncertain due to conflicting data; may depend on ARDS etiology [Not Sure]
Key Evidence	- Observational studies: Improved survival (RR 1.31) [Pro] - EuroPronECMO cohort: Early PP linked to better outcomes [Pro]	- PRONECMO RCT: No difference in ECMO weaning (sHR 1.11) or mortality [Con] - Higher complication rates (pressure ulcers: 57%) [Con]	- PRONECMO mostly COVID-19 ARDS; unclear for non-COVID [Not Sure] - Trend toward improved compliance with PP [Not Sure]
Patient Population	Non-COVID ARDS likely benefits most [Pro]	93% COVID-19 ARDS in PRONECMO; results not generalizable [Con]	- COVID-19 ARDS may mask benefits due to prolonged ECMO duration [Not Sure]
Timing of PP	Early PP during ECMO improves survival [Pro]	PP before ECMO (95% patients) negates additional benefits [Con]	Early PP (≤24h post-ECMO) may help; late PP ineffective [Not Sure]
Ventilation Strategy	Maintains lung recruitment during ultraprotective ventilation [Pro]	Ultra-lung-protective ventilation (tidal volume ~3 mL/kg) negates PP benefits [Con]	PP may lose efficacy with very low tidal volumes [Not Sure]
Clinical Implications	Use PP in non-COVID ARDS with recruitable lungs [Pro]	Avoid routine PP during ECMO; prioritize pre-ECMO PP [Con]	Reserve PP for selected patients (e.g., non-COVID, early ECMO) [Not Sure]
Safety	Safe in experienced centers [Pro]	Cannula dislodgement risk (8.1%); no mortality benefit [Con]	Safe but resource-intensive (90 min/session) [Not Sure]
Limitations	Observational data bias [Pro]	PRONECMO lacked ARDS phenotyping [Con]	Small RCTs (e.g., Tong et al. 2024: n=97) limit conclusions [Not Sure]

Key Takeaways

- ✓ **Pro: PP during ECMO may benefit non-COVID ARDS with recruitable lungs, supported by observational data.**
- ✓ **Con: PRONECMO RCT showed no benefit for COVID-19 ARDS; PP adds risks without survival gains.**
- ✓ **Not Sure: Conflicting evidence; PP may help in specific subgroups (early ECMO, non-COVID) but requires validation.**

Ongoing Research

- ✓ **NCT05249452: RCT evaluating PP in non-COVID ARDS on ECMO.**
- ✓ **Personalized approaches: Biomarker-guided PP (e.g., lung recruitability via CT/EIT).**

Intensive Care Med (2024) 50:944–946, 947-949, 950-952

Intensive Care Med (2024) 50:1021–1034
https://doi.org/10.1007/s00134-024-07492-7

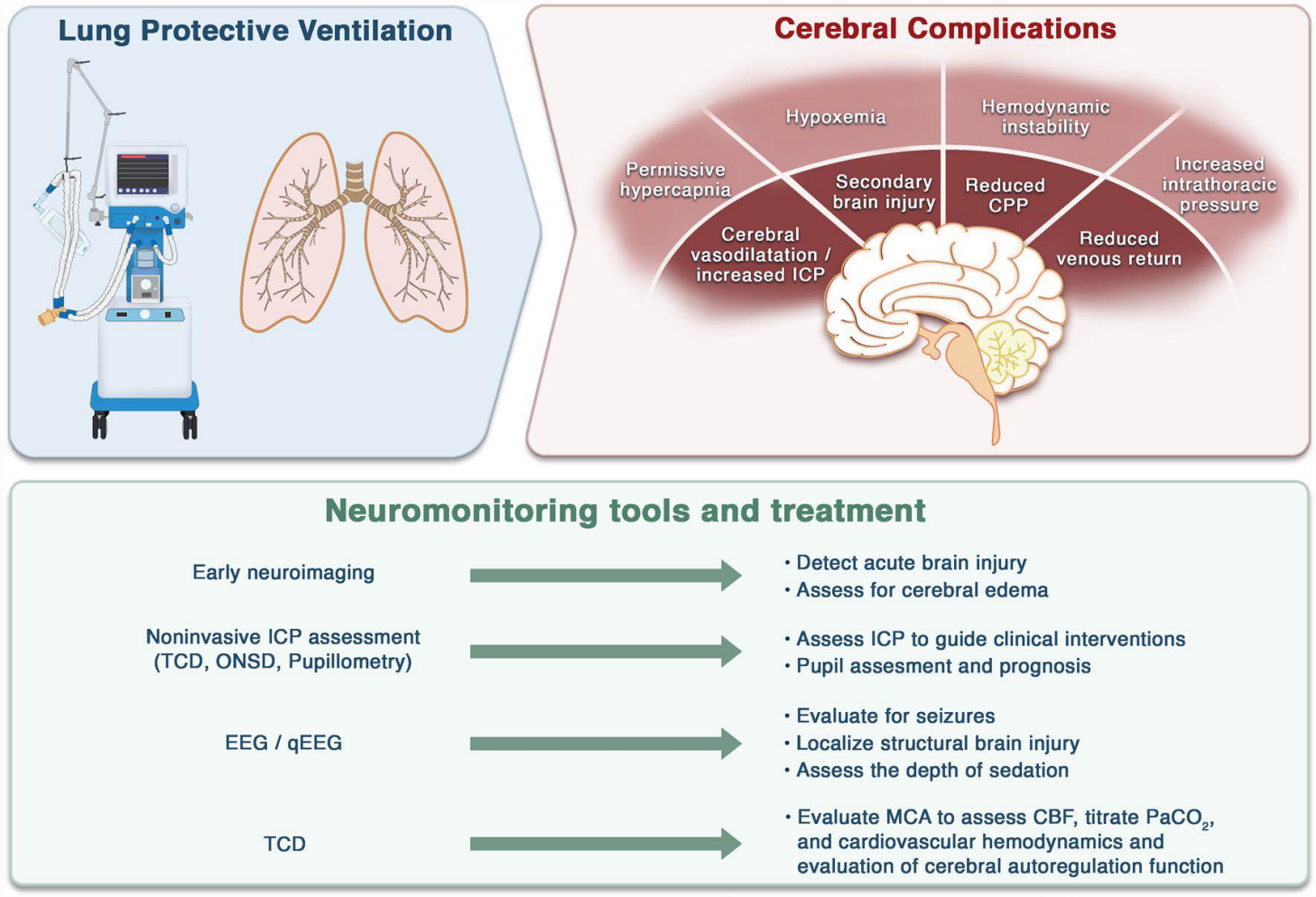
SYSTEMATIC REVIEW

Comparison of venovenous extracorporeal membrane oxygenation, prone position and supine mechanical ventilation for severely hypoxemic acute respiratory distress syndrome: a network meta-analysis

Sachin Sud[1,2*], Eddy Fan[3,4], Neill K. J. Adhikari[3,4,5], Jan O. Friedrich[3], Niall D. Ferguson[3,4], Alain Combes[6,7], Claude Guerin[8] and Gordon Guyatt[9]

ARDS Cerebral monitoring

Managing cerebral complications of ARDS



Intensive Care Med (2024) 50:1149-1151

ARDS Cerebral monitoring

New Diagnostic Device:

“Brain Ultrasound”

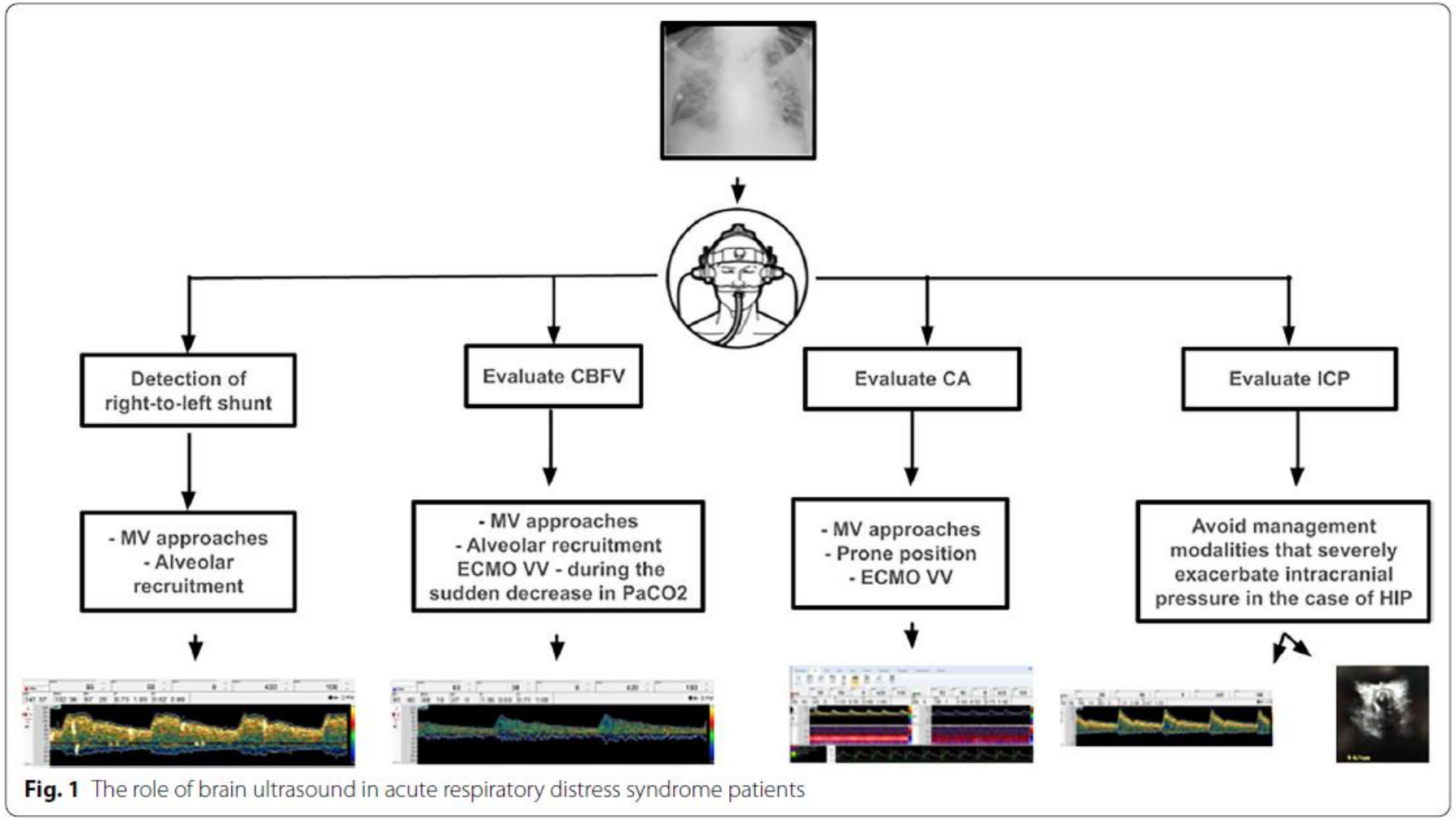


Fig. 1 The role of brain ultrasound in acute respiratory distress syndrome patients

Intensive Care Med (2024) 50:1725-1726

ARDS PEEP titration

How to Titrate the Best PEEP? : Assessing “Lung Recruitability”

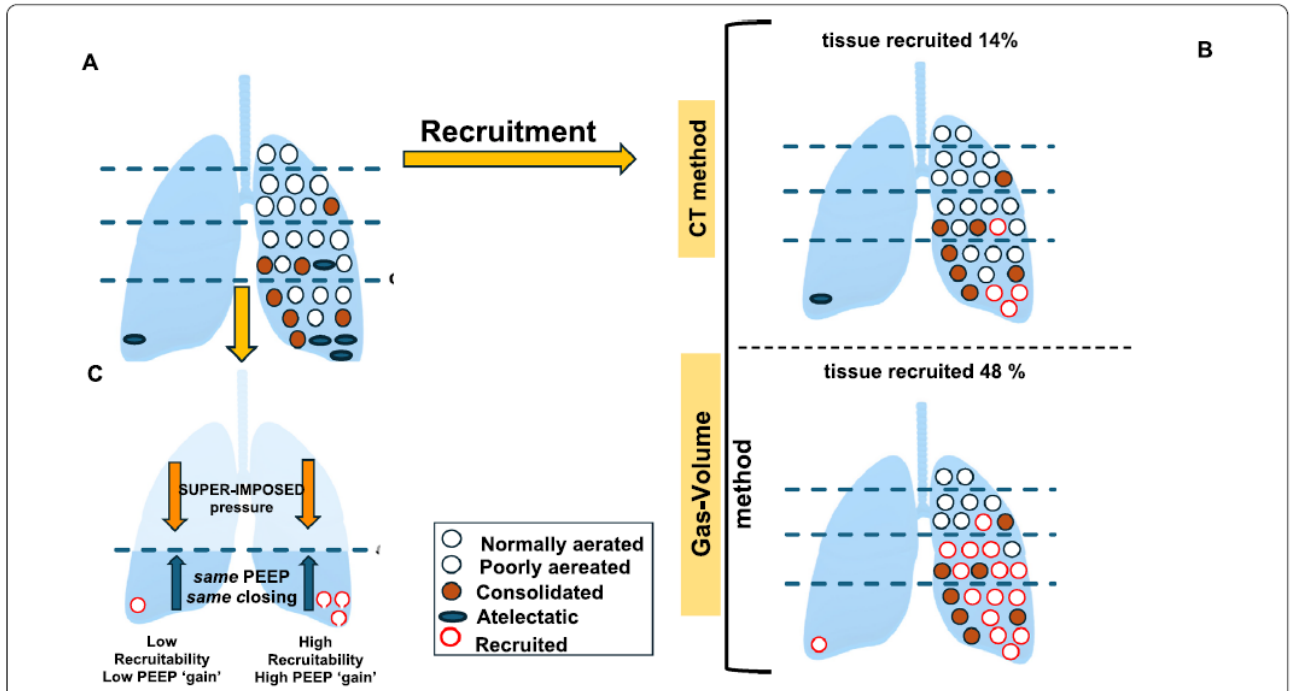
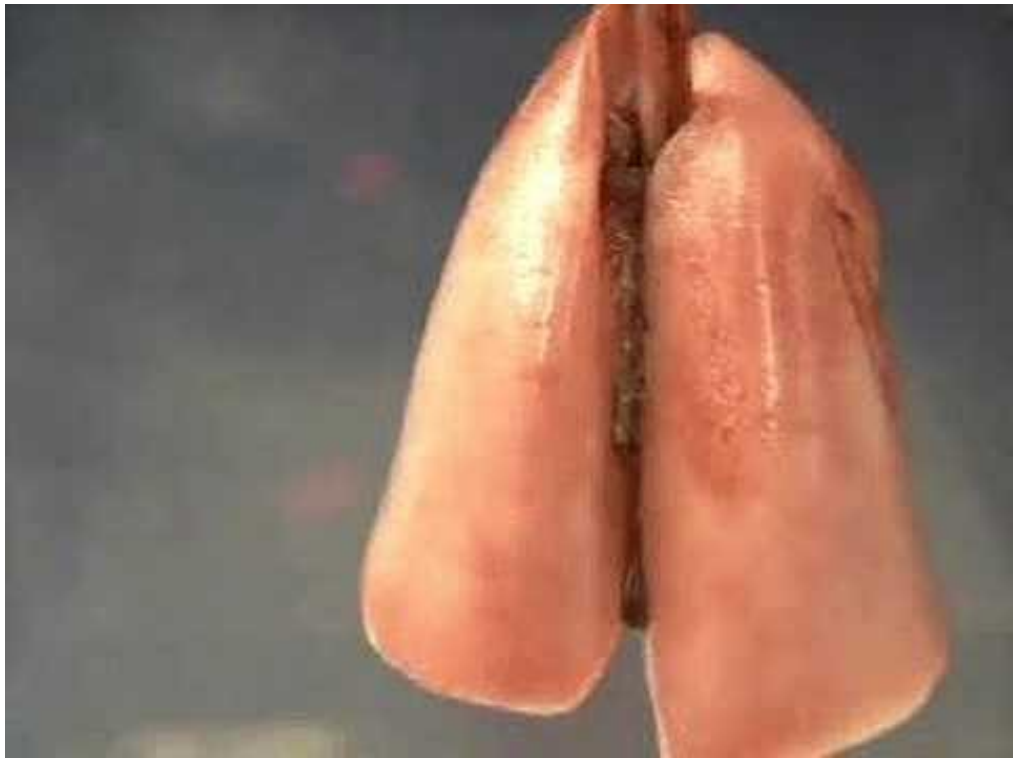


