Review

What is New in Management of ARDS

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Acute Respiratory Distress Syndrome (ARDS) was first described in 1967 by Dr Ashbaugh & colleagues based on oxygenation status and infiltrates in the lung.[1] Over the years, modifications were made to make the definition more inclusive and comprehensive.

Currently accepted definition is known as the Berlin definition.[2] There is a widely accepted modification for resource limited setting as well, known as Kigali modification.[3] The definitions are described in the table below.

	AECC definition	**Berlin criteria**	**Kigali modification of Berlin criteria**
Timing	Acute onset	Within 1 week of a known clinical insult or new worsening respiratory symptoms	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	PaO_2/ FiO_2 ≤ 200 mmHg [defined as acute lung injury if ≤ 300 mmHg	Mild: PaO_2/ FiO_2 > 200 mmHg but 300 mmHg Moderate: PaO_2/ FiO_2 > 100 mmHg but ≤200 mmHg Severe: PaO_2/ FiO_2 ≤ 100 mmHg	SpO_2 / FiO_2 ≤ 315
PPEP requirement	None	Minimum 5 cmH_2O PEEP required by invasive mechanical ventilation (noninvasive acceptable for mild ARDS)	No PEEP requirement, consistent with AECC definition
Chest imaging	Bilateral infiltrate seen on frontal chest radiograph	Bilateral opacities not fully explained by effusion, lobar/lung collapse or nodules by chest radiograph or CT	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules by chest radiograph or ultrasound
Origin of oedema	Pulmonary artery wedge pressure < 18 mmHg when measured or no evidence of left atrial hypertension	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)	Respiratory failure not fully explained cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)

PEEP: positive end-expiratory pressure; PaO_2: arterial oxygen tension; FiO_2: inspiratory oxygen fraction; SpO_2: arterial oxygen saturation measured by pulse oximetry; CT: computed tomography

Novel research has found that there is clinical and biologic heterogeneity among ARDS patients which might affect response to different treatments and also differ in prognosis. Based on it, ARDS is classified into various physiological, clinical and biological phenotypes and sub-phenotypes. Further research guided towards precision medicine in different phenotypes of ARDS, holds promise of changing clinical and prognostic trajectory of ARDS[4]

ARDS in Cancer Patients

Cancer patients have higher susceptibility of getting ARDS due to primary lung insults like pneumonia, aspiration, surgery etc. However, some secondary causes are specific to malignancy and the treatment related to it like drug toxicity, radiation toxicity, hypertransfusion, post haematopoetic stem cell transplantation (HSCT), sepsis, or septic shock that originates from extrapulmonary infections or non-infectious etiologies.[5]

An important primary cause of ARDS, specific to certain malignancies include ALI/ARDS due to pulmonary spread of tumor i.e. Lymphangitic Carcinomatosis and Pulmonary Leukostasis. Diagnosis and management of ARDS can be complex in a cancer patient due to multiple associated conditions. Also, mortality and morbidity of a cancer patient with ARDS is higher than general population.[5] The corner-stone of management remains identifying and correcting the inciting factor and at the same time preventing ventilator induced lung injury (VILI). Immunomodulators and other phenotype guided novel therapies are still under research and not yet established. However, early prognostication and rationalisation of treatment is necessary in cancer patients.[5]

Management Strategy of ARDS

A. Oxygen therapy

Primary component of ARDS definition is hypoxaemia. So, delivery of oxygen remains the main stay of treatment. The superiority of one modality above the other is still debated. However, based on the latest literature by the European Society of Intensive Care medicine, following is recommended.[6]

1. High frequency nasal cannula (HFNC) reduces risk of intubation over conventional oxygen therapy (COT), hence recommended in acute hypoxemic respiratory failure (AHRF), however, there is no difference in mortality.
2. No recommendation for HFNC or Non-invasive ventilation (NIV) being superior to the other in reducing intubation or mortality in AHRF, except in COVID -19 ARDS, where NIV proved to reduce intubation rate as compared to HFNC/COT.

B. Ventilator strategies

Tidal Volume (Vt)

The ARDS network came up with the concept of lung protective ventilation strategy in 1994 to prevent further lung damage with ARDS caused by mechanical ventilation. The main component of lung protective ventilation was demonstrated to be low tidal volume (Vt) ventilation. ARDSnet study in the year 2000 and several randomised controlled trials (RCTs) since then established that a Vt of 4-8 ml/kg of predicted bodyweight limits the Plateau pressure in the alveoli and thus limits overdistension related lung injury.[7] The current guidelines also suggest a Vt of 4-8ml/kg of PBW with permissive hypercapnia to prevent Ventilator induced lung injury (VILI).

