

# Extracorporeal Life Support: Four Decades and Counting

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**Abstract** Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) is a form of heart lung bypass that is used to support neonates, pediatrics, and adult patients with cardiorespiratory failure for days or weeks till organ recovery or transplantation. Venoarterial (VA) and venovenous (VV) ECLS are the most common modes of support. ECLS circuit components and monitoring have been evolving over the last 40 years. The technology is safer, simpler, and more durable with fewer complications. The use of neonatal respiratory ECLS use has been declining over the last two decades, while adult respiratory ECLS is growing especially since the H1N1 influenza pandemic in 2009. This review provides an overview of ECLS evolution over the last four decades, its use in neonatal, pediatric and adults, description of basic principles, circuit components, complications, and outcomes as well as a quick look into the future.

**Keywords** Extracorporeal life support · Extracorporeal membrane oxygenation · ECLS · ECMO · Venoarterial · Venovenous · Respiratory failure · Cardiac ECLS · ARDS ·

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Congenital diaphragmatic hernia · Internal jugular vein · Double lumen cannula

## Introduction

ECMO or ECLS has been around for more than four decades. ECLS, which is the name better describes this technology, is a modified form of cardiopulmonary bypass that is used to support patients with cardiopulmonary failure unresponsive to conventional treatment. ECLS is performed to drain blood from the venous system, remove carbon dioxide (CO<sub>2</sub>), add oxygen (O<sub>2</sub>) through an artificial lung (the oxygenator), and return the blood using a pump to the body via an artery as in VA ECMO or a vein as in VV ECMO [1•, 2–6]. It is important to recognize that ECLS is a support modality but not a cure. It provides time for other diagnostic and therapeutic measures to be pursued allowing injured organs to recover meanwhile abundance of oxygenation and optimum tissue perfusion is guaranteed. ECLS is a complex, invasive, high-risk, and costly technology, and it should only be conducted in centers with sufficient experience, knowledge, and expertise in that field.

## History

ECLS finds its roots in the first blood oxygenator, designed by Dr. Gibbon in the 1950's. It was first created to sustain patients during heart surgery and relied on direct blood-air contact for oxygenation [7]. The utilization of this machine was limited to only few hours because of the hemolysis and bleeding resulting from direct blood-gas contact. The early work done by Clowes on developing an artificial lung using ethyl cellulose membrane and soon after by Kammermeyer to optimize

the use of silicone rubber membrane in the 1950's [8, 9] provided a strong framework until Kolobow perfected the development of the silicone membrane oxygenator in the 1960's [10]. This invention allowed the prolonged use of the heart lung bypass machine by clinicians outside the operating room. Several groups were working on this concept in the 1960's and 70's. Dr. Bartlett and bioengineer Drinker successfully applied ECLS in the laboratory for 4 days using the newly developed membrane oxygenator with lower heparin dosage to minimize bleeding. Dr. Bartlett, who is considered by many as the father of ECMO, moved to the University of California at Irvine in 1970, where he continued to do his work in the laboratory to optimize cardiopulmonary bypass for prolonged use. In 1972, Dr. Hill reported the first successful use of ECLS in a young adult who suffered from severe hypoxic respiratory failure secondary to motorcycle accident in Santa Barbara, California [11]. Same year, Dr. Bartlett performed the first successful use of VA ECMO on a baby who suffered from low cardiac output syndrome immediately after Mustard atrial baffle operation for transposition of great vessels. The first neonatal respiratory survival was not reported until 1975 when Drs Bartlett and Gazzaniga successfully used VA ECMO for a full-term newborn who was suffering from severe hypoxic lung disease thought to be secondary to meconium aspiration (MA) [2]. In 1982, Dr. Bartlett and colleagues published their experience in the use of ECMO for newborn respiratory failure [3]. He described the use of ECMO in 45 moribund newborn infants; 25 patients survived. All were deemed unresponsive to conventional therapy. The right atrium (RA) and the aortic arch (AA) were cannulated via the internal jugular vein (IJV) and the carotid artery (CA), respectively. Primary diagnoses were hyaline membrane disease, sepsis, and persistent fetal circulation including congenital diaphragmatic hernia (CDH) and MA. This paper concluded that ECMO use has decreased mortality and morbidity in newborn respiratory failure, and that ECMO may be used effectively in older patients with respiratory failure if used before irreversible lung damage occurs.

This report was a milestone in the evolution of ECMO around the world. Many clinicians took notice and came to Michigan to learn ECMO. They took this technology back to their hospitals which lead to the widespread use of ECLS globally especially in neonatal respiratory failure.

