# Extracorporeal Life Support in Respiratory Failure

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**KEYWORDS**

• Extracorporeal membrane oxygenation (ECMO) • Extracorporeal life support (ECLS)
• Respiratory failure

**KEY POINTS**

- Extracorporeal life support (ECLS) is used in different types of respiratory failure including acute respiratory distress syndrome (ARDS), acute decompensated pulmonary hypertension, bridge to lung transplantation, and primary graft dysfunction after lung transplantation.
- ECLS in ARDS supports gas exchange which allows for low-volume low-pressure ventilation with the goal to reduce the risk of ventilator-induced lung injury.
- ECLS should be considered in severe ARDS when conventional management strategies fail to provide adequate and safe oxygenation or in the setting of elevated airway pressures and severe respiratory acidosis.
- Future directions in ECLS research aim to identify optimal management strategies while supported by ECLS, including optimal mechanical ventilation settings, role of prone positioning, weaning ECLS support, and long-term outcomes.

## INTRODUCTION

Extracorporeal life support (ECLS) has an established role in the treatment of acute respiratory failure. First used in the 1970s,[1] its use has increased, and indications have broadened over the last few decades. Its initial growth was driven by advances in technology and improved safety profiles. Then, two separate events occurred in 2009[2]: the 2009 influenza A (H1N1) pandemic[3] and the publication of the extracorporeal membrane oxygenation (ECMO) conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR trial).[4] A decade after these events, data support the move of ECLS from salvage mode to standard of care in patients with very severe acute respiratory distress syndrome (ARDS).[5,6]

This review examines recently published studies and discusses current indications for ECLS in adults with respiratory failure. Finally, we explore future directions in patient care and research.

### *Extracorporeal Life Support Terminology*

ECLS encompasses several modalities to provide support of the lungs or heart. ECLS includes ECMO and extracorporeal carbon dioxide removal ($ECCO_2R$). ECMO supports blood oxygenation and carbon dioxide removal, whereas $ECOO_2R$ only supports carbon dioxide removal. Both ECMO and $ECCO_2R$ have been studied in acute respiratory failure. The two major ECMO modalities are venovenous (VV) ECMO and venoarterial (VA) ECMO. VV-ECMO supports respiratory gas exchange, and VA-ECMO provides circulatory support.[6,7] Details of ECLS circuits,

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configurations, and gas exchange membranes have been described.[6,8]

## Rationale for Extracorporeal Life Support in Respiratory Failure

Early use of ECMO for respiratory failure focused on improving oxygenation with the goal to avoid tissue hypoxia. Historically, it was most often deployed as a salvage mode to support refractory hypoxemia. Over the last 20 years, it has become evident that ventilator-induced lung injury (VILI) is a significant driver of mortality[9] and that ventilator strategies to mitigate VILI decrease mortality in patients with ARDS.[10] Furthermore, secondary analyses of the Acute Respiratory Distress Syndrome Network trial[10] suggests a safe upper limit for plateau pressure may not exist thus shifting the role of ECLS in hypoxemic respiratory failure toward supporting gas exchange with the goal to facilitate low-volume low-pressure ventilation and reduce the risk of VILI.[9]

## Extracorporeal Life Support in Respiratory Failure

Interest in ECLS for adults with respiratory failure increased in 2009 during H1N1 pandemic[3] and with the publication of CESAR.[4] In the CESAR trial, patients with severe ARDS transferred to a single ECMO center were more likely to survive compared with those who received conventional treatment (63% vs 47%, $P$ = 0.03); however, only 76% of transferred patients received ECMO and lung-protective ventilation was not mandated in the conventional arm.[4] Despite limitations in the evidence base, use of ECMO for ARDS significantly increased after 2009.[11]

## Evidence for the Use of Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome

The ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, an international multicenter randomized controlled trial (RCT) of ECMO in patients with very severe ARDS, was published in 2018.[12] Eligible patients (**Fig. 1**) were randomized to conventional low tidal volume ($V_T$) ventilation or VV-ECMO with lower tidal volumes and lower airway pressures than current standards ($V_T$ decreased to maintain plateau pressure $\leq$ 24 cm $H_2O$ with positive-end expiratory pressure [PEEP] $\geq$10 cm $H_2O$; corresponding driving pressure $\leq$ 14 cm $H_2O$).