Fig. 1 Effect of recruitment as a function of the method used and effect of the PEEP applied. Panel **A**: In the right lung of the figures the different percentages (%) of pulmonary units in a typical ARDS patient are depicted (consolidated 24%, atelectatic 14%, poorly ventilated 34%, normally ventilated 28%). The left lung of the figure displays a single isolated atelectatic unit. (Panel **B**–upper) Using the percentages as in panel **A**, if the recruitment is assessed as reinflation of atelectatic unit (CT method) the resultant recruitment is 14%. (Panel **B**–lower) If the recruitment is assessed by the gas method, (which also includes increased aeration of poorly aerated units) the measured recruitment is of 48%. Panel **C**: The maintenance of recruitment is independent of the number of lung units recruited but depends on their physical characteristics such as closing pressures which are independent on the recruitability (intensive property of the system). Although the PEEP necessary to maintain the recruitment may be the same (independent of recruitment) the gain from the application of PEEP will be affected by recruitment and higher in the patients with higher potential for lung recruitment



Intensive Care Med (2024) 50:749–751

ARDS PEEP titration

How to Titrate the Best PEEP? "최적의 PEEP 설정 전략"

■ 좌측 (높은 PEEP 옹호)

주요 주장
- 폐 재개방 증가 → 가스교환 향상
- 무기폐 감소 → Atelectrauma 예방
- PROSEVA 연구: 복와위 + high PEEP 조합 효과 입증

근거 기반 접근
- Esophageal pressure 측정 (EPVent 연구)
- Driving pressure 최적화 (Amato 연구)

주의점
- Risk of hyperinflation ↑
  → Mechanical Power 모니터링 필수

■ 중립 영역: "현대적 합의점"

조건부 접근법
- 중증도 기반 조정(PaO_2/FiO_2 <150 → 적극적 재개방)
- Chest CT/초음파로 재개방 가능성 평가
- 역동적 모니터링(호흡역학, 산소화 추적)

미해결 쟁점
- COVID-19 ARDS의 특이성
- ECMO 병용 시 최적 PEEP 전략
- 인공지능 기반 실시간 최적화 가능성

ESICM 2023 권고 핵심
"개별화된 접근 필수 → 단일 전략 고수 금지"

■ 우측 (낮은 PEEP 옹호)

주요 주장
- 혈역학적 불안정성 ↓
- Barotrauma 발생률 감소 (ART 연구)
- $PEEP/FiO_2$ 테이블의 단순성과 적용 용이성

근거 기반 접근
- 표준화된 저 $PEEP/FiO_2$ 테이블 (ALVEOLI 연구)
- 폐 재개방 가능성 평가 후 보수적 적용

주의점
- 무기폐 → P-SILI 유발 가능성

"In conclusion, while recruitability gives important information on the severity of disease and the amount of atelectatic lung, PEEP selection requires an integrated assessment of other variables such as elastance and transpulmonary pressures and hemodynamics to be truly personalized. Attempts to PEEP selection only to recruitability may lead to confusion and potentially injurious ventilatory settings."

Intensive Care Med (2024) 50:749-751

ARDS PEEP titration

How to Titrate the Best PEEP?

Intensive Care Med (2024) 50:1175–1176
https://doi.org/10.1007/s00134-024-07445-0

CORRESPONDENCE

Entangled in stagnant recruitment delusions

George Briassoulis[1*], Panagiotis Briassoulis[2], Marianna Miliaraki[3] and Stavroula Ilia[1,3]

Maybe it is time for the era of recruitment strategies in ARDS to give way to a new approach. This approach would involve titrating PEEP based on hemodynamic monitoring and real-time EELV, stress, and strain calculations guided by artificial intelligence (AI)-generated mechanical power algorithms.

Intensive Care Med (2024) 50:1177–1178
https://doi.org/10.1007/s00134-024-07465-w

As always, technology can provide the monitoring capability and potential solutions, but the goals of care remain—fortunately still a prerogative of the clinician in partnership with the patient and their families.

CORRESPONDENCE

Are we ready to harness AI and digital modelling for precision in PEEP settings?

Francesca Collino[1*], Luciano Gattinoni[2] and Luigi Camporota[3,4]

ARDS PEEP titration

How to Titrate the Best PEEP?

"Monitoring esophageal pressure" vs "Electrical Impedance Tomography"

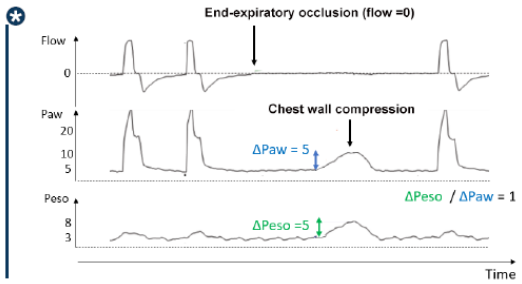
Esophageal pressure (Peso) monitoring in ARDS

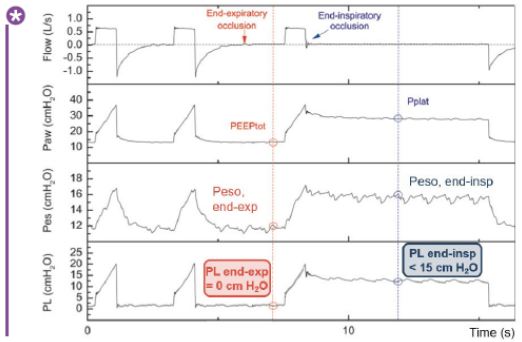
PREPARE AND CHECK

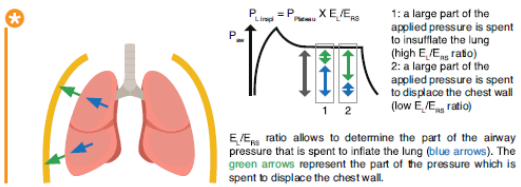
1. Position the balloon in the retrocardiac esophagus (usually 35-40 cm from the nostrils or lip to the end of the balloon). Check mouth to exclude coiling of catheter in posterior oropharynx.
2. Fill the balloon with air (manufacturer's volume to start) and inspect Peso tracing for cardiac oscillations suggestive of correct position behind the heart.
3. Perform an airway occlusion test and monitor the Peso- and Paw-time waveforms to evaluate for correct positioning as follows:
   a) Press on the thorax (slow, bilateral, symetric compression during 3 to 4 seconds followed by gentle release). Alternatively, if the patient is actively breathing, wait for a patient's inspiratory effort.
   b) Measure maximum simultaneous change in Peso and Paw and compute ΔPeso/ΔPaw. Target 0.8-1.2. If ok, start the measurements. If not, reposition the balloon from 0.5 to 1 cm, then recheck.
4. Carefully titrate the volume of air in the balloon to obtain the maximal variation of Peso amplitude during tidal ventilation.

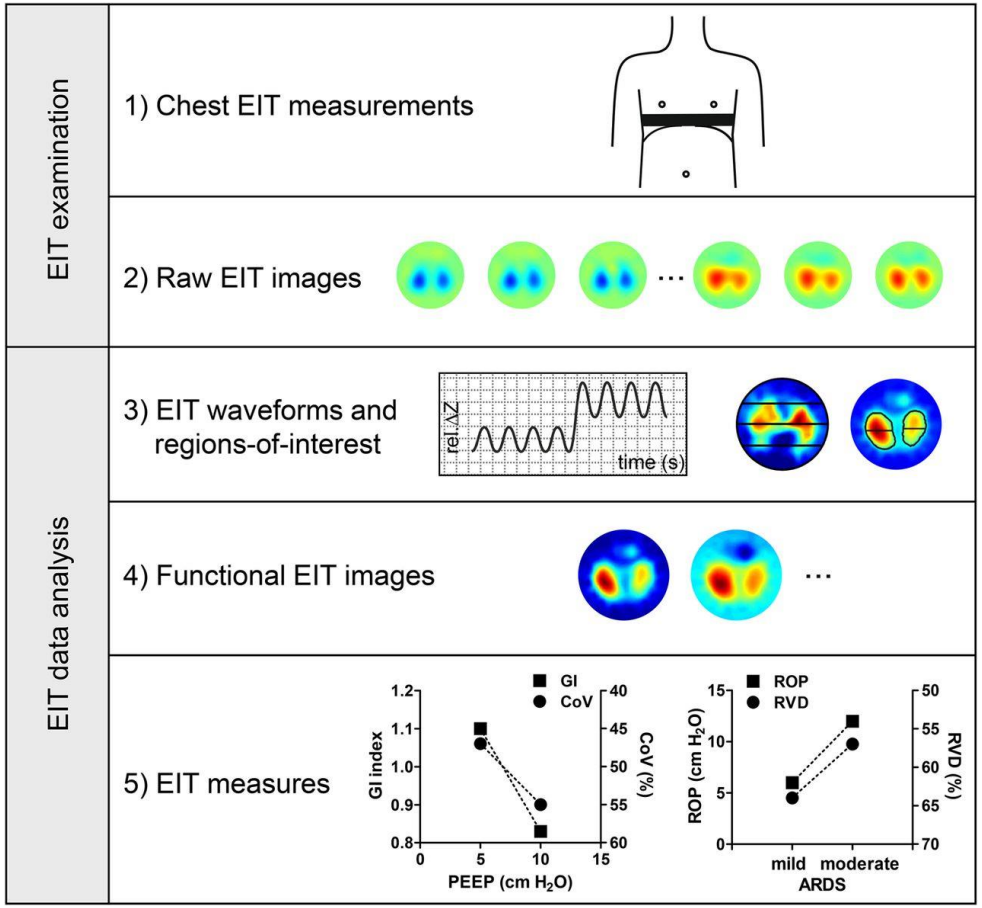
USE

- Measure direct end-expiratory PL (= Total PEEP – Peso) with an occlusion and titrate PEEP for end-exp PL = 0-2 cmH_2O.
- Measure end-inspiratory PL with the direct technique (= Pplat – Peso) and check that PLdirect < 15 cmH_2O. If not, consider decreasing VT and/or PEEP.
- Measure end-inspiratory PL with the elastance ratio based strategy (PL= Paw x EL/ERS) then check that PL measured this way < 20 cmH_2O. If not, consider decreasing VT and/or PEEP.