### ECLS Physiology and Support Modes

VA and VV ECLS are the most commonly used modes of support [1•, 5, 6, 12, Redbook-13]. VA ECLS provides cardiac and pulmonary support. Therefore, this can be used in ARDS patients suffering from cardiac or circulatory failure as in severe septic shock. It is the ideal mode of support in cases of severe cardiogenic shock (e.g., cardiomyopathy, myocarditis).

Support can be partial or total depending on site of cannulation, size and position of the cannulae used, and the native cardiac function. Oxygen delivery (DO<sub>2</sub>) is the amount of oxygen delivered to the tissues each minute. It equals the oxygen content times the cardiac output. The more blood diverted to the ECLS circuit (maximum cardiac output) with the presence of normal hemoglobin (maximizing oxygen content); DO<sub>2</sub> is maximized. VA ECLS cannulation can be done using one of three access points: first by using the transcervical approach, placing the venous cannula in the RA via the right IJV and the arterial cannula in the AA via the right CA. It is important to assure that the tip of the arterial cannula is away from the aortic valve as this can damage the valve and hinders the myocardial recovery. This approach may provide 50–80% extracorporeal support as part of the blood volume still passes through the patient's native heart and lung. The second approach is the central or transthoracic approach with direct venous cannula placement in the right atrial appendage and arterial cannula placement in the AA. This approach is typically used in post-operative cardiac patients once they fail coming off CPB. This may provide total ECLS support as the ECLS circuit captures all blood volume and none passes through the native heart. It also has been described in patients with severe septic shock [12]. The third approach is cannulating the femoral artery and the femoral vein. This approach has been described in adults and older children and has been used in cases of emergency cannulation or extracorporeal cardiopulmonary resuscitation (ECPR). VA ECLS provide circulatory support. In most cases, inotropes and vasopressors are weaned off soon after ECLS initiation. Coronary perfusion is provided by retrograde flow via the arterial cannula, which emphasizes the importance to have its tip accurately placed in the aortic arch away from the aortic valve.

On the other hand, VA ECLS requires accessing and mostly ligating the carotid artery. There is an increased risk of systemic embolization with potential end organ damage mainly brain strokes. Left ventricular afterload is increased, which may hinder myocardial recovery.

VV ECLS is ideal for pulmonary support in cases of severe respiratory failure. It does not provide cardiac nor circulatory support. Blood is typically drained from the venae cavae and retained to the right atrium. That can be done either by multi-site cannulation; usually by draining from a venous cannula in the inferior vena cava via the femoral vein and returning to the RA via the IJV; or single-site cannulation with the use of a double lumen catheter, draining the blood from the venae cavae and returning it to the RA. Currently, most of venovenous access is achieved by cannulating the right IJV using a double lumen catheter, which minimizes the problem of recirculation that dominates the multisite access approach. Other than sparing the carotid artery and minimizing the risk of systemic embolization especially embolic strokes [13], the benefits of VV ECLS for pediatric respiratory ECLS are

evident. The pulmonary blood flow is maintained in VV ECLS with well-oxygenated blood, which is considered a great vasodilator of the pulmonary circulation that leads to reduction of pulmonary vascular resistance (PVR). As a result, the afterload of the RV will decrease, augmenting its systolic and diastolic function. These effects continue through to the left side of the heart as the LV preload is optimized and coronary perfusion is maintained with highly oxygenated blood. There is no increase in LV afterload, and the risk of “myocardial stun” is minimized, with resulting improvement in myocardial oxygen delivery and myocardial performance [14, 15].

Other modes of ECLS support are used. Venovenous or VVA ECLS has been increasingly used as a hybrid between VA and VV ECLS. This is typically used in older pediatric and adult patients with initial VA ECLS using femoral vein and artery. Coronary and upper body perfusion may be inadequate. This can be overcome by adding another venous cannula in the RA via the IJV and connecting it via a Y-connection to the returning “arterial” limb, so oxygenated blood is returned to the RA, passes through the native heart to perfuse the coronaries, the carotid arteries and the upper body, meanwhile providing circulatory support via the femoral arterial access.

Arteriovenous or AV ECLS is not commonly used in pediatrics. This method can be very effective for CO<sub>2</sub> removal utilizing only 15–20% of the cardiac output. The femoral artery and vein are accessed; blood flows through a membrane lung (oxygenator) without a pump using the gradient difference between the arterial and venous pressures. This method, also known as the extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R), is ideal for adults with chronic obstructive pulmonary disease (COPD) with exacerbation and patients with near-fatal asthma where hypercapnia is the main problem [16, 17]. The circuit is usually very simple which potentially makes it safer to maintain.