There was a large, albeit not statistically significant, decrease in mortality in the ECMO arm (35% vs 46%, $P$ = 0.09). Two deaths were attributed to ECMO and the ECMO group had significantly higher rates of severe thrombocytopenia (27% vs 16%) and bleeding requiring transfusion (46% vs. 28%) without statistically significant differences in ischemic or hemorrhagic strokes.

A post hoc Bayesian analysis of EOLIA found a high probability that ECMO had a 60-day mortality benefit in patients with severe ARDS.[13] Likewise, a meta-analysis pooling mortality data from 429 patients enrolled in CESAR or EOLIA found a significantly lower 60-day mortality in the ECMO group compared with the control group (34% vs 47%; $P$ = 0.008),[14] and an individualized patient data meta-analysis in severe ARDS also found improved 90-day mortality in patients receiving ECMO compared with conventional management (36% vs 48%; $P$ = 0.013).[15] Taken all together, these data strongly suggest a mortality benefit with ECMO in patients with severe ARDS.

## Extracorporeal Membrane Oxygenation in Coronavirus Disease 2019-Related Acute Respiratory Distress Syndrome

The role of ECMO for coronavirus disease 2019 (COVID-19)-related ARDS evolved throughout the pandemic. Early reports of high mortality rates with ECMO (84%–94%) deterred some from recommending its use,[16,17] whereas subsequent studies reported more favorable outcomes with mortality rates similar to EOLIA.[18,19] One of the largest studies found an in-hospital 90-day mortality of 37.4% among 1035 ECMO-supported patients with COVID-19.[18] More recently, higher mortality rates have been reported[20,21] with one study reporting an in-hospital mortality of 73% among 768 ECMO-supported patients with COVID-19-related ARDS.[20]

Although the benefit of ECMO in COVID-19-related ARDS remains unclear, several society guidelines recommend ECMO to support patients with severe COVID-19-related ARDS who meet EOLIA eligibility criteria.[22–24] Throughout the pandemic, the overall use of ECMO has grown as COVID-19 is now the leading cause of ARDS globally.[25]

## Extracorporeal Life Support During a Public Health Crisis

As critically ill patients with COVID-19 overwhelmed hospitals[26] experts tempered enthusiasm for the role of ECMO early in the pandemic.[27] Efficacy of ECMO in COVID-19-related ARDS was unknown, and ECMO is a resource-consumptive technology requiring highly trained staff, lower nurse-to-patient ratios, and more space per patient.[27,28] At a time when hospitals experienced critical shortages in staff and

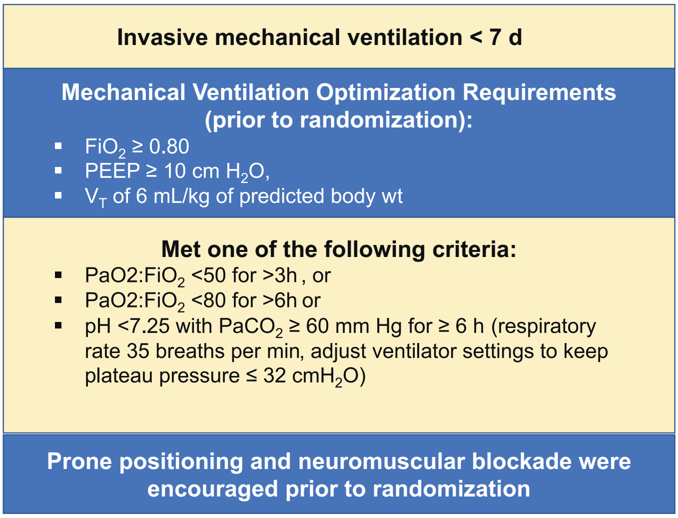


**Fig. 1.** Eligibility criteria for EOLIA: Criteria used to consider ECMO in severe ARDS. ARDS, acute respiratory distress syndrome; cm$H_2O$, centimeters of water; $FiO_2$, fraction of inspired oxygen; mm Hg, milliliter of mercury; $Pa_{CO_2}$, partial pressure of carbon dioxide; $PaO_2$, partial pressure of oxygen; PEEP, positive-end expiratory pressures; VILI, ventilator-induced lung injury; VT, tidal volume.

space,[22,26] a call for ECMO was met with a call for pause and discussion around the ethics of resource allocation.[29,30]

The role of ECMO during public health crises extends beyond COVID-19, but the principles remain the same. Ultimately, the decision to ration ECMO in a public health crisis should be based on ethical principles and grounded within triage guidelines based on these principles.[29]