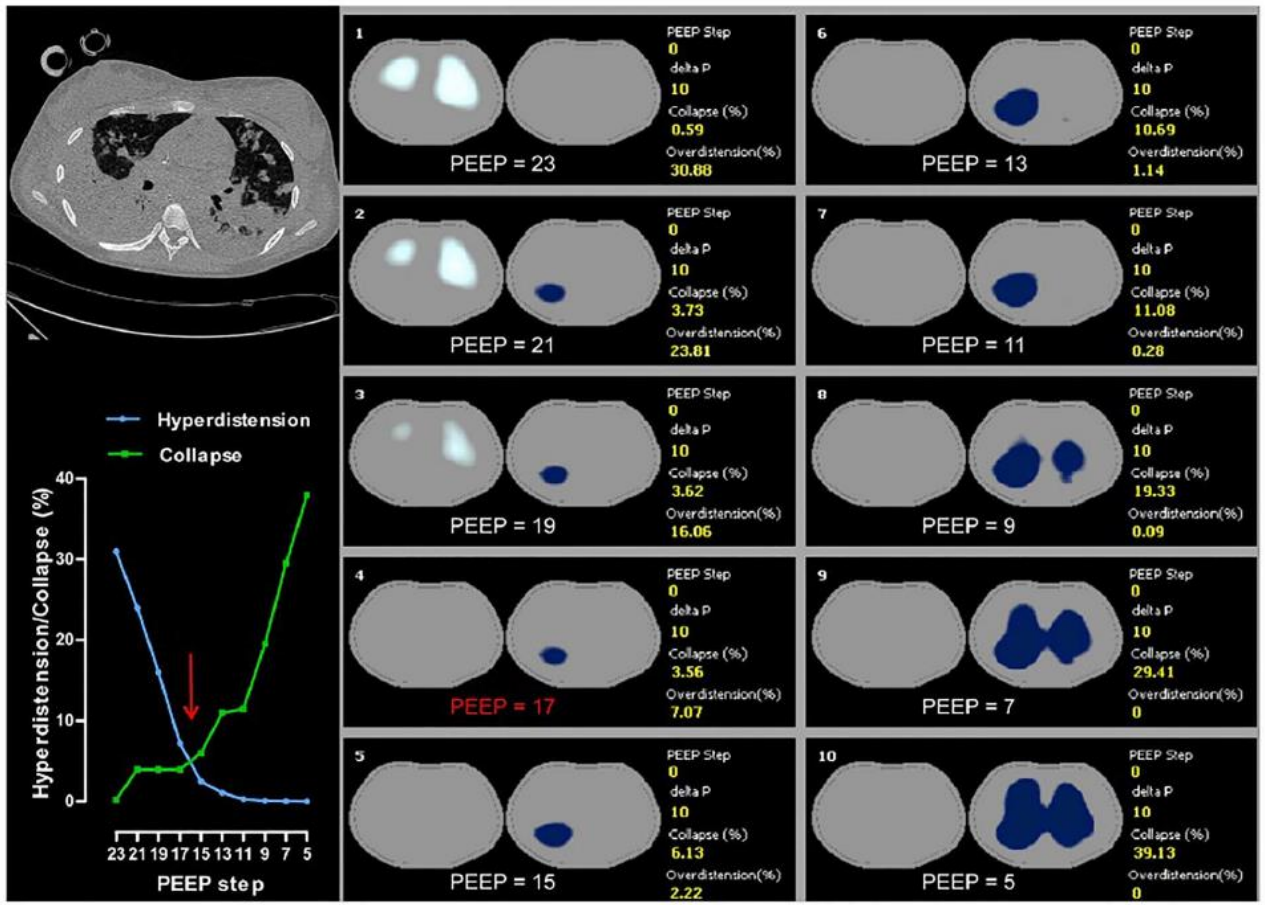


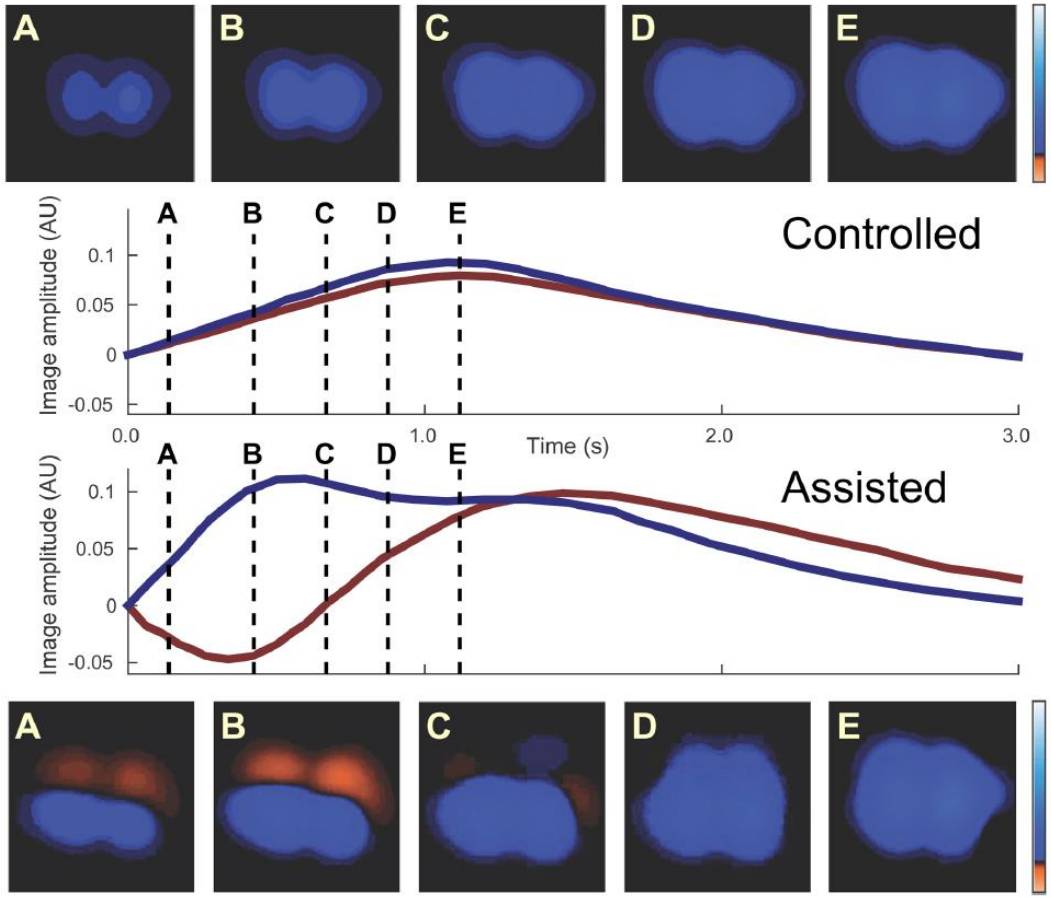




Intensive Care Med (2024) 50:953-956; Thorax (2017) 72:83-93

How to Titrate the Best PEEP?





Thorax (2017) 72:83-93

ORIGINAL ARTICLE

Lung Recruitment Assessed by Electrical Impedance Tomography (RECRUIT)

A Multicenter Study of COVID-19 Acute Respiratory Distress Syndrome

Annemijn H. Jonkman[1,2,3*], Glasiele C. Alcala[4*], Bertrand Pavlovsky[5,6], Oriol Roca[7,8], Savino Spadaro[9,10], Gaetano Scaramuzzo[9,10], Lu Chen[1,2], Jose Dianti[2,11], Mayson L. de A. Sousa[1,2,4], Michael C. Sklar[1,2], Thomas Piraino[1,2], Huiqing Ge[12], Guang-Qiang Chen[13], Jian-Xin Zhou[13], Jie Li[14], Ewan C. Goligher[2,11,15], Eduardo Costa[4], Jordi Mancebo[16†], Tommaso Mauri[17‡], Marcelo Amato[4‡], and Laurent J. Brochard[1,2‡]; for the Pleural Pressure Working Group (PLUG)

ARDS PEEP titration

How to Titrate the Best PEEP?

SYSTEMATIC REVIEW

Electrical impedance tomography-guided positive end-expiratory pressure titration in ARDS: a systematic review and meta-analysis

Nickjaree Songsangvorn[1,2], Yonghao Xu[1,3*], Cong Lu[1], Ori Rotstein[1,4], Laurent Brochard[1,5], Arthur S. Slutsky[1,5], Karen E. A. Burns[1,5] and Haibo Zhang[1,5,6,7*]

CORRESPONDENCE

Concern for meta-analysis combining randomized parallel and cross-over trials

Wan-Jie Gu*

CORRESPONDENCE

Methodological considerations in meta-analysis: evaluating RCTs, NRS, and crossover trials for electrical impedance tomography in PEEP titration

Nickjaree Songsangvorn[1,2], Arthur S. Slutsky[1,3], Karen E. A. Burns[1,3*] and Haibo Zhang[1,3,4,5*]

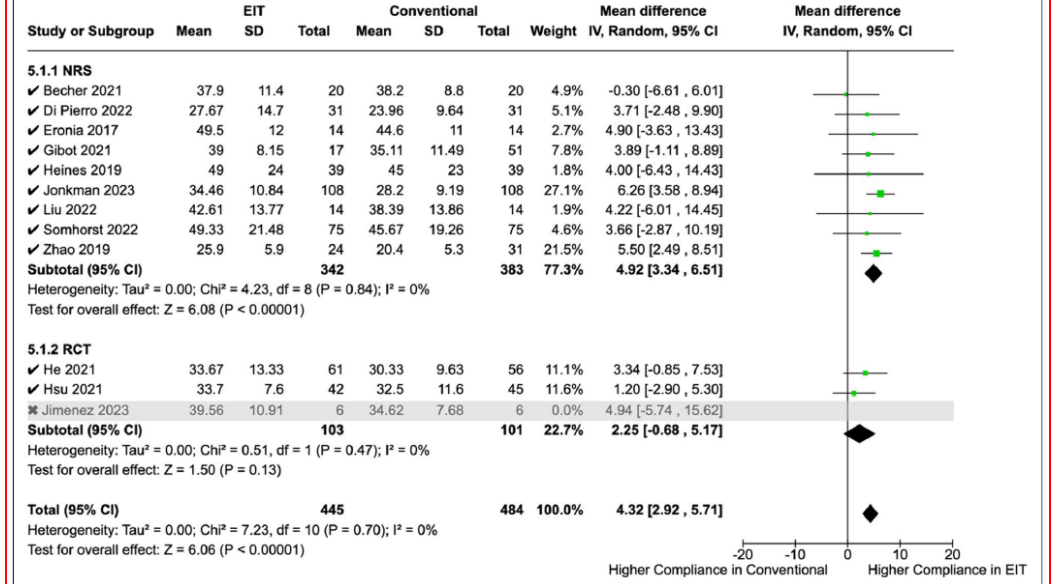


Fig. 1 Forest plots of sensitivity analysis for lung compliance: excluding RCT crossover study. EIT-guided PEEP significantly increased lung compliance compared to conventional methods. *CI* confidence interval, *df* degrees of freedom, I^2 heterogeneity statistic, *IV* inverse variance method

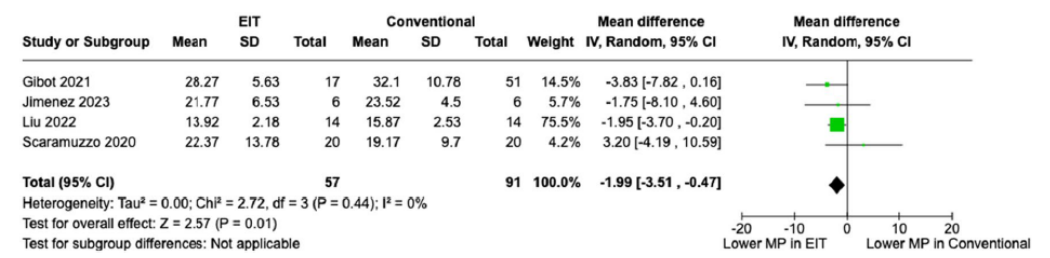


Fig. 3 Comparison of mechanical power between EIT-guided and conventional PEEP titration. *MP* mechanical power, *CI* confidence interval, *df* degrees of freedom, I^2 heterogeneity statistic, *IV* inverse variance method

Intensive Care Med (2024) 50:617-631; 1187; 1188-1189

Critical Care

BRIEF REPORT Open Access

Electric impedance tomography-guided PEEP titration reduces mechanical power in ARDS: a randomized crossover pilot trial

Jose Victor Jimenez[1], Elizabeth Munroe[1], Andrew J. Weirauch[2], Kelly Fiorino[2], Christopher A. Culter[2], Kristine Nelson[1], Wassim W. Labaki[1], Philip J. Choi[1,2], Ivan Co[1], Theodore J. Standiford[1], Hallie C. Prescott[1,3] and Robert C. Hyzy[1*]

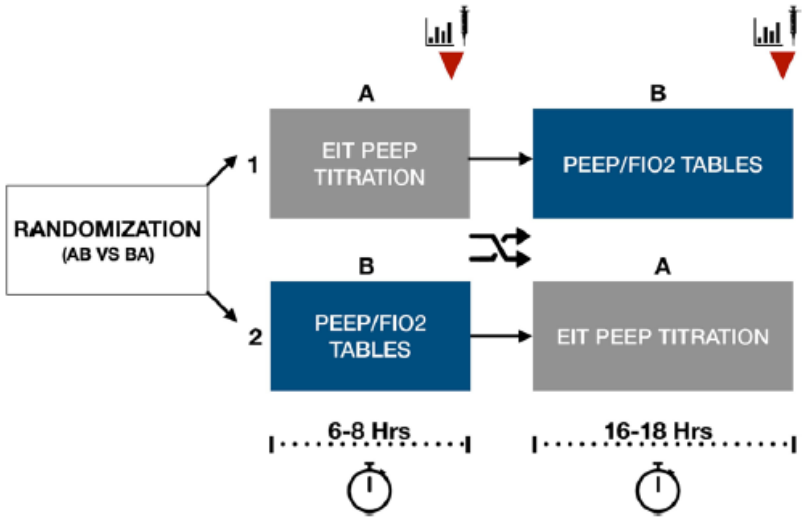


Fig. 1 Trial design and crossover. Red arrows represent the time point at which post-intervention data were collected. Center crossed arrows represent the time of crossover

Abstract

Background In patients with acute respiratory distress syndrome undergoing mechanical ventilation, positive end-expiratory pressure (PEEP) can lead to recruitment or overdistension. Current strategies utilized for PEEP titration do not permit the distinction. Electric impedance tomography (EIT) detects and quantifies the presence of both collapse and overdistension. We investigated whether using EIT-guided PEEP titration leads to decreased mechanical power compared to high-PEEP/FiO2 tables.

Methods A single-center, randomized crossover pilot trial comparing EIT-guided PEEP selection versus PEEP selection using the High-PEEP/FiO_2 table in patients with moderate–severe acute respiratory distress syndrome. The primary outcome was the change in mechanical power after each PEEP selection strategy. Secondary outcomes included changes in the 4 × driving pressure + respiratory rate (4 ΔP, + RR index) index, driving pressure, plateau pressure, PaO_2/FiO_2 ratio, and static compliance.

Results EIT was consistently associated with a decrease in mechanical power compared to PEEP/FiO_2 tables (mean difference − 4.36 J/min, 95% CI − 6.7, − 1.95, $p = 0.002$) and led to lower values in the 4ΔP + RR index (− 11.42 J/min, 95% CI − 19.01, − 3.82, $p = 0.007$) mainly driven by a decrease in the elastic–dynamic power (− 1.61 J/min, − 2.99, − 0.22, $p = 0.027$). The elastic–static and resistive powers were unchanged. Similarly, EIT led to a statistically significant change in set PEEP (− 2 cmH_2O, $p = 0.046$), driving pressure, (− 2.92 cmH2O, $p = 0.003$), peak pressure (− 6.25 cmH_2O, $p = 0.003$), plateau pressure (− 4.53 cmH_2O, $p = 0.006$), and static respiratory system compliance (+ 7.93 ml/cmH_2O, $p = 0.008$).

Conclusions In patients with moderate–severe acute respiratory distress syndrome, EIT-guided PEEP titration reduces mechanical power mainly through a reduction in elastic–dynamic power.

Trial registration This trial was prospectively registered on Clinicaltrials.gov (NCT 03793842) on January 4th, 2019.

Keywords Acute lung injury, Electrical impedance tomography, Respiratory distress syndrome, Mechanical ventilators, Ventilator-induced lung injury

n=12...