## Cannulation Techniques

Vascular access and cannulae placement has evolved over the years. Open surgical technique using the neck vessels and through the chest have been the main traditional methods especially for VA support in neonates and young children with cardiorespiratory failure. Percutaneous cannulation is becoming more popular and is currently considered the standard of care for VV ECLS in pediatrics and adults using the current double lumen cannulae and for VA support when accessing the femoral vein and artery. The open surgical approach provides the advantage of visualizing the vessel(s), estimating the appropriate-size cannula, and placement under vision. However, this approach is more time consuming, can lead to more bleeding at the site, and in many instances, requires ligation of the distal end of the vessel [1••]. Percutaneous techniques are faster, may decrease the risk of surgical site bleeding, no distal ligation of vessel is required, and provides

a simpler way of decannulation without the need to explore the cannulation site or ligating the vessel.

The semi-open technique or the percutaneous-assisted technique has been described especially for vascular access in neonates requiring VV support using double lumen catheter. A small transverse incision is made just above the right clavicle, the right IJV is visualized and then a percutaneous approach is used by accessing the vein 2 cm distally using Seldinger technique.

Transthoracic cannulation is used as an extension of cardiopulmonary bypass if the patient is not able to come off bypass in the operating room. The chest is open via median sternotomy; cannulae are placed directly in the RA and the aorta.

Decannulation is the procedure that is needed to terminate ECLS. Cannulae that are surgically placed have to be removed by exploring the surgical site, carefully pulling them out while maintaining homeostasis and ligating the vessels. Cannulae placed percutaneously can be withdrawn at the bedside with pressure applied over the site for 10–15 min. There is no need for vessel ligation. However, percutaneously placed arterial cannulae may need surgical exploration and vessel repair.

## Circuit Components

ECLS circuit designs differ among institutions, although the main components and principles are similar. These components experienced significant evolution especially over the last decade [18•, 19•].

Roller head (semi-occlusive) pumps have been traditionally used in ECLS. They are similar to the pumps used in CPB. The blood is squeezed forward through the tubing “the raceway” against a plate at two pressure points in the pump housing while the roller head is rotating. This provides continuous forward motion of the blood towards the oxygenator and then back to the body. These pumps depend on gravity for the venous drainage into the pump (preload), so the patient has to be at a certain height (100–150 cmH<sub>2</sub>O) from the pump and the bladder reservoir for it to work. Whenever there is an interruption to that flow either secondary to hypovolemia, pleural or pericardial tamponade pathology, or kinking in the tubing; the pump will just slow down or stop till the venous return is reestablished or the cause of the problem is corrected. Newer pumps have servo-regulation capabilities that allow the ECLS specialists to set the alarms so the pump will slow down once certain negative venous (access) pressures are reached. This allows the specialist to troubleshoot and address the problem preventing many interruptions and stoppage of pump flow [14, 19•, Fuhrman, 20].

The centrifugal pumps are also used for ECLS support. They are used in most pediatric and all adult patients ECLS supported. Many centers have transitioned from roller head to centrifugal pumps over the last 20 years.

Centrifugal pumps are non-occlusive. Earlier designs used spinning rotor with bearings and seals that lead to excessive head generation. Those pumps needed to be replaced frequently, adding to the morbidity and mortality of these patients. With advancement in technology, the newer pumps utilize magnetic levitation to suspend and spin the impeller. Their blood-handling qualities have also improved, minimizing heat generation that lead to reduction in circuit related hemolysis and air cavitation. The blood enters these pumps at the apex and gets expelled at the base towards the membrane oxygenator.

Other advantages include easy set up, small priming volume, ability to trap air and debris within the vortex, and lack of dependency on gravity for blood drainage. These pumps can be placed at any level relative to the patient, which make them suitable for inter and intrahospital transport.

The membrane oxygenator, also known as the artificial lung, is responsible for gas exchange in ECLS. The Kolobow silicone membrane oxygenator was, for decades, the only available gas exchange device in the market. It was constructed of a flat, reinforced silicone membrane envelope that is wound in a spiral coil around a polycarbonate spool. There was a highly gas-permeable barrier separating blood and gas compartments, with no direct blood-gas interface. Gas transfer occurs by molecular diffusion as it does in the human lung. The silicone membrane oxygenator was effective in gas exchange, but its compact design created long blood path and high resistance that made it harder to de-air and more challenging to prime. A separate blood warmers (heat exchanger) was needed for most of these devices. It was not unusual to replace these devices during ECLS or to need more than one oxygenator to support older pediatric and adult patients. The silicone membrane oxygenators are not available in the market anymore. These hurdles lead to the development of newer generation of devices, the hollow fiber oxygenators. These devices consist of micro porous material where gas exchange takes place by bulk gas transfer via a direct gas to blood interface. These devices are easy to prime, have low resistance, and provide efficient gas exchange. But the longevity of these devices is limited, plasma leak into the gas phase would occur as early as few hours from ECLS initiation, that lead to early failure of these devices and the need to be replaced urgently.