### *Best Practice Ventilation Strategies in Extracorporeal Life Support-Supported Acute Respiratory Distress Syndrome*

In ARDS, VV-ECMO allows for ultra-protective ventilation ($V_T \leq 4$ mL/kg of predicted body weight [PBW] and plateau pressure $\leq$ 24 cm $H_2O$), which may further decrease the risk of VILI compared with standard lung-protective ventilation ($V_T$ of 6 mL/kg of PBW and plateau pressure $\leq$ 30 cm $H_2O$).[31–33] Optimal ventilation strategies during ECMO are unknown; however, data from EOLIA and other studies have informed best practice recommendations (Fig. 2) for ventilator strategies.[34]

### *Key Take-Home Points on Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome*

- ECMO may improve mortality in patients with severe ARDS.
- In patients with severe ARDS refractory to conventional management strategies (lung-protective ventilation, PEEP titration, deep sedation, prone positioning, and consideration of neuromuscular blockade), ECMO should be considered.
- In ECMO-supported patients, initiate ultra-protective ventilation strategies to minimize risk of VILI, a major cause of mortality in ARDS.

### *Extracorporeal Life Support in Non-Acute Respiratory Distress Syndrome Respiratory Failure*

The role of ECLS to support respiratory failure in patients without ARDS (Box 1) is not well studied. RCTs supporting the use of ECMO for these are unlikely, as there is either lack of clinical equipoise or the event is uncommon thereby limiting the ability to rigorously study.

Outside of ARDS, BTT,[35,37] and VA-ECMO for decompensated PH with right heart failure[45] have the most data.

### *Extracorporeal Membrane Oxygenation in Bridge to Lung Transplantation*

Long wait times on transplant lists increase the risk of patients developing respiratory failure requiring mechanical support with invasive mechanical ventilation, ECMO, or both. ECMO as BTT may reduce the need for invasive mechanical ventilation and thus avoid known ventilator-associated complications. Furthermore, ECMO as BTT mitigates deconditioning by allowing patients to actively participate in physical therapy; thereby maintaining transplant eligibility—even with prolonged wait times.[35–37]

The goal of ECLS in BTT is not simply survival to lung transplant. Instead, it is to decrease wait-list mortality rates while achieving favorable long-term survival. In 2019, two centers published similar long-term survival outcomes in BTT

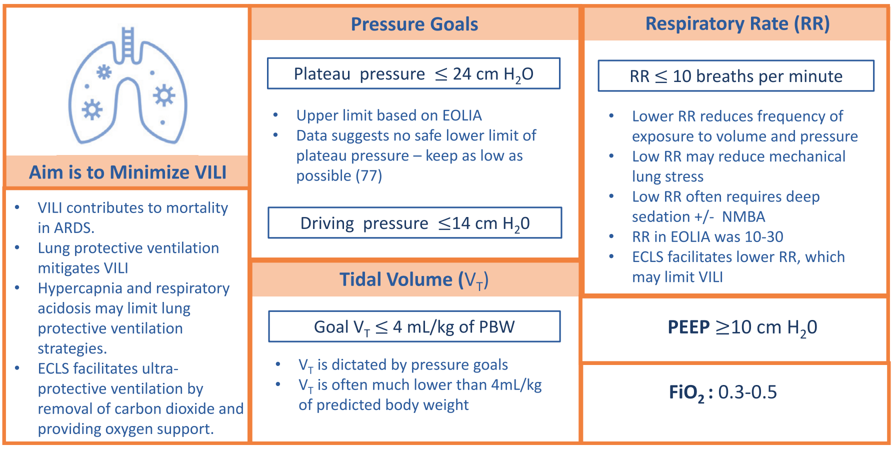


**Fig. 2.** Ventilator strategies for ECLS-supported ARDS: Best practice recommendations. Figure depicting recommended ventilator strategies for patients with ARDS requiring ECLS. Refer to text for reference citations. ARDS, acute respiratory distress syndrome; $cmH_2O$, centimeters of water; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; $FiO_2$, fraction of inspired oxygen; mL/Kg, milliliters per kilogram; NMBA, neuromuscular blockade; PBW, predicted body weight; PEEP, positive-end expiratory pressures; RR, respiratory rate.