Table 1 Baseline characteristics of participants across study arms

	All ($n=12$)	EIT first ($n=6$)	Tables first ($n=6$)
Age, median [IQR], years	61 [48, 68]	62 [50, 72]	59.5 [46, 67]
Female sex, n(%)	3 (25)	1 (16)	2 (33)
White race, n(%)	11 (91)	6 (100)	5 (83)
BMI, median [IQR], kg/m^2	32 [25, 36]	32 [26, 36]	32 [24, 36]
CCI, median [IQR]	2 (1, 5)	2 (1, 5)	2.5 (1, 5)
Tobacco Use, n(%)	9 (75)	4 (66)	5 (83)
SAPS II at ICU admission, median [IQR]	38 [33, 46]	38 [33, 45]	40 [33, 48]
SOFA at ICU admission, median [IQR]	8 (6, 9)	7 (6, 9)	8.5 (7, 10)
Etiology of ARDS, n(%)			
COVID-19	7 (58.3)	4 (66.7)	3 (50.0)
Bacterial pneumonia	4 (33.3)	2 (33.3)	2 (33.3)
Extrapulmonary	1 (8.3)	0 (0)	1 (16.7)
Pre-intubation NIV and/or HFNC, n(%)	11 (91.7)	6 (100)	5 (83.3)
PaO2/FiO2 Ratio, median [IQR], mmHg	130 [112, 140]	117 [111, 143]	136 [125, 138]
MV duration before inclusion, median [IQR], days	0.6 [0.2, 2]	0.5 [0.2, 2]	1 [0.2, 1]
Vasopressor at baseline, n(%)	9 (75)	5 (83.3)	4 (66.7)
Sedation at baseline (RASS), median [IQR]	− 4 [− 3, − 4.5]	− 4 [− 3, − 5]	− 3.5 [− 3, − 4]
Baseline Ventilator Settings, median [IQR]*			
Tidal Volume, ml/kg/PBW	6.0 [5.9, 6.3]	6.1 [5.7, 6.3]	6.0 [5.8, 6.3]
Respiratory rate, breaths/min	26 [20, 30]	26 [21, 30]	26 [20, 31]
PEEP, cmH$_2$O	15 (14, 16)	14 (14, 16)	16 (14, 16)
Cstat, ml/cmH$_2$O	36 [29, 40]	34 [28, 39]	36 [32, 42]
Ppeak, cmH$_2$O	27 [25, 31]	29 [27, 35]	25 [25, 27]
Pplat, cmH$_2$O	26 [25, 28]	27 [26, 28]	26 [25, 27]
Driving Pressure, cmH$_2$O	11 (10, 12)	12 (12, 14)	10 (10, 11)
Mechanical Power[†], J/min	20 [19, 28]	24 [20, 35]	19 [18, 22]
4ΔPxRR Index[§], J/min	70 [64, 83]	76 [68, 84]	70 [60, 73]
Non-Survivors, n(%)	6 (50)	3 (50)	3 (50)

*Baseline ventilator settings are defined as ventilator settings at the start of the study, after randomization but prior to initiation of any study intervention

[†] Mechanical Power calculate using Gattinoni's simplified equation

[§] Mechanical Power calculated using 4ΔPxRR index

Table 2 Comparison of changes in ventilator parameters with EIT vs tables, for all participants, $n=12$

	Change with EIT*	Change with tables**		95% CI of mean difference	*p* value
Mechanical Power[1], J/min	− 2.50 ± 3.70	1.87 ± 1.61	− 4.36	(− 6.77, − 1.95)	0.002
4ΔP + RR Index, J/min	− 6.80 ± 9.36	4.62 ± 6.25	− 11.42	(− 19.01, − 3.82)	0.007
Elastic–static power[2], J/min	− 1.37 ± 2.11	0.19 ± 2.28	− 1.56	(− 3.71, 0.58)	0.138
Elastic–dynamic power[3], J/min	− 1.13 ± 1.66	0.48 ± 0.88	− 1.61	(− 2.99, − 0.22)	0.027
Resistive power[4], J/min	0.01 ± 3.30	1.15 ± 2.48	− 1.14	(− 4.59, 2.30)	0.48
Driving Pressure, cmH$_2$O	− 1.58 ± 2.32	1.34 ± 1.31	− 2.92	(− 4.59, − 1.24)	0.003
PEEP (set), cmH$_2$O	− 1.17 ± 1.80	0.83 ± 1.80	− 2	(− 3.95, − 0.05)	0.046
Ppeak, cmH$_2$O	− 2.75 ± 3.55	3.5 ± 2.78	− 6.25	(− 9.79, − 2.71)	0.003
Pplat, cmH$_2$O	− 2.48 ± 3.22	2.06 ± 1.88	− 4.53	(− 7.45, − 1.62)	0.006
RR, breaths/min	− 0.5 ± 2.35	− 0.75 ± 2.73	0.25	(− 2.71, 3.21)	0.856
Cstat, ml/cmH$_2$O	3.24 ± 9.85	− 4.6 ± 5.26	7.93	(2.54, 13.32)	0.008
PaO2/FiO2 ratio	25.14 ± 27.11	− 0.89 ± 60.05	26.03	(− 16.01, 68.06)	0.2

Data are listed as mean ± SD

P value calculated using paired *t* test

*Change with EIT: ventilator parameter at the end of EIT intervention minus ventilator parameter at the start of the EIT intervention

**Change with tables: ventilator parameter at the end of the table intervention minus ventilator parameter at the start of the table intervention

n=30...

How to Titrate the Best PEEP?

ORIGINAL

Check for updates

Personalized positive end-expiratory pressure in spontaneously breathing patients with acute respiratory distress syndrome by simultaneous electrical impedance tomography and transpulmonary pressure monitoring: a randomized crossover trial

Tommaso Mauri[1,2*], Domenico L. Grieco[3,4], Elena Spinelli[2], Marco Leali[1], Joaquin Perez[5,6], Valentina Chiavieri[1], Tommaso Rosà[3,4], Pierluigi Ferrara[7,8], Gaetano Scaramuzzo[7], Massimo Antonelli[3,4], Savino Spadaro[7,8] and Giacomo Grasselli[1,2]

Intensive Care Med (2024) 50:2125-2137

IPERPEEP trial

Monitoring esophageal pressure

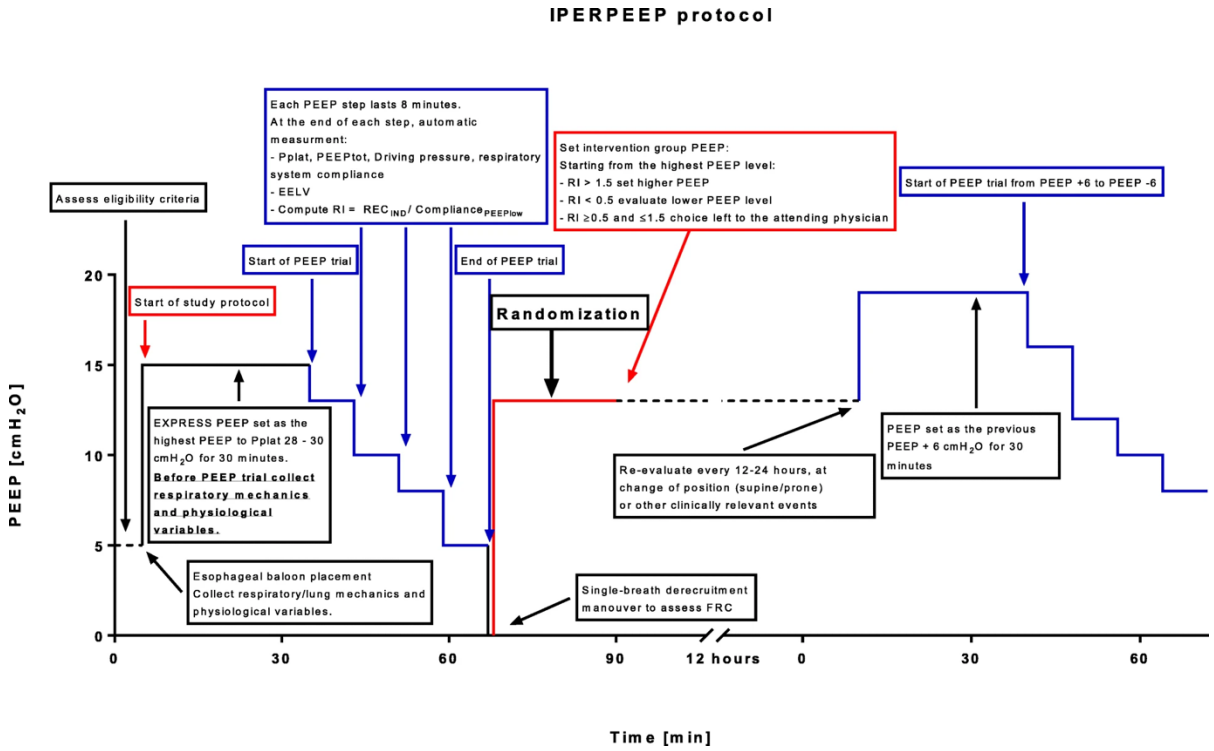
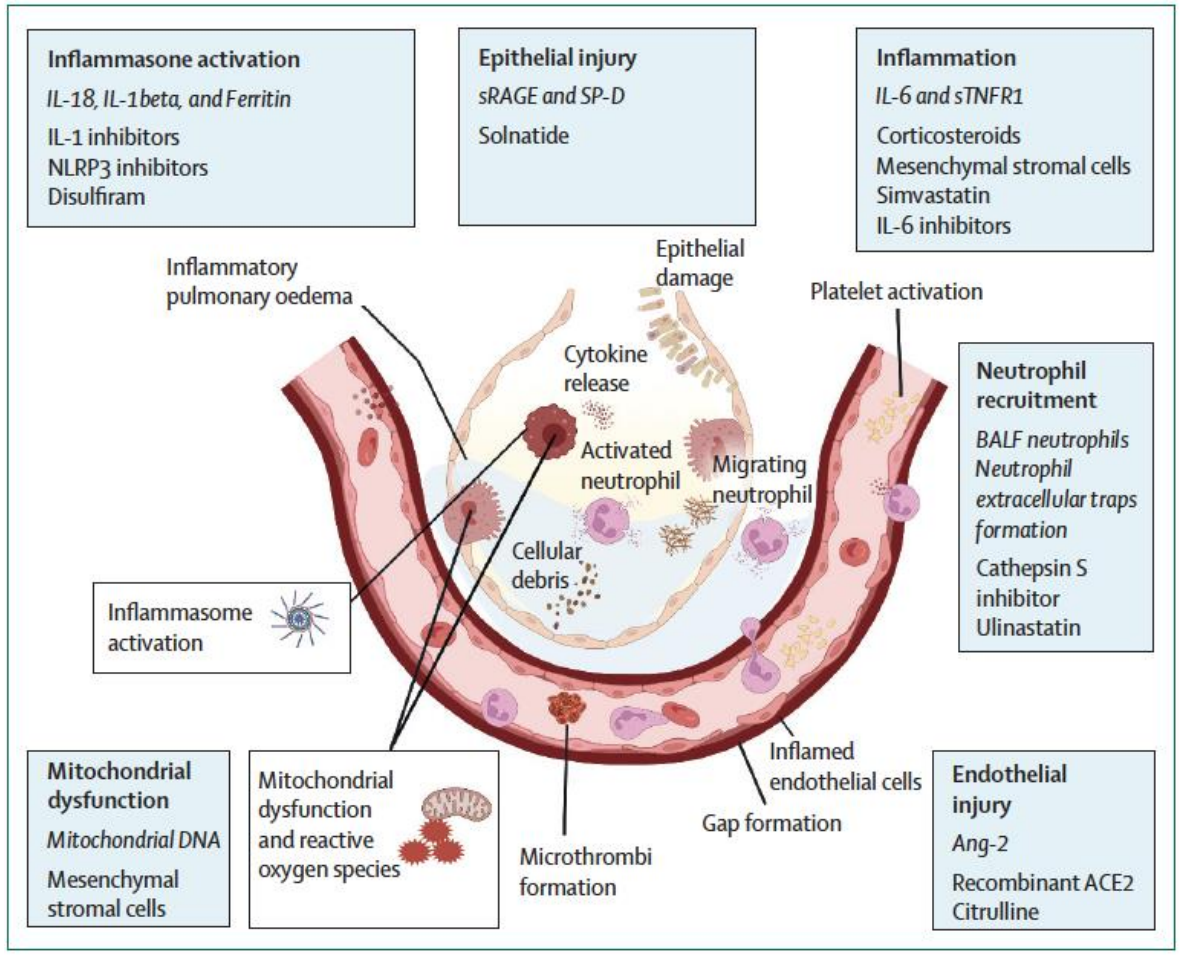


Table 1 Computed respiratory mechanics parameters

Parameter	*Formula*
Airway driving pressure	$\Delta P = Pplat_{aw} - PEEP_{aw}$
Transpulmonary end-inspiratory pressure	$Pplat_L = Plat_{aw} - Pplat_{es}$
Transpulmonary end-expiratory pressure	$PEEP_L = PEEP_{aw} - PEEP_{es}$
Lung driving pressure	$\Delta P_L = Pplat_L - PEEP_L$
Lung plateau pressure, elastance-derived	$Pplat_{L,EL} = Pplat_{aw} \times (\Delta P_L/\Delta P)$
Static respiratory system compliance	$Cst_{RS} = V_T/\Delta P$
Static lung compliance	$Cst_L = V_T/\Delta P_L$
Static chest wall compliance	$Cst_{CW} = V_T/(Pplat_{es} - PEEP_{es})$
Oxygenation-stretch index	$OSI = PaO_2/(FiO_2 \times \Delta P)$
Dynamic strain	Dynamic strain $= V_T/FRC_{PEEPset}$
Static strain (strain due to PEEP)	Static strain $= (PEEP_{volume} - Rec_{ZEEP\text{-}PEEP})/FRC_{PEEPset}$
Static stress (stress due to PEEP)	Static stress $= PEEP_{aw} \times (\Delta P_L/\Delta P)$
Dynamic stress	Dynamic stress $= Pplat_{aw} \times (\Delta P_L/\Delta P)$

ARDS Emerging treatments



1. Mesenchymal stromal cells and extracellular vesicles

- ✓Multiple beneficial effects including promoting macrophage and T cell polarization to pro-resolving phenotypes, promoting endothelial barrier integrity, and enhancing alveolar fluid and pathogen clearance
- ✓Umbilical vs. BM