In the early 2000s, a newer design of these devices became available [21]. These new devices incorporate the advantageous characteristics of the membrane oxygenator and the hollow fiber oxygenator together using polymethylpentene (PMP) and polyurethane fibers. The PMP is a micro porous material that is very efficient in gas exchange for extended period of time. These devices are durable and may attenuate the inflammatory response during ECLS initiation. They have low resistance to blood flow, which makes them easy to prime, reducing the potential for thrombus formations and

oxygenator failure. The rated flow is a measure that is used to describe the function of all gas exchange devices. The rated flow, which is the amount of normal venous blood that can be raised from 75 to 95% oxyhemoglobin saturation in a given period of time, is high which allows many centers to use one-size device for all patients regardless of their size and weight [14, 19•].

## Patient Population and Clinical Applications

### Neonatal ECLS (0–30 days)

Neonates still comprise the majority of patient population supported by ECLS. As of July 2016 Extracorporeal Life Support Organization's (ELSO) report, a total of 36,964 neonates were supported by ECLS, the majority (29,153) with severe respiratory failure with a survival rate of 74% [22]. The most common diagnoses are meconium aspiration syndrome (MAS), CDH, sepsis [23], persistent pulmonary hypertension of the newborn, and respiratory distress syndrome. MAS used to be the most common diagnosis till recently. In the early 1990's, other treatment options such as high frequency ventilation (HFV), surfactant, and inhaled nitric oxide (iNO) became more available [24–26]. It is believed that the increasing use of these therapies has led to the significant reduction of ECLS use in this patient population [4, 24, 25, 27] especially in neonates with MAS. There were around 800 neonatal ECLS runs reported every year for the last 15 years compared to almost 1500 annual cases in the early 1990s. The use of neonatal ECLS peaked in 1992 with a total of 1516 neonates that year from approximately 100 centers around the globe. VA ECLS is still the most common mode used in neonates, followed by VV ECLS using the double lumen cannula [28]. Therapeutic hypothermia during neonatal ECLS did not result in improved outcome up to 2 years of age [29].

In contrast to neonatal respiratory ECLS; neonates requiring ECLS for cardiac reasons have poorer survival rate of 39% [30••]. Mortality in neonates with congenital heart disease requiring ECLS has not significantly changed over the last 20–30 years, despite the dramatic increase in its use for that purpose [31]. In a recent study, low body weight, single ventricular physiology, lower pH before ECLS, and longer time from intubation and mechanical ventilation to ECLS deployment were associated with increased mortality in neonates requiring ECLS for cardiac indications. Mortality in this category is similar in surgical and nonsurgical patients. This data highlighted the importance of early initiation of ECLS before acidosis and organ dysfunction occur [30••, 31, 32••, 33, 34]. This concept was described previously; there is no well-defined criteria defining the optimal timing of ECLS initiation in this population.