recipients compared with non-BTT recipients.[35,37] In the largest series, 121 adult patients were placed on ECMO as BTT from 2009 to 2018. Of the 121 patients, 70 (59%) were successfully transplanted, and 64 (91%) of the transplant recipients survived to hospital discharge with an 83% 3-year survival rate, which was not significantly different than propensity-matched, non-BTT transplant recipients. Ambulation was the only independent predictor of successful BTT (OR 7.6, 95% CI 2.16–26.6; $P = 0.002$).[37]

### *Extracorporeal Membrane Oxygenation in Acute Decompensated Pulmonary Hypertension*

VA-ECMO has been successfully used to support decompensated PH with right-sided heart failure as a BTT and a bridge to recovery.[40,46] Recently, a single-center cohort study reported outcomes of 98 patients with decompensated PH placed on ECMO[47] for BTT (55%) and non-BTT indications (45%). In this cohort, patients had severely elevated right ventricular systolic pressures (73 mm Hg; interquartile range (IQR) 58–100 mm Hg) and were not expected to live without ECMO support. The overall survival to hospital discharge was 54%. These findings suggest a role for ECLS in patients with decompensated PH at centers with PH and ECMO expertise.[47]

**Box 1**
**Potential indications for extracorporeal membrane oxygenation in non-acute respiratory distress syndrome respiratory failure**

- Bridge to lung transplantation (BTT)[35–37]
- Primary graft dysfunction after lung transplantation[38]
- Decompensated pulmonary hypertension (PH)[36,39,40]
- Status asthmaticus[41,42]
- Massive acute pulmonary embolism[43,44]

### *Extracorporeal Carbon Dioxide Removal in Hypoxemic Respiratory Failure*

The use of ultra-protective ventilation in ARDS, to further limit VILI, may be limited by hypercapnia and severe acidosis. It was theorized that $ECCO_2$-R, through carbon dioxide removal, would facilitate ultra-protective ventilation, reduce VILI,[48,49] and improve survival in ARDS. The Strategy of UltraProtective Lung Ventilation With Extracorporeal CO2 Removal for New-Onset Moderate to seVere ARDS (SUPERNOVA) trial demonstrated feasibility of $ECCO_2R$ to allow lower volume and lower pressure ventilation strategies ($V_T$ 4 mL/kg of PBW and plateau pressure $\leq$ 25 cm $H_2O$) in patients with moderate ARDS ($Pao_2$:$Fio_2$ ratio of 100–200 mm Hg with PEEP$\geq$5 cm $H_2O$).[50]

In the recent pRotective vEntilation With VenovenouS Lung assisT in Respiratory Failure (REST) Randomized Clinical Trial, 412 patients with acute hypoxemic respiratory failure ($Pao_2$:$Fio_2$ ratio <

150 mm Hg with PEEP $\geq$ 5 cm H2O) were randomized to $ECCO_2R$ with lower tidal volume ventilation (goal $V_T \leq$ 3 mL/kg of PBW) or standard care with conventional lung-protective ventilation (recommended $V_T$ of 6 mL/kg of PBW). $ECCO_2R$ was deployed for at least 24 hours and no more than 7 days.

This multicenter, randomized, pragmatic clinical trial found no difference in 90-day mortality between the $ECCO_2R$ and standard care groups (41.5% vs 39.5%, $P$ = 0.68). Of note, there were significantly fewer ventilator-free days in the $ECCO_2R$ group compared with the standard care group (7.1 vs. 9.2, $P$ = 0.02), and serious adverse events were more common in the $ECCO_2R$ group compared with the standard care group (31% vs 9%, respectively), including intracranial hemorrhages (9 vs 0). The trial was stopped early due to futility.[51]

Although SUPERNOVA demonstrated feasibility of $ECCO_2R$ to allow for ultra-protective ventilation, REST failed to demonstrate a 90-day mortality benefit. The results from the REST pragmatic clinical trial do not support the use of $ECCO_2R$ for hypoxemic respiratory failure.

## Future Directions in Patient Care and Research

The role for ECMO in severe ARDS refractory to conventional strategies has been established; thus, future trials investigating survival in ECMO-supported severe ARDS are unlikely. Instead, ECLS research efforts on optimal management strategies of patients during ECLS and long-term outcomes of ECMO-supported ARDS survivors are needed. Moreover, future research should work to identify patients who will most likely benefit from ECLS support. Ongoing technological advances in the field will not be discussed in this review but have a central role in this technology-centered field.