2. Biologic therapies

- ✓Targeted biologics therapies such as Anti-IL-6, IL-1 RA

3. Potential therapeutic targets

- ✓Ang-2 or RAGE

Lancet 2022; BMJ 2024

Cell therapy (from Japan)

RESEARCH Open Access

Clinical efficacy and safety of multipotent adult progenitor cells (invimestrocel) for acute respiratory distress syndrome (ARDS) caused by pneumonia: a randomized, open-label, standard therapy–controlled, phase 2 multicenter study (ONE-BRIDGE)

Kazuya Ichikado[1*†], Toru Kotani[2], Yasuhiro Kondoh[3], Hideaki Imanaka[4], Takeshi Johkoh[5], Kiminori Fujimoto[6], Shin Nunomiya[7,13], Tomotaka Kawayama[8], Masanori Sawada[9], Eric Jenkins[10,14], Sadatomo Tasaka[11] and Satoru Hashimoto[12†]

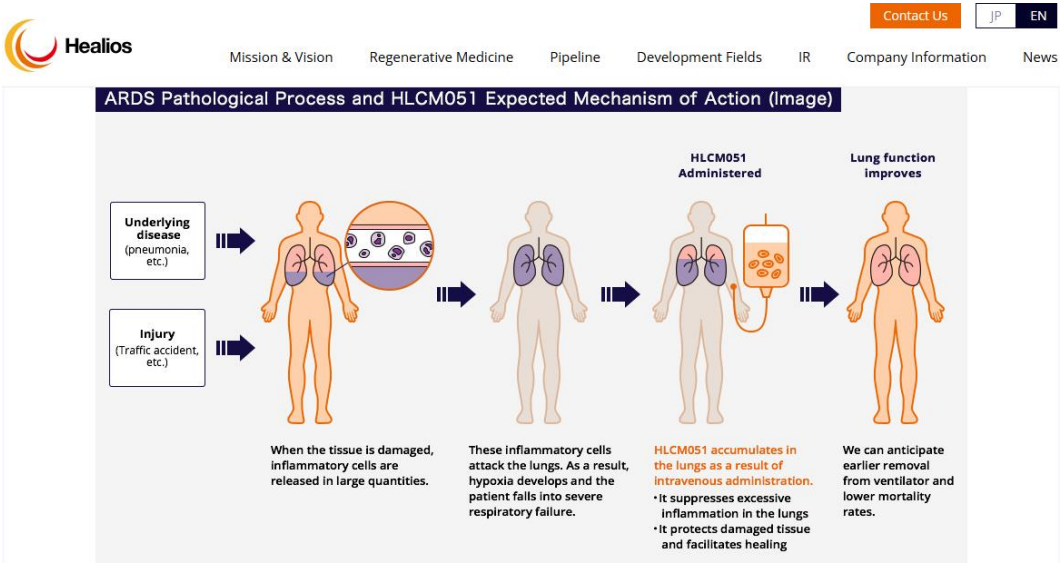


Table 2 Ventilator-free days, ventilator weaning, re-intubation rate, and mortality rate (modified intent-to-treat analysis set)

	Invimestrocel group (N = 20)	Standard group (N = 10)	*p* value
Primary outcome			
VFD from day 0 to day 28, days			
Mean (SD)	14.8 (11.0)	10.6 (10.0)	
Median (IQR)	20.0 (0.0–24.0)	11.0 (0.0–14.0)	
LS mean[a] (95% CI)	11.6 (6.9–16.3)	6.2 (–0.4 to 12.8)	
LS mean difference (95% CI)	5.4 (–1.9 to 12.8)		0.1397[b]
Secondary outcomes			
Ventilator weaning at day 28			
n (%)	13 (65)	3 (30)	–
Missing, n	5	5	
Number of patients with ventilation weaning at least once	15	9	
Re-intubation	4/15 (27)	3/9 (33)	–
Ventilation weaning after re-intubation	4/15 (27)	1/9 (11)	–
Mortality			
Day 28			
n/non-missing (%)	4/19 (21)	2/7 (29)	1.000[c]
Missing, n	1	3	
Day 60			
n/non-missing (%)	5/19 (26)	3/7 (43)	0.6353[c]
Missing, n	1	3	
Day 90			
n/non-missing (%)	5/19 (26)	3/7 (43)	0.6353[c]
Missing, n	1	3	
Day 180[d]			
n/non-missing (%)	5/19 (26)	3/7 (43)	0.6353[c]
Missing, n	1	3	

Percentages are calculated using the N as the denominator except where indicated (invimestrocel group, N = 20; standard group, N = 10)

APACHE II Acute Physiology and Chronic Health Evaluation II, *IQR* interquartile range, *LS* least squares, PaO_2/F_IO_2 partial pressure arterial oxygen/fraction of inspired oxygen, *VFD* ventilator-free days

[a] Analysis of covariance using treatment group, age at enrollment (< 75 years, ≥ 75 years), PaO_2/F_IO_2 ratio (> 100 mmHg, ≤ 100 mmHg), and APACHE II score as covariates

[b] Wilcoxon rank sum test

[c] Fisher's exact test

[d] Those who completed the study before day 180 were considered alive

Intensive Care Med (2023) 49:1226–1228
https://doi.org/10.1007/s00134-023-07183-9

EDITORIAL

Back to the future: ARDS guidelines, evidence, and opinions

Luciano Gattinoni[1*], Giuseppe Citerio[2,3] and Arthur S. Slutsky[4,5]

Table 1 Enrolment rate in representative ARDS trials

Trials (years)	Number of patients	Partici-pating ICUs	Months	Rate (pts/month/ICU)
ARMA [7] (1996–1999)	861	10	36	2.39
ALVEOLI [8] (1999–2002)	549	23	29	0.82
LOV [9] (2000–2006)	983	30	68	0.48
EXPRESS [10] (2002–2005)	767	37	40	0.52
ACURASYS [11] (2006–2008)	340	20	24	0.71
PROSEVA [6] (2008–2011)	466	27	43	0.40
ART [12] (2011–2017)	1010	120	65	0.12
ROSE [13] (2016–2018)	1006	49	28	0.73
Very severe ARDS				
CESAR [14] (2001–2006)	180	103	61	0.03
EOLIA [15] (2012–2017)	240	64	64	0.06

- Average enrolment rate in major ARDS trials was < 1 patient/unit/month.
  - To achieve statistical power, a trial aiming for a credible outcome benefit of 6% from a baseline mortality rate of 40% requires > 2000 patients. (involving 25 centres would require approximately ten years)
    - ✓ Broadening the entry criteria to increase the enrolment rate would only increase heterogeneity and reduce the likelihood of success.
    - ✓ Conversely, setting unrealistic benefits—such as a 20–30% absolute decrease in mortality—inevitably leads to no treatment effect.

- How to overcome? Two approaches
  - The first is the improvement of clinical trials by using novel trial designs such as adaptive platform designs.
  - Rediscovering and emphasizing the importance of physiological studies, which can be integrated into classical trials.

Prone positioning First in Subtyped ARDS (PFiSAR)

Young-Jae CHO, MD, MPH, PhD

Department of Internal Medicine, Seoul National University College of Medicine,
Division of Pulmonary and Critical Care Medicine, Seoul National University Bundang Hospital

Timeline of criteria and directions in ARDS

	Previous criteria AECC	Current criteria Berlin	Short-term possible revisions	Future areas of research
	1994	2012	2022+	Onwards
Timing	Acute, not specified	New or worsening within 7 days		
Chest imaging	Bilateral infiltrates on chest radiograph	Bilateral infiltrates on chest radiograph (or CT)	Ultrasound	
Oxygenation	PaO_2/FiO_2 Acute lung injury <300 mm Hg ARDS <200 mm Hg	PaO_2/FiO_2 Mild >200 mm Hg to ≤300 mm Hg Moderate >100 mm Hg to ≤200 mm Hg Severe ≤100 mm Hg	SpO_2/FiO_2 ratio	
PEEP	Not specfied	Minimum PEEP 5 cm H_2O (continuous positive airway pressure in mild ARDS)	High-flow nasal oxygen, no requirement for minimum PEEP	
Origin of oedema	Pulmonary artery wedge pressure ≤17 mm Hg	Not fully explained by cardiac failure		
Biological markers	None	None		

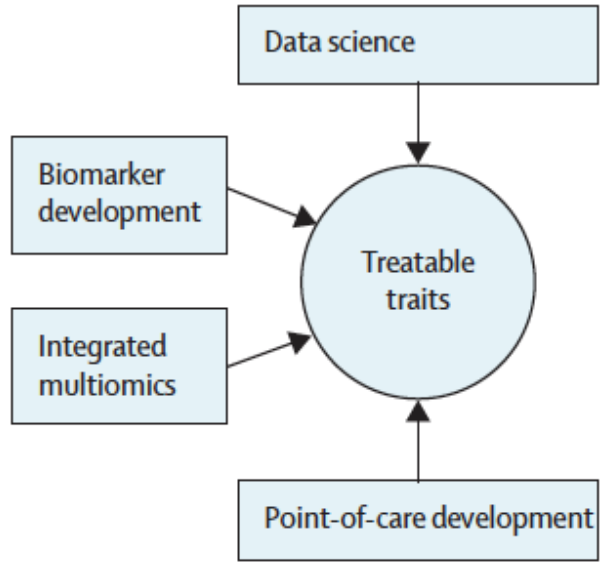


Figure 1: **Timeline of ARDS criteria and future directions**
The first consensus ARDS criteria were the AECC in 1994, followed by the Berlin Consensus Criteria in 2012. ARDS criteria are being revised and potential revisions are illustrated. The future of ARDS in the era of precision medicine strives towards identifying treatable traits. AEEC=American–European Consensus Criteria. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen. SpO_2=oxygen saturation. ARDS=acute respiratory distress syndrome. PEEP=positive end expiratory pressure.

Lancet 2022; 400: 1157–70

Importance of Sub-Phenotype

- Phenotype: Clinically observable set of traits resulting from an interaction of genotype and environmental exposure (Ex. ARDS is a phenotype)
- Sub-Phenotype

: Distinct subgroup that can be reliably discriminated from other subgroups based on a set or pattern of observable or measurable properties.

: Sub-phenotypes should also be reproducible in different populations

- Short term (up to day 90) mortality was different between sub-phenotypes
  - ✓ Systemic inflammatory response by plasma proteins (IL-6, Interferon gamma, angiopoietin 1,2, Plasminogen activator inhibitor-1)
    : *Hyper-inflammatory > Hypo-inflammatory*
  - ✓ **Lung radiographic morphology**: ***Non-focal > focal***
  - ✓ Recruitabillity : *Recruitable > Non-recruitable*
  - ✓ Organ failure / Comorbidities / Acidosis
  - ✓ Longitudinal changes in respiratory parameters *: Upward trajectory of ventilatory ratio > steady trajectory*

ARDS Sequential interventions

Sequential Interventions

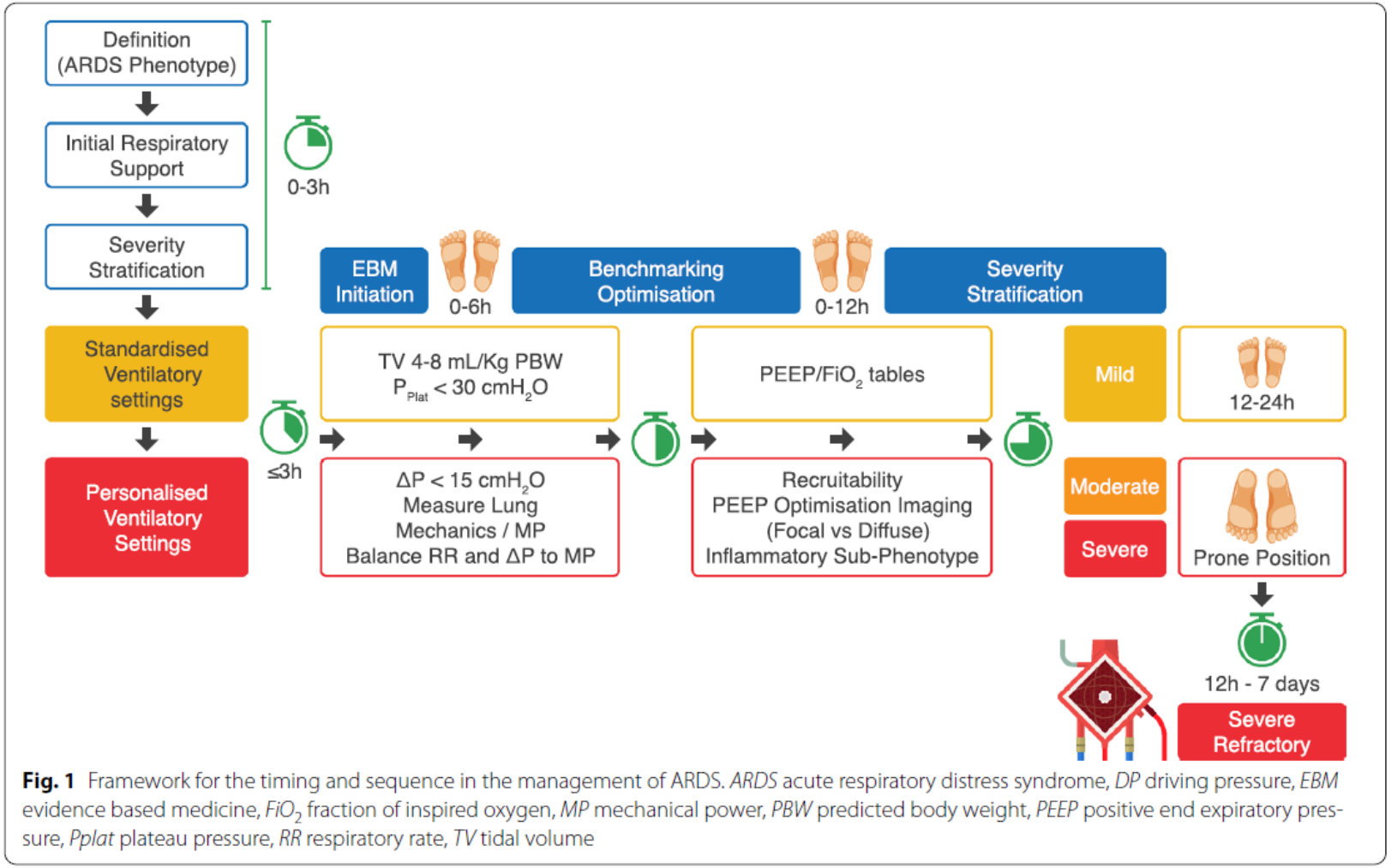


Fig. 1 Framework for the timing and sequence in the management of ARDS. *ARDS* acute respiratory distress syndrome, *DP* driving pressure, *EBM* evidence based medicine, *FiO_2* fraction of inspired oxygen, *MP* mechanical power, *PBW* predicted body weight, *PEEP* positive end expiratory pressure, *Pplat* plateau pressure, *RR* respiratory rate, *TV* tidal volume

Rescue therapies for ARDS

- Single: Prone positional ventilation(A), Systemic steroid(B), Inhaled NO*(C)
- Combination 1: A+B, A+C, B+C
- Combination 2: A+B+C, A+B+C + ECMO*(D)

*NO: nitric oxide, ECMO: extracorporeal membrane oxygenation

	The Intensive Care Society and the Faculty of Intensive Care Medicine[49]	The French Intensive Care Society[50]	The American Thoracic Society, European Society of Intensive Care Medicine, and the Society of Critical Care Medicine[51]	WHO living guideline (COVID-19 ARDS)[14]
Non-invasive ventilation	..	..	..	Conditional recommendation in mild ARDS
Lung protective ventilation	Recommended	Recommended	Recommended	Recommended
Prone positioning	Recommended in moderate-to-severe ARDS	Recommended PaO_2/FiO_2 ratio <150 mm Hg.	Recommended in severe ARDS	Recommended PaO_2/FiO_2 ratio <150 mm Hg
High positive end expiratory pressure strategy	Recommended in moderate-to-severe ARDS.	Recommended in moderate-to-severe ARDS	Recommended in moderate-to-severe ARDS	Conditional recommendation for moderate-to-severeARDS
Driving pressure	..	No recommendation due to insufficient evidence	Research recommendation	Consider driving pressure as part of an individualised positive end expiratory pressure titration strategy
Spontaneous ventilation	..	No recommendation due to insufficient evidence	Research recommendation	..
Recruitment manoeuvres	..	Not recommended	Not routinely recommended	..
High-frequency oscillatory ventilation	Not recommended	Not recommended	Not recommended	..
Extracorporeal membrane oxygenation	Recommended in severe ARDS	Recommended when PaO_2/FiO_2 ratio is <80 mm Hg or lung protective ventilation is not possible	Research recommendation	Conditional recommendation for when PaO_2/FiO_2 ratio is <80 mm Hg despite lung protective ventilation
Extracorporeal carbon dioxide removal	Research recommendation	No recommendation due to insufficient evidence	Research recommendation	..
Conservative fluid strategy	Recommended	..	..	Recommended
Neuromuscular blockade	Recommended in early moderate to severe ARDS	Recommended in early ARDS with a PaO_2/FiO_2 ratio of <150 mm Hg	..	Not routinely recommended for all patients
Inhaled vasodilators	Not recommended	Can be used when hypoxaemia persists despite lung protective ventilation and prone position, and before extracorporeal membrane oxygenation	..	..
Corticosteroids	Research recommendation	..	..	Recommended
Other pharmacological agents	..	..	..	IL-6 receptor blockers (eg, tocilizumab or sarilumab) or baricitinib (Janus kinase inhibitor) is a strong recommendation; monoclonal antibodies (casirivimab and imdevimab) is a conditional recommendation for patients who are seronegative

ARDS=acute respiratory distress syndrome. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen.

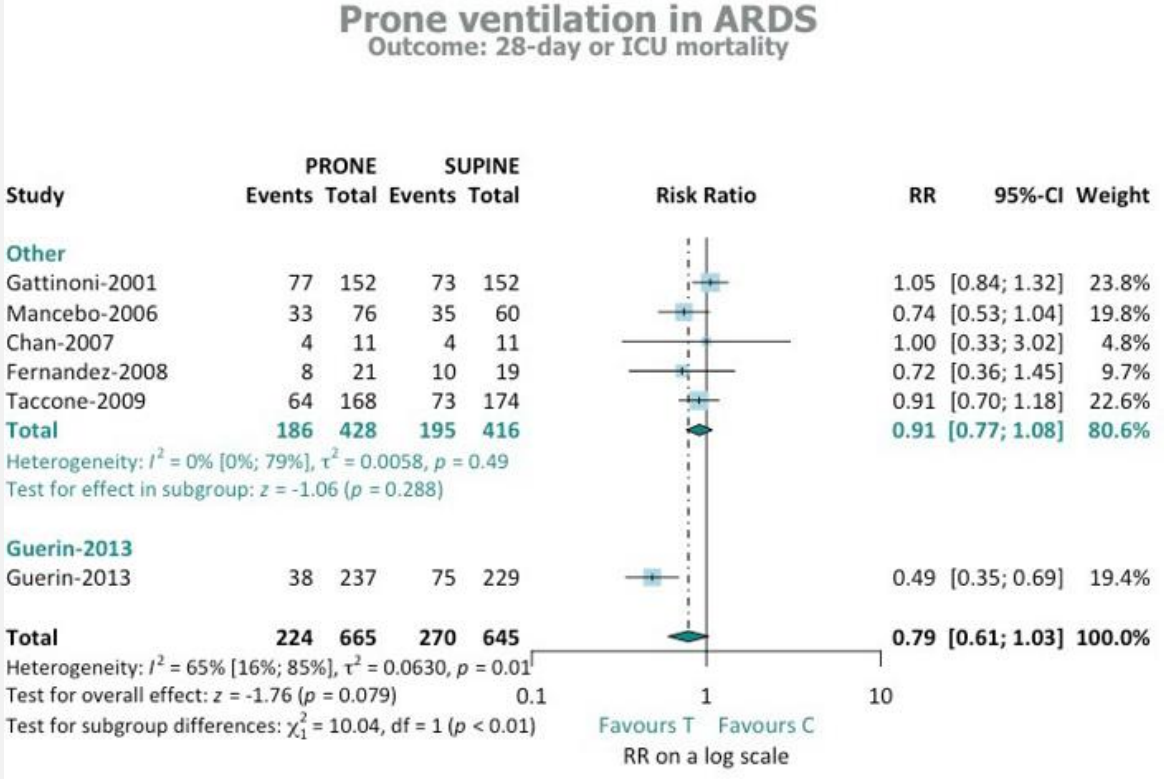
Lancet 2022; 400: 1157–70

Why Prone positioning First?

Most evident and efficacy, No additional cost

- Improve oxygenation, better homogenization of lung stress, decrease of RV strain
- PROSEVA trial (Prone positioning in Severe ARDS, 2013): Multicenter, prospective RCT (466 patients)

  - *Short term mortality*: Significant lower in PROSEVA trial (RR 0.49 95% CI [0.35–0.69])



Recommendation 7.1

We **recommend** using prone position as compared to supine position for patients with moderate-severe ARDS (defined as $PaO_2/FiO_2 < 150$ mmHg and PEEP $\geq$ 5 cmH_2O, despite optimization of ventilation settings) to reduce mortality.
Strong recommendation, high level of evidence in favor.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; moderate level of evidence in favor for indirectness.

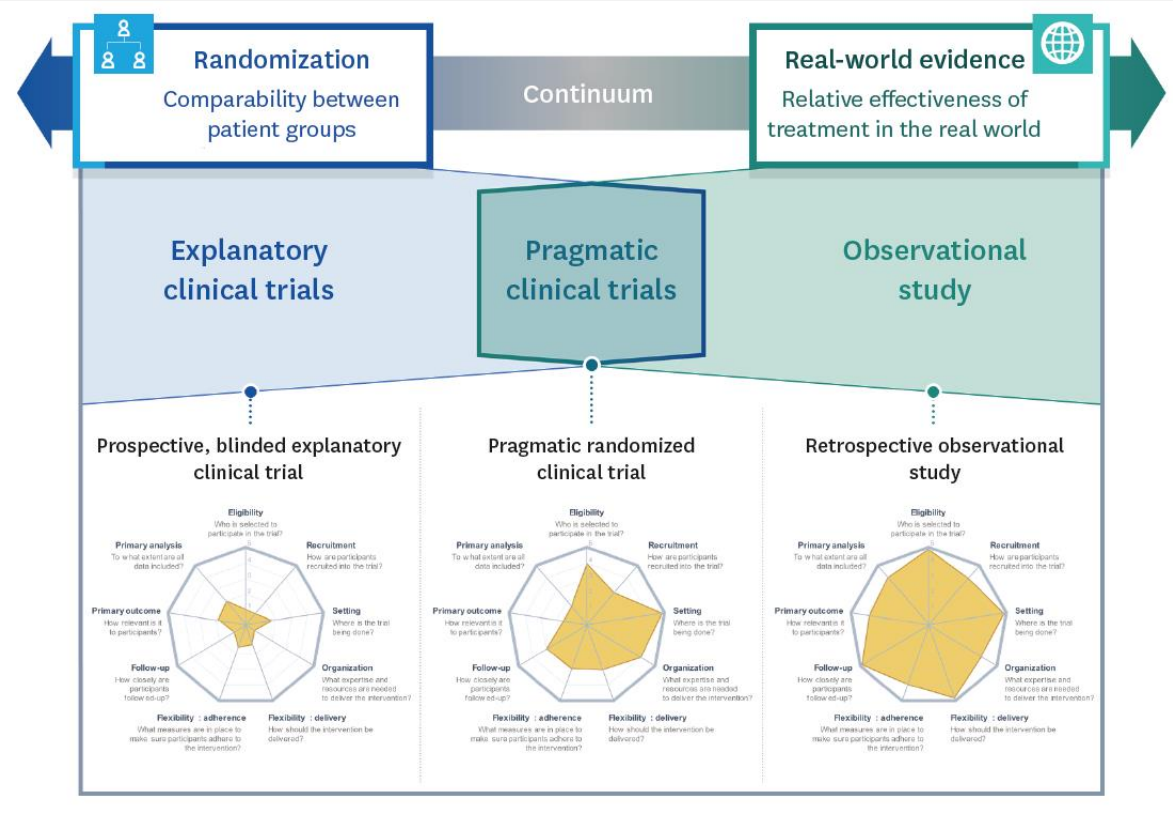
Recommendation 7.2

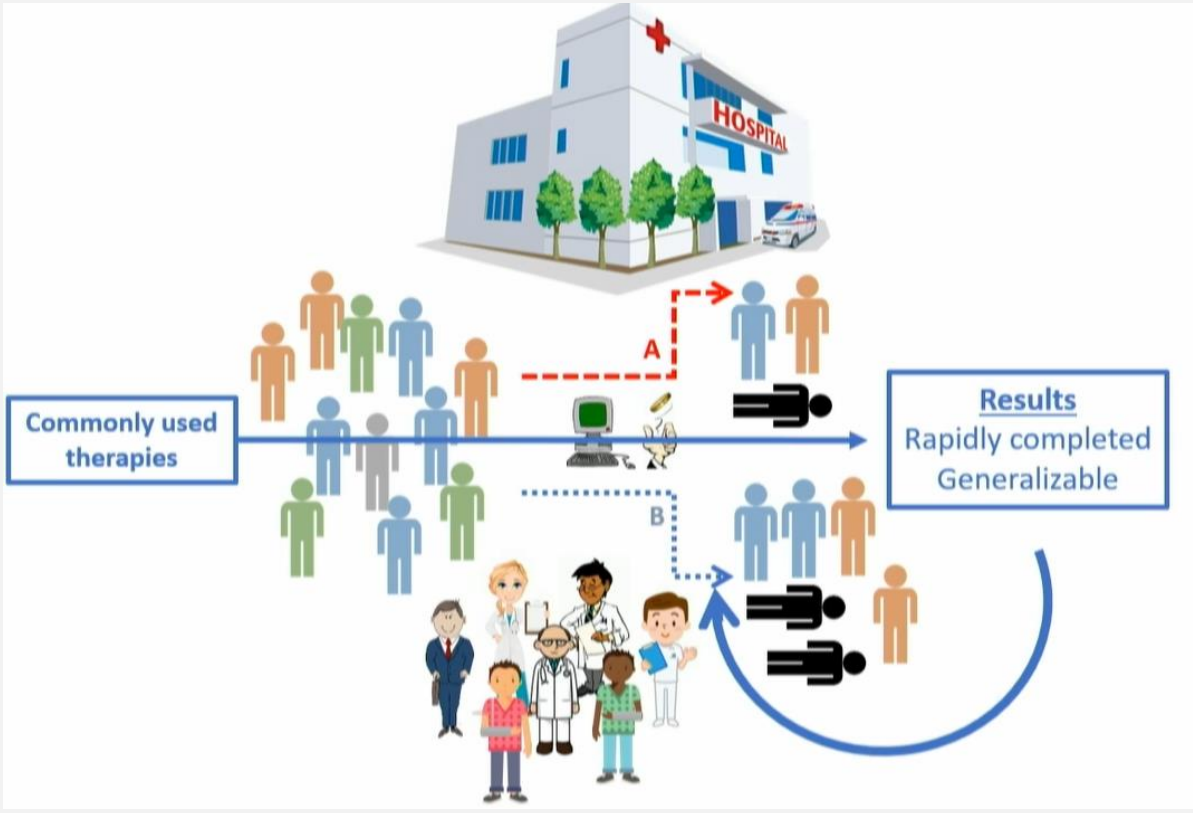
We **recommend** starting prone position in patients with ARDS receiving invasive mechanical ventilation early after intubation, after a period of stabilization during which low tidal volume is applied and PEEP adjusted and at the end of which the PaO_2/FiO_2 remains < 150 mmHg; and proning should be applied for prolonged sessions (16 consecutive hours or more) to reduce mortality.
Strong recommendation; high level of evidence in favor.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; moderate level of evidence in favor for indirectness.

Why Pragmatic trial?

- **Pragmatic Trial**: Examining effectiveness of interventions in **real-world conditions** using broad eligibility criteria, patient-centered outcomes, and embedding of trial procedures into clinical care

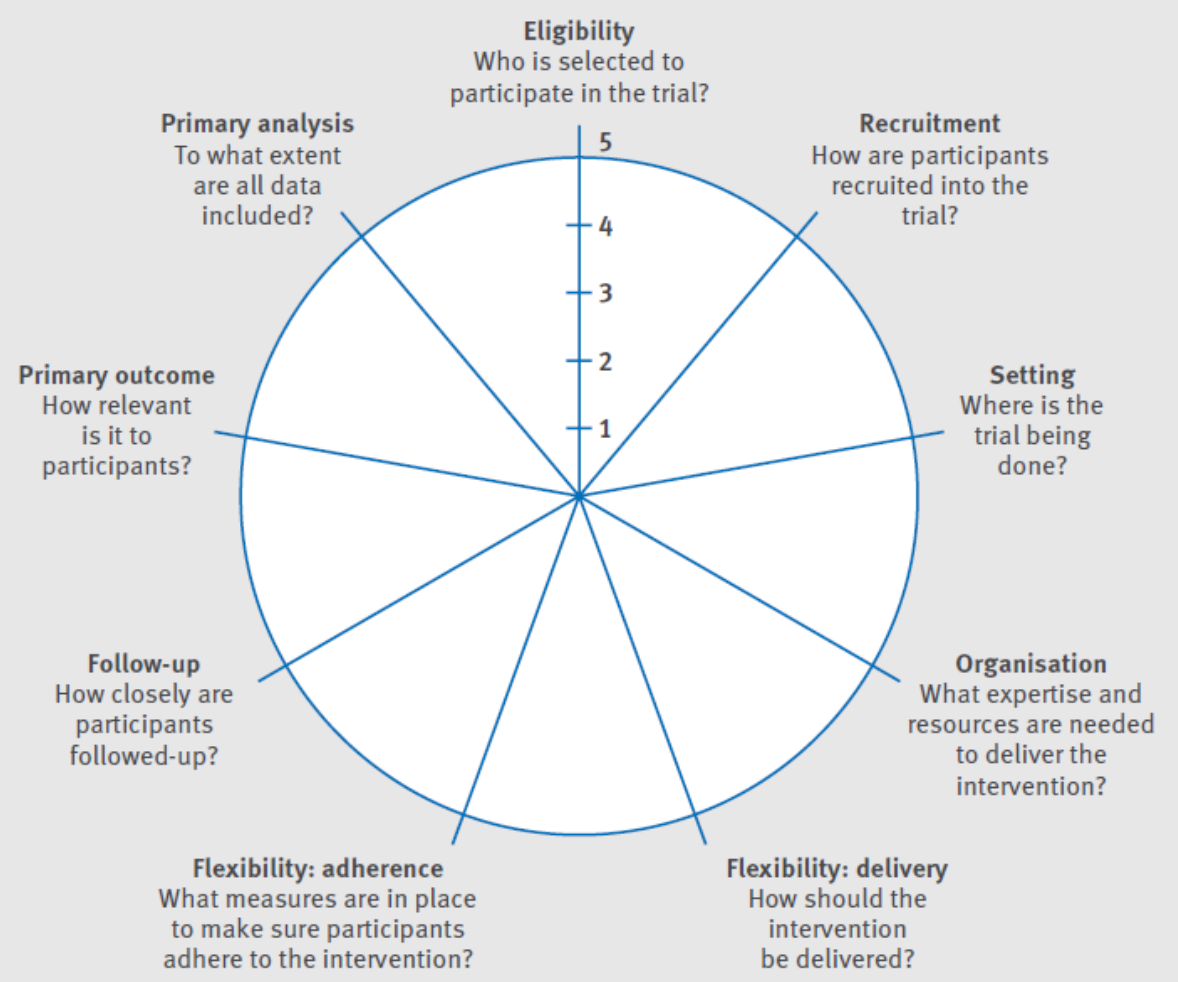




Cardiovasc Prev Pharmacother. 2020; ATS 2023 Next Generation Critical Care Trials

Explanatory vs. Pragmatic

9 domains



1. *Eligibility*—To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
2. *Recruitment*—How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
3. *Setting*—How different are the settings of the trial from the usual care setting?
4. *Organisation*—How different are the resources, provider expertise, and the organisation of care delivery in the intervention arm of the trial from those available in usual care?
5. *Flexibility (delivery)*—How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?
6. *Flexibility (adherence)*—How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
7. *Follow-up*—How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?
8. *Primary outcome*—To what extent is the trial's primary outcome directly relevant to participants?
9. *Primary analysis*—To what extent are all data included in the analysis of the primary outcome?

BMJ 2015;350:h2147

Explanatory vs. Pragmatic

	Explanatory trials	Pragmatic trials
Patient population	Inclusion criteria are tight, often with multiple exclusion criteria, intended to minimise the number of patients needed to detect a treatment effect, including any of the following approaches: • Creating a homogeneous trial population (to minimise statistical noise) • Enrolling patients who are likely to respond to the treatment (predictive enrichment) • Enrolling patients who are likely to experience the primary outcome (prognostic enrichment) • Excluding patients who are expected to have poor adherence to treatment or follow-up • Excluding patients with comorbidities that might lead to poor outcomes through mechanisms other than those targeted by the trial intervention (competing risks) • Excluding patients at high risk of adverse events on the basis of their age or comorbidities	Inclusion criteria are broad, with few exclusions; trial population tends to be larger and more similar to those who receive treatment as part of usual care
Recruitment and enrolment	Screening and enrolment are conducted by a research team, separate from treating clinicians	Screening (identification of trial candidates) and enrolment are conducted by treating clinicians (embedded in routine care)

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Explanatory vs. Pragmatic

	Explanatory trials	Pragmatic trials
Delivery of intervention	Intervention is delivered by the research team in a way that differs from delivery in usual care, including the following approaches: • Providing additional study-specific resources (eg, a study physician dedicated solely to ventilator titration for enrolled participants) • Providing substantial levels of trial-specific training on the delivery of the intervention beyond what would be available during future clinical use • Using experts to deliver the intervention (eg, using plastic surgeons in a trial that compares available techniques for repairing lacerations even though this is normally done by emergency medicine physicians in routine care) • Incorporating additional measures to improve adherence to treatment • Incorporating co-interventions into the protocol to minimise variability	Intervention is delivered in the way that it would be delivered as part of usual care outside of a trial (eg, by treating clinicians without any additional trial-specific resources or training)
Follow-up	Follow-up is more intense than would occur in usual care, and can include: • Additional research visits • Follow-up phone calls to increase treatment adherence or measure outcomes • Clinical visits triggered by study outcomes or adverse events in a way that might mitigate their severity	Treatment and follow-up are performed as they would be in usual care with minimal (if any) trial-specific follow-up
Primary outcome	Outcomes might not be relevant to patients (eg, surrogate outcomes, biomarkers, laboratory or radiographic outcomes) or might require testing that would not occur in usual care (adjudication of the primary outcome(s) by a blinded panel of experts, study-specific imaging, biopsies)	Patient-centred outcomes are routinely available from data collected as part of usual care (eg, mortality, intubation, hospital admission)

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Explanatory vs. Pragmatic: Examples

	Study population and enrolment	Interventions and study type	Sample size	Duration	Outcomes	Findings
Explanatory acute care trials						
Trial of 12 mL/kg *vs* 6 mL/kg tidal volume positive-pressure ventilation for treatment of acute lung injury and ARDS (ARMA)[41]	Highly selected population of patients (≥18 years) with ARDS recruited by a dedicated research team at multiple sites in the USA	Traditional ventilator management (an initial tidal volume of 12 mL/kg ideal bodyweight) versus ventilation with a lower tidal volume (6 mL/kg ideal bodyweight); protocol specified tight control of all ventilator management and co-interventions such as ventilator weaning; multicentre, randomised controlled trial	861 patients randomly assigned (1:1) to traditional ventilator management (n=429) or ventilation with a lower tidal volume (n=432)	3 years (287 patients per year)	Primary outcomes: death before discharge home and number of ventilator-free days from day 1 to day 28; additional outcomes included extensive physiological data and biomarkers	Ventilation with lower tidal volumes reduced mortality
Pragmatic acute care trials						
Isotonic Solutions and Major Adverse Renal events Trial (SMART)[33]	All patients (≥18 years) admitted to one of five ICUs at an academic medical centre during the study period; enrolment, intervention delivery, and outcome assessment using electronic health records	Physiologically balanced isotonic crystalloids (lactated Ringer's solution or Plasma-Lyte A, according to treating clinician's preference) versus 0·9% saline; intervention delivery embedded into routine clinical care; open-label, cluster-randomised, multiple-crossover trial	15 802 patients randomly assigned (according to randomisation unit) to balanced crystalloids (n=7942) or saline (n=7860)	2 years (7901 patients per year)	Primary outcome: major adverse kidney event within 30 days (composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction)	Use of balanced crystalloids reduced the rate of death from any cause, new renal-replacement therapy, or persistent renal dysfunction

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Advantages of Pragmatic trials

	ORCHID trial	RECOVERY trial
Design	Explanatory	Pragmatic
Patient population	Patients admitted to hospital with COVID-19	Patients admitted to hospital with COVID-19
Study setting	34 academic medical centres	176 hospitals (range of urban or rural, academic or community hospitals)
Intervention(s)	Hydroxychloroquine	Hydroxychloroquine, corticosteroids, lopinavir–ritonavir, azithromycin, tocilizumab, convalescent plasma
Control	Placebo (blinded)	Usual care (unblinded)
Screening and enrolment	Research team	Treating clinicians
Consent	Research team using seven-page informed consent document	Treating clinicians using one-page consent document
Drug delivery	Investigational pharmacy (placebo-controlled)	Clinical pharmacy
Safety monitoring	Daily assessments by research staff during the intervention period; electrocardiography according to protocol; systematic collection of safety outcomes	Patients monitored as they would be in usual care; no study-specific adverse event monitoring; systematic collection of safety outcomes[71]
Data collection	Manual collection with follow-up phone calls	Limited to in-hospital outcomes available in electronic health records
Patients enrolled from March 2020 to June 2020[31,72] (proportion of reported cases)[73,74]	479 patients (1 in 5000 of the 2·2 million cases reported in the USA)	11 874 patients* (1 in 25 of the 300 000 cases reported in the UK)
Results	Hydroxychloroquine is highly unlikely to improve clinical status at 14 days after initiation of treatment	Hydroxychloroquine, lopinavir–ritonavir, azithromycin, and convalescent plasma are highly unlikely to improve mortality; dexamethasone and tocilizumab improve mortality

ORCHID=Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among Inpatients With Symptomatic Disease. RECOVERY=Randomised Evaluation of COVID-19 Therapy. *Enrolment continues in the RECOVERY trial, which had enrolled more than 45 000 patients as of May 31, 2022.

Table 3: **Comparison of ORCHID and RECOVERY trials in patients with COVID-19**

- **Real-World Evidence**
  - Capture data in real-world settings, enhancing the external validity and applicability of findings.
- **Diverse Population**
  - Include a broader patient population, reflecting the variability in treatment responses.
- **Practical Insights**
  - Offer practical insights into the effectiveness of interventions in routine clinical practice.
- **Cost-Effective**
  - Often more cost-effective due to less stringent controls and monitoring.
- **Policy and Practice Impact**
  - Directly inform health policy and clinical practice due to their real-world nature.

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KATRD RG proposal: “Intensive Care”

Effects of early prone positioning on the clinical prognosis of Acute Respiratory Distress Syndrome (ARDS) patients : a pragmatic randomized clinical trial

1. Objectives

- 흡인성 폐렴에 의한 ARDS로 중환자실에 입실한 환자에게 다양한 구조요법 중 복와위 환기의 선제적 조기 적용이 예후에 미치는 영향을 알아보기 위한 실용적 전향적 무작위비교 임상시험을 시행하는 것임.
- 또한, 다양한 구조요법 적용 대상자 선별에 현장 초음파 검사가 유용하고 안전하게 활용될 수 있을지 함께 알아보고자 함.

2. Rationale

- ARDS의 치료방법은 오랜 시간에 걸쳐 발전 되어 왔으나, 원인이 다른 이질적인 ARDS의 특성 상 환자에 따라 상이한 치료가 다양하게 적용되며, 다양한 약물적/비약물적 치료가 미치는 영향 또한 매우 상이함.
- 각 치료법이 생존율과 예후에 미치는 영향을 완전히 통제된 상황을 가정하고 분석하는 기존의 설명적, 실험적 무작위 대조 임상연구로 설명하기엔 한계가 있음.

3. Methods

- 흡인성 폐렴에 의한 ARDS 환자들을 대상으로, 인구학적 정보, 임상 정보, 각종 검사 결과(현장 초음파 포함), 기타 설문조사지 정보를 수집함.
- ARDS 발생 기전에 따른 아형 중 흡인성 폐렴에 해당하는 군에 복와위 환기 선제 적용 여부를 무작위 배정한 후 제28일 사망률을 비교함.

4. Endpoint

- 유효성 평가: 급성호흡곤란증후군의 임상 경과, 사망률, 치료 효과 및 단, 장기적 예후에 영향을 미치는 인자를 알아봄.
- 안전성 평가: 시행하는 일련의 검사는 임상진료지침에 따라 임상적 필요에 의해 시행하며, 현장 초음파를 적용하여 진단에 보조할 경우 보다 안전하면서도 아형 선택에서의 진단적 가치가 높아지는지 평가해 봄.

Feasibility

✓ 연구대상자 수 산출 계산에 따라 최소 군당 86명(86 x 0.95 = 81.7>81), 총 172명(86 x 2) 등록이 필요할 것임.
(참여기관 당 평균 20명 등록 기준, 6개 이상 참여; 주관기관 50명 이상 등록 목표).

✓ 평균적으로 중환자실 입실 환자의 20% 정도가 ARDS 진단됨. 주관기관 월 2-3명, 참여기관당 월 1-2명 이상 등록 시 1년 반 동안 목표 연구대상자 등록 가능.

✓ 연구 등록을 위한 서면 동의 면제로 IRB 심의 계획임.

✓ 주관 연구기관에서는 e-CRF 및 현장 초음파 시행 표준 프로토콜을 제공할 예정임.