Positive end Expiratory Pressure (PEEP)/ Recruitment Manoeuvre

The latest guidelines by the European Society of Intensive Care Medicine (ESICM 2023) based on pooled analysis of multiple RCTs, fails to give any recommendation for a high PEEP/FiO_2 ratio vs low PEEP/FiO_2 ratio in improving outcome.[6] The ventilator free days were higher in two studies in higher PEEP group; however, no difference could be established in terms of mortality and barotrauma.[8]

Recently multiple researches had taken place to compare PEEP titration based on lung mechanics vs standard PEEP/FiO_2 table guided titration. Transpulmonary pressure guided or driving pressure guided PEEP titration shows some promise in preventing overdistension of alveoli and thus VILI but studies failed to show any significant mortality benefit or reduction in barotrauma to find a place in the recommended guidelines. However, mechanics-based PEEP titration showed reduction in ventilator free days in one study but further research is needed to substantiate that finding.[9,10]

Different recruitment manoeuvres have been tried but the current guidelines recommend against them because of

lack of demonstrated benefit and isolated evidence of increased mortality and barotrauma.[8,11]

Proning

In 2017, ESICM and American Thoracic society (ATS) recommended proning in refractory hypoxaemia in ARDS. The recommendation was mainly based upon PROSEVA trial (2013) and a meta-analysis of 4 large trials.[12] The established recommendation suggests proning when PaO_2/FiO_2 is persistently below 150 mmHg with a PEEP of ≥ 5 cmH_2O and adequately optimized ventilatory settings. The recommendation also suggests early recruitment of patients to proning and sustaining them in prone position for at least 16 hrs.

Current guidelines also recommend awake proning position (APP) in non- intubated patients with acute hypoxaemic respiratory failure (AHRF) due to COVID-19 pneumonia. The recommendation is based on meta-analysis of five trials demonstrating that APP decreases rate of intubation in COVID-19 related AHRF.[13]

Neuro-Muscular Blocking Agent (NMBA)

The ACURASYS trial published in 2010, demonstrated that early administration of a 48-h infusion of NMBA in patients with moderate-to-severe ARDS (PaO_2/FiO_2 < 150 mm Hg with PEEP ≥ 5 cmH_2O) resulted in lower mortality than a strategy of deep sedation without routine NMBA use, after an adjusted analysis. However, ROSE trial published in 2019, challenged this finding. No mortality benefit could be elicited in the NMBA group in this trial. However, sedation and ventilatory strategies were different in control group in both these studies and presumably that could explain partly the reason for difference in findings. A meta-analysis of five trials published in 2022 couldn't elicit a mortality benefit either.[14] Thus the current recommendation recommends against routine use of NMBA infusion in ARDS patient.

Extra-corporeal Life Support (ECLS-ECMO/$ECCO_2R$)

The use of ECMO for ARDS demonstrated some benefit in the CESAR trial published in 2009. However, EOLIA trial published in 2019 questioned its usefulness. However, meta-analysis of these two trials and some post-hoc analysis of EOLIA trial in chosen subgroups demonstrated 60 day and 90 day survival benefit of ECMO in severe ARDS.[15] During COVID-19 pandemic, ECMO was widely used and observational studies showed protective effect, however, RCTs are lacking to provide good quality evidence. Based on whatever evidence is currently available, the current guidelines recommend use of VV-ECMO for patients with severe ARDS, matching the inclusions criteria used in EOLIA study, in an ECMO center matching defined organizational standards.[16]

While ECMO is recommended in ARDS, the use of $ECCO_2R$ in ARDS is recommended against. This recommendation is based on a meta-analysis of two trials (REST and Xtravent) which failed to show any mortality benefit. Also, REST trial attributed some serious side effects like intra-cranial and extra-cranial hemorrhage to the use of $ECCO_2R$.[17]

Experimental Treatment in ARDS

Apart from the recommended treatments for ARDS, multiple pharmacological and non-pharmacological treatment modalities are being tried for ARDS.[4] The concept of precision medicine based on sub- phenotypes is still at a budding stage and needs further research. Some pharmacological agents that are currently being tried targeting the pathophysiology of ARDS are mentioned in the table below.

Epithelial and endothelial barrier repair	**Anti-inflammatory effects**	**Reduced oxidative stress**	**Enhanced edema clearance**	**Anti-thrombotic**
-Mesenchymal stem cell (MSC) -Vitamin C -Adrenomedullin -Ulinastatin -Recombinant ACE-2	-MSC -Vitamin C -Steroids -Statins -Dilmapimod -Anti-TNFR1 -ALT-*#^	-Vitamin C -Statins -Acetaminophen -Recombinant ACE2 - Citruline	- MSC -Steroids -Inhaled beta agonists -Vitamin C	-Nebulized heparin -Streptokinase

Conflict of Interest: Not declared.

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