## Key Research Area: Management Strategies During Extracorporeal Life Support

### Optimal ventilation strategies

With the focus of ECLS in respiratory failure shifting toward limiting VILI, there is a notable paucity of data on optimal ventilator strategies (Fig. 3). In fact, no prospective trials have studied the optimal ventilation strategy to mitigate VILI and improve outcomes. Patients enrolled in EOLIA[12] for elevated airway pressures and severe respiratory acidosis had the greatest reduction in mortality suggesting a mortality benefit from decreased VILI with ultra-protective ventilation.

Future trials are needed to delineate optimal ventilator settings to mitigate VILI and improve outcomes in ECMO-supported ARDS. Specifically, different intensities of low-volume low-pressure ventilation and different respiratory frequencies (ultra-protective vs "near-apneic" ventilation) have been proposed as potential strategies to more effectively limit VILI.[52,53]

Research on the impact of spontaneous breathing and extubation while on ECMO and specific goals for gas exchange during ECMO-supported respiratory failure is also needed.[34]

### Prone positioning

The role of prone positioning in ECMO-supported ARDS is not well studied. There is strong data for improved mortality with prone positioning in ARDS[54] but it is unknown if the same benefits extend to patients supported by ECMO with ultra-protective ventilation. A small study suggested benefit,[55] and in a recent retrospective multicenter cohort study, prone positioning was associated with lower hospital mortality compared with propensity-matched supine ECMO-supported patients (30% vs 53%; $P$ = 0.024).[56] An RCT comparing prone position to supine position, in ECMO-supported patients with severe ARDS, is currently enrolling PRONing to Facilitate Weaning From ECMO in Patients With Refractory Acute Respiratory Distress Syndrome (PRONECMO).[57] Results from this trial will inform the role of prone positioning in ECMO-supported ARDS.

### Weaning form mechanical support

Recently, two small studies investigated weaning strategies for VV-ECMO.[58,59] Gannon and colleagues[58] studied a proactive, systematic, and standardized approach to weaning ECMO, similar to standardized approaches to weaning mechanical ventilation, whereas Al Fares and colleagues[59] sought to identify parameters associated with safe weaning from VV-ECMO. Future studies should measure survival in addition to successful decannulation, as most often patients remain on invasive mechanical ventilation and are critically ill.

### Adjunctive therapies: anticoagulation, sedation, and mobilization

Blood circulation through a foreign membrane increases the hypercoagulable state of patients requiring ECMO.[60] Antithrombotic agents are frequently used to decrease the risk of clot formation, yet anticoagulation protocols are center-specific.[60] Consensus across centers on anticoagulant type, therapeutic goal, and monitoring are lacking;[61] however, small feasibility studies have shown safety in using thromboelastography and anti-Xa compared with activated partial thromboplastin time.[62,63] Future research on anticoagulation

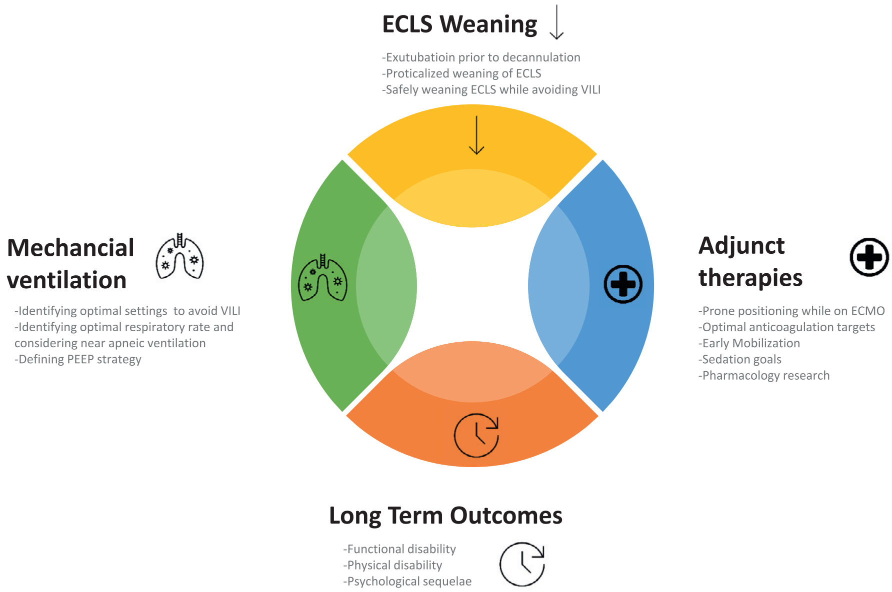


**Fig. 3.** Future directions. Figure depicting future directions in research and patient care for ECLS. ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; PEEP, positive-end expiratory pressures; VILI, ventilator-induced lung injury.