KATRD RG proposal: “Intensive Care”

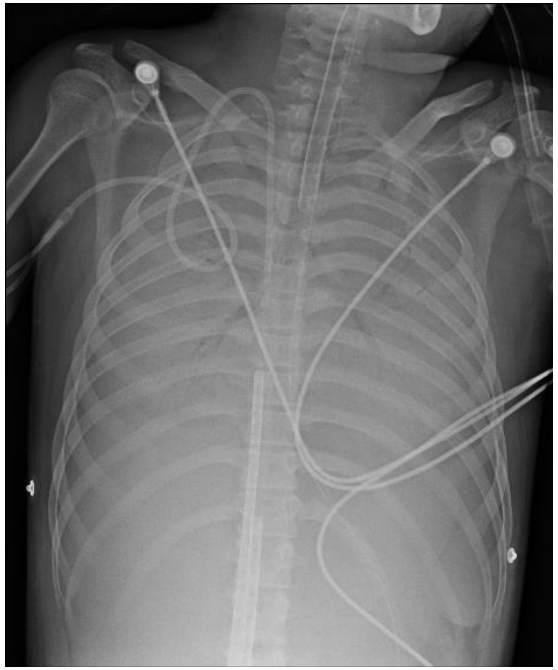
Inclusions & Exclusions

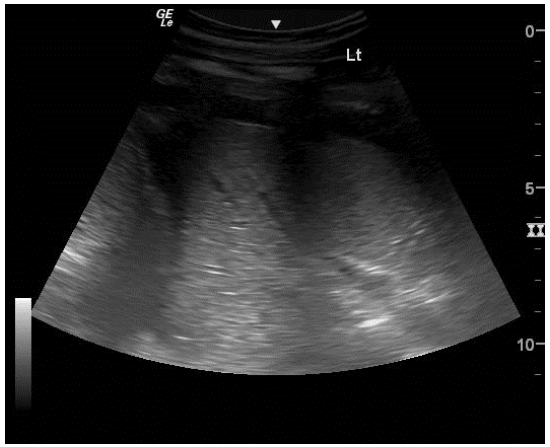
1) 선정기준
a. 시험 선정 시점 연령 만 19세 이상; b. 남성 및 임신하지 않은 여성
c. ARDS 환자: 심부전, 체액 과부하, 폐엽/폐 허탈, 삼출/결절로 완전히 설명되지 않는 양측성 음영(X-ray, CT, 현장 초음파)을 보이며 PEEP ≥5 cmH2O 또는 고유량산소요법으로 ≥30 L/min의 산소를 사용 중 PaO2/FiO2 <300 mmHg 또는 SpO2/FiO2 ≤315 에 해당.
d. 아형 구분
i. 폐렴(Pneumonia), ii. 흡인(Aspiration); iii. 패혈증(Sepsis), iv. 그외 다른 2차적 원인
e. 무작위배정 전, 4시간 이상 동안 지속적으로 PaO2/FiO2 ≤300 mmHg 소견이 관찰되는 저산소증
f. 마지막 ARDS 진단 기준(개정된 기준)을 처음으로 충족한 시점부터 무작위배정까지의 시간은 48시간 이내

2) 제외기준
a. 무작위배정 전 4시간 이내 PaO2/FiO2 >300 mmHg (정의상 ARDS에서 벗어난 경우)
b. 나이 85세 이상, 다발성 장기부전, 급성 출혈 등의 구조요법 중 ECMO/ECCO2R 적용이 불가능하다고 판단된 환자
c. 24시간의 생존이 기대되지 않는 임상적 빈사 상태(Moribund participants)
d. 침습적 기계 환기의 예상 기간이 48시간 미만(임상적 판단)
e. 장기/가정 산소 사용이 필요한 동반 이환 또는 비침습적 환기, 또는 환기 이탈 자체를 불가능하게 하는 병력
f. 연기흡입 손상, 광범위 화상 또는 외상/두부 손상의 동반 상태; g. 폐전절제술 또는 폐이식의 이력; h. 혈관염으로 인한 미만성 폐포 출혈; i. 현재의 폐 악성종양(폐전이 포함), 또는 1개월 이내 화학요법 또는 방사선을 필요로 한 기타 악성종양;
j. 신대체요법(예: 혈액투석)의 이력을 동반한 만성 신장 질환; k. 만성 간 질환 Child-Pugh C 등급; l. 만성 심부전 NYHA IV
m. 기타

Key interventions of this study

- **PPV First**
- **Sub-phenotyping aspiration pneumonia by Lung US: “C” pattern +- PLAPS in R4/L4**





Timeline and Randomization

N=172*	Study period					
	Enroll & Allocation	On-study				Termination
Timepoint	ICU admission	ICU day 1	ICU day 4	ICU day 7	ICU day 14	28 days after enrollment
Enrollment: Screened Allocation	 X X					
Interventions: Prone First Screening for contraIx Added other	 X	 X X	 X X	 X X	 X X	
Assessments: Baselines CXR Lung US Labs	 X X X X	 X X X X	 X X X X	 X X X X	 X X X X	
Primary outcomes:						X

* Study Parameters: Incidence, group 1 vs. 2 40% vs. 20% (Alpha 0.05, Beta 0.2, Power 0.8)

	Time	First
2025	Sep Oct Nov Dec	Prone Prone
2025	Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec	Prone Prone Prone Prone Prone Prone
2026	Jan Feb	Prone

Intensive Care Med (2025) 51:137–139
https://doi.org/10.1007/s00134-024-07760-6

EDITORIAL

Gattinoni's Legacy: Personalizing ARDS Management Through Physiology

Richard Greendyk[1,2,3], Ewan C. Goligher[1,2,4,5] and Arthur S. Slutsky[4,6*]

Pesenti *et al. Critical Care* (2024) 28:423
https://doi.org/10.1186/s13054-024-05210-9

Critical Care

OBITUARY **Open Access**

Luciano Gattinoni: a tribute to a pioneer in intensive care medicine

Antonio Pesenti[1*], Gaetano Iapichino[1] and Jean Louis Vincent[2]

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Obituary: Luciano Gattinoni

Last updated : 06/12/2024 - 30100 views

In Memory of Professor Luciano Gattinoni

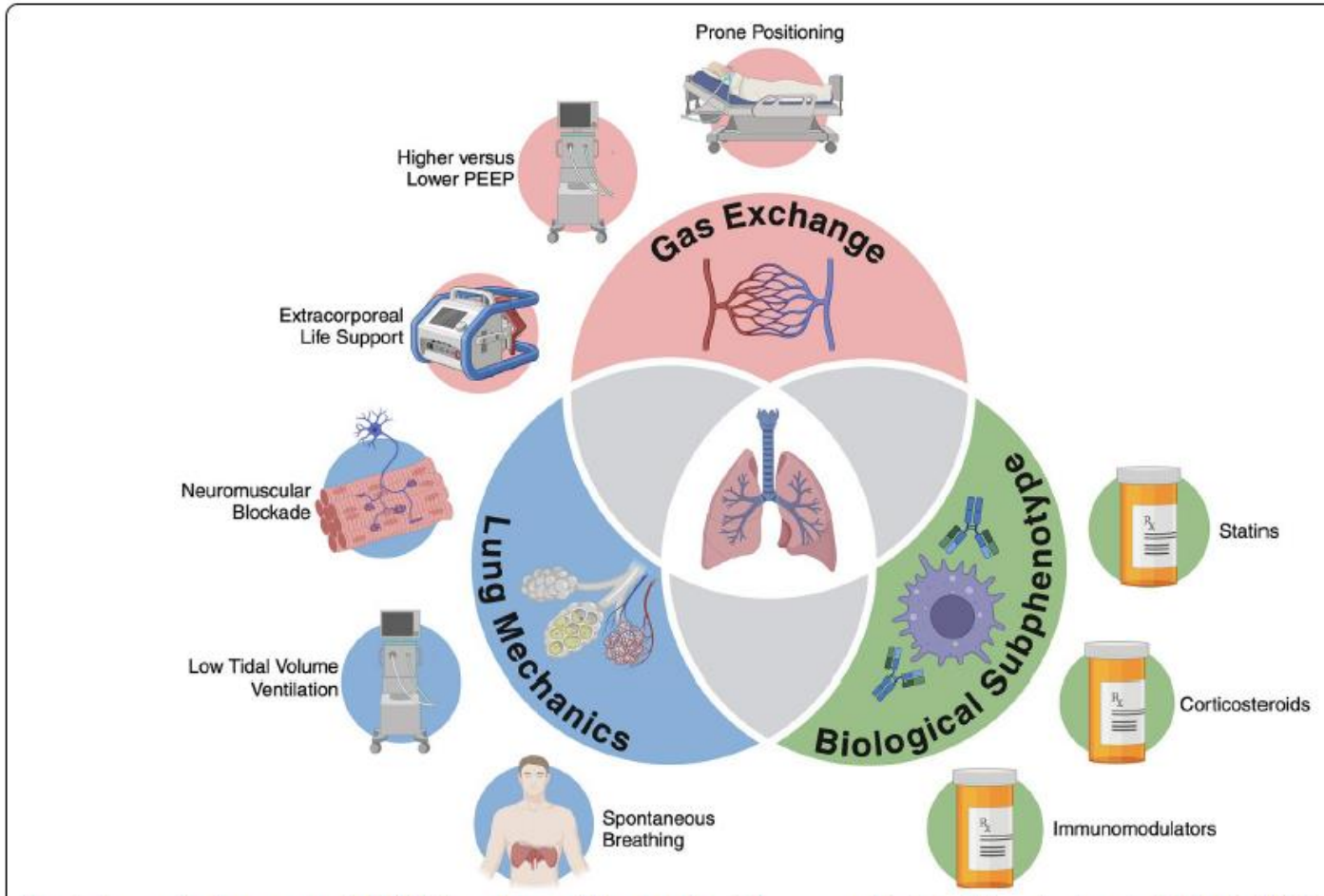


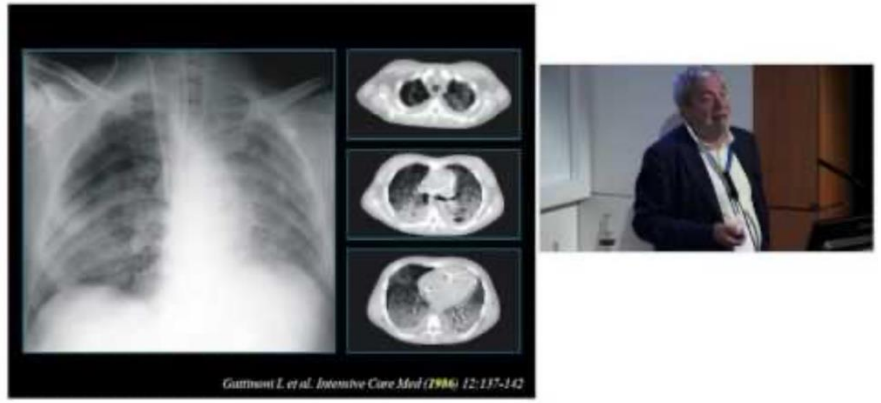
Fig. 1 Personalized management of ARDS based on multiple domains of disease severity. In the future, treatment selection in ARDS could depend on a multi-dimensional assessment of ARDS severity, where each domain reflects different relevant mechanisms of action and different therapeutic targets (e.g., lung recruitment versus lung stress versus hyperinflammatory state)

EDITORIAL

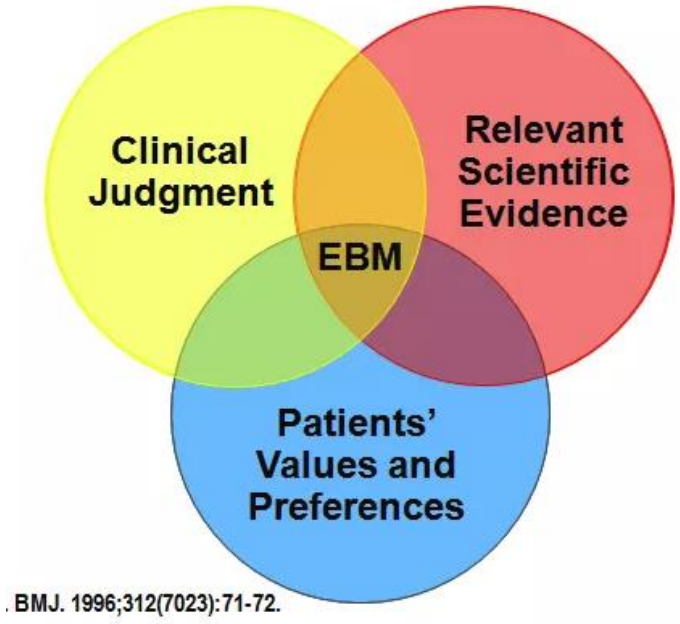
Definitions, guidelines and opinions: the white, the black and the grey

Luciano Gattinoni*

- It is, therefore, worthwhile to question the real value of guidelines in defining and managing ARDS, especially today when two leading societies have issued markedly different recommendations for three key aspects: positive end-expiratory pressure (PEEP) selection, venovenous extracorporeal membrane oxygenation (VV-ECMO) indications, and use of neuromuscular blockade.
- Guidelines are a collaborative effort by experts who, through a combination of scientific evidence and personal opinions, produce recommendations. The generation of evidence relies heavily on the analysis of randomised clinical trials (RCTs), and methods like the Delphi technique for consensus building, culminating in a “democratic” vote.
- The major limitations of RCTs in providing scientific evidence are clear: they typically include a small fraction of screened patients (about 10%) and overlook fundamental aspects of medicine such as patient history, age, prior health status, and comorbidities, which are theoretically neutralised by randomisation.
- The production of “evidence” has become a profession and an industry, characterised by rising costs, and rules dictated by professional trialists. Consequently, common clinical sense is sometimes lost.
- This highlights the limitations of relying solely on RCTs for guideline development. However, the "recent evidence" from guidelines suggests that opinions frequently outweigh the evidence provided by RCTs.
- The recent differences in the guidelines produced by the American Thoracic Society (ATS) and the European Society of Intensive Care Medicine (ESICM) clearly underline these issues. I will limit my discussion to PEEP selection and VV-ECMO indication.
- From this simple “evidence”, a complicated methodological approach led ESICM to conclude, and I paraphrase: “choose the PEEP you prefer” and the ATS: “you should use higher PEEP” (following the PEEP/FiO_2 table, which recommend, as an example, a PEEP of 16 when the set FiO_2 is 40%!).
- In this framework, with similar levels of evidence (negative trial!), the ESICM strongly recommended against extracorporeal CO_2 removal and strongly recommended in favour of ECMO when in accordance with the EOLIA protocol. In contrast, the ATS opted for a more prudent recommendation.
- In summary, the recent guidelines for ARDS treatment from ATS and ESICM cast reasonable concerns about their usefulness and applicability.
- Before doing so, it is interesting to consider that the ARDS approach currently undertaken by the intensivists is the exact opposite to that of oncologists.
- My belief is that in the intensive care practise, which focuses on symptomatic treatment to sustain life until the underlying disease is resolved, the most logical approach is to identify the mechanisms at play in a given patient. For example, ventilatory treatment in ARDS cannot be rationally applied without understanding lung volumes and esophageal pressures, which are crucial for estimating lung strain and stress. Whilst guidelines can be useful in certain situations, their creation and application should not replace medical reasoning, which is aimed at addressing individual patient needs rather than population-wide issues.



Intensive Care Med (2024) 50:934–936



BMJ. 1996;312(7023):71-72.

Thank you for your attention

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