## Congenital Diaphragmatic Hernia and ECMO

CDH occurs in about 1:2500 live births. The presence of pulmonary hypoplasia may result in pulmonary hypertension (PHTN) with hypoxia, hypercapnia, and acidosis that could be evident soon after birth. Variety of ventilation strategies and other treatment modalities (e.g., iNO) may be needed in the first few days of life [35••, 36]. ECLS have been used for more than three decades in CDH patients with PHTN unresponsive to maximum conventional therapy. VA and VV ECLS have been used effectively; however, VA ECLS is more commonly used as it unloads the RV that may aid in restoring myocardial function. Looking at ELSO data, CDH mortality did not change significantly over the last two decades. Overall, the reported survival rates for CDH and ECLS is about 50–65% [37]. As in other neonatal ECLS, the oxygenation index (OI) has been used to determine need for ECLS support. OI more than 40 for more than 4 h is considered an indication for ECLS. Pre-ECLS factors (e.g., Apgar score, PaO<sub>2</sub>, PCO<sub>2</sub>, pH) failed to predict outcome or prognosis [35••] and clinicians should reevaluate selection criteria for not offering ECLS to this selected group of patients. The timing of defect repair of ECLS-managed patients is controversial. There are two main groups, on or off ECLS. Surgery performed during ECLS can be either early in the ECLS course or when PHTN is resolved just before decannulation. A review of over 600 cases from the CDH study group (CDHSG) registry [37] over a 10-year period evaluated the outcome of surgery either during or after ECLS. Taking into account other outcome-associated variables such as duration of ECLS run, type of surgical repair, and patient factors, patients repaired post ECLS had a significantly better outcome. The odds of dying were 1.4 times greater if the repair was performed during ECLS. This may be associated with a reduced bleeding risk as well as bias towards patients who have improved more quickly allowing ECLS decannulation. The ability to wean off ECLS within a two-week period may contribute positively to the outcome with respect to the timing of surgery [38]. If the patient was weaned off ECMO within 2 weeks, surgical correction post ECMO was associated with a significantly better outcome and a significantly reduced risk of bleeding when compared to patients at that institution who were repaired on ECLS. The early repair on ECLS has been suggested to offer the benefit of surgery before the anasarca becomes extensive and allows recovery from the physiologic insult while on ECLS, hopefully without prolonging the ECLS duration. A review of repair within 3 days of ECLS [39] demonstrated that the risk of bleeding at surgical site was <10%, the operative repair took less than 2 h with a survival rate of 70%. Other ECLS-related bleeding complications were no different from those reported to the ELSO registry. Anticoagulation management during ECLS for CDH is pivotal especially if CDH repair is performed during ECLS run. A

review of ATIII use in (target activity >65%) CDH ECLS patients [40] when compared to the institutions historical control demonstrated that the use of ATIII lead to significant reduction in the utilization of FFP, packed red cells, and platelets in the first 3 days of ECLS. The use of large volumes on blood products may adversely affect lung mechanics and delay recovery. Amicar and tranexamic acid used peri-operatively could be helpful to minimize bleeding.

Pulmonary hypoplasia is an important component with respect to the need for ECLS support related to hypoxia and hypercapnia. There have been case reports on the use of perfluorocarbons (PFC) to support alveolar maturation. A prospective randomized study of CDH patients on ECLS [41] with or without PFC use evaluated lung growth using L1 vertebral body size for comparison. There was about 130% increase in the left (affected) lung size during the PFC use. There were no noted side effects or complications from the PFC use. However, there was no comment on the lung growth in the non PFC group, and mortality was not significantly different (small  $n = 16$ ).

## Pediatric ECLS (>30 days to <18 years)

Viral and bacterial pneumonia causing acute respiratory failure and acute respiratory distress syndrome (ARDS) are common causes of morbidity and mortality in the PICU. ECLS has been successfully used as a rescue therapy for these patients unresponsive to conventional methods [42–45]. As of July 2016, a total of 12,275 pediatric patients received ECLS, with 5036 patients supported for respiratory indications with a survival rate of 58% (ELSO) and in one report up to 90% [46]. Patients with respiratory syncytial virus infection, aspiration pneumonia, and near-fatal asthma [47] has better chances to survive while those with ARDS related to sepsis, pertussis, fungal pneumonia, disseminated herpes simplex virus infection, immunodeficiency, multiorgan failure, and longer duration of mechanical ventilation (>14 days) before ECLS deployment have higher odds of mortality [12, 23, 43, 44, 47–53]. Pre-ECLS severe acidosis in addition to renal failure and need for continuous renal replacement therapy (CRRT) have been related to lower survival, longer ECLS duration, and higher complication rate [54, 55].

ECLS utilization in pediatric population has slightly increased over the last 25–30 years [22, 43]. This increase has been steadier since 2002 with a total of 210 cases reported that year, later peaked in 2015 with 516 pediatric ECLS in total. This increase is believed to be due to expanding the inclusion criteria for this patient population [12, 49], increase use of ECLS in patients after congenital heart surgery, widespread use of VV ECLS, the advancement and the use of double lumen cannula in children, in addition to the expansion in extracorporeal cardiopulmonary resuscitation (ECPR) use [56, 57].

Conditions and comorbidities like immunosuppression, malignancy, and sepsis are considered acceptable indications for ECLS these days, but would have been contraindications to ECLS 15–20 years ago [26, 44, 49, 58–63]. Patients are more complex with more comorbidities. Paden et al. [26] reported an increase in pediatric ECLS comorbidities from 19% in 1993 to 47% in 2007. Recent reports showed that pediatric ECLS patients with malignancies and immunodeficiency could have a reasonable outcome with a survival rate 35–48% [26, 49, 58]. Patients with bone marrow (BMT) and stem cell transplant present a particular challenge. Gow et al. [62] showed ECLS survival rate of 21% based on the ELSO registry data in 2006. Of those four patients who survived ECLS in that study, only one patient was able