methods as well as developing materials to reduce the hypercoagulable effect of ECLS are needed.[64]

It has been shown that reducing sedation and increasing mobilization mitigates intensive care unit acquired weakness and delirium.[65] Mobilization is frequently delayed and moderate to deep sedation is regularly targeted in patients requiring ECMO.[66] Although sedation is often needed at the initiation of ECLS support, the goal is to minimize sedation similar to patients not requiring ECLS.[67] A recent retrospective study demonstrated feasibility and safety of mobilization while on ECMO.[68] Future research is needed to investigate risks and benefits of early mobilization and decreased sedation.

### *Key Research Area: Long-Term Outcomes*

Long-term outcomes for ECMO-supported ARDS survivors have not been well studied. A recent, relatively small meta-analysis[69] reported greater decrements in health-related quality of life in ARDS survivors managed with ECMO compared with survivors of mechanical ventilation, and interestingly, ECMO survivors had significantly less depression and anxiety compared with those managed with mechanical ventilation.

Short-term survival alone should not be considered an adequate outcome measure for the use of ECMO in ARDS. Functional disability and psychological sequelae have been shown to persist 5 years after surviving ARDS.[70] Prospective systematic evaluation of long-term outcomes in survivors of ECMO-supported ARDS is necessary and should mirror similar work done in survivors of ARDS.[70]

### *Key Research Area: Extracorporeal Carbon Dioxide Removal in chronic obstructive pulmonary disease (COPD)*

Use of $ECCO_2R$ in patients with an acute COPD exacerbation, who are failing noninvasive positive pressure ventilation, may avoid the need for invasive mechanical ventilation.[71] Likewise, its use in patients who are already intubated may facilitate early liberation from invasive mechanical ventilation.[72,73] Thus far, studies have not shown survival advantages or reduced ventilator-free days and have been associated with high rates of ECLS-related complications.[71,73] Currently, $ECCO_2R$ for the management of COPD exacerbations should be restricted to research studies.

The Vent-Avoid trial is an ongoing multicenter, international RCT is investigating $ECCO_2R$ as an alternative or adjunct to mechanical ventilation in COPD exacerbations requiring respiratory support. The primary outcome is ventilator-free days.[74]

### *Research Challenges for the Future*

Acute respiratory failure requiring ECLS is a relatively uncommon event making research in this field challenging but not unsurmountable. Using study designs with predictive enrichment strategies that identify populations most likely to benefit from ECLS might be necessary.[75] Furthermore, coordinated efforts between high-volume ECLS centers are essential, and research networks, such as the international ECMO Network (ECMONet; www.internationalecmonetwork.org) and large registries, such as the Extracorporeal Life Support Organization (www.elso.org) are critical if research on ECLS for acute respiratory failure is going to be successful.[76]

## SUMMARY

ECLS in acute respiratory failure is most widely accepted for severe ARDS; however, its role has evolved over time to include several other indications, most commonly BTT and acute decompensated PH. An essential element of ECLS-supported ARDS management is to reduce VILI, with the goal to improve survival and long-term outcomes. Future research efforts should focus on optimal management strategies while on ECLS, long-term outcomes, and technological advancements.

## CLINICS CARE POINTS

- Extracorporeal life support (ECLS) use in severe acute respiratory distress syndrome (ARDS) should be considered when conventional management strategies fail to provide adequate and safe oxygenation or in the setting of elevated airway pressures and severe respiratory acidosis.
- ECLS in ARDS allows for ultra-low lung-protective ventilation, thereby reducing the risk of ventilator induced lung injury, a significant contributor to mortality in ARDS.
- Potential indications for ECLS in acute respiratory failure include bridge to lung transplantation, decompensated pulmonary hypertension, status asthmaticus, primary graft dysfunction after lung transplant, and massive pulmonary embolism.
- Future directions in ECLS research and patient care include identifying optimal management strategies while supported by ECLS including optimal mechanical ventilation, role of prone positioning, weaning ECLS support, and strategies for mobilization, sedation, and anticoagulation.
- Future research efforts need to include survival and long-term outcomes.

## DISCLOSURE

None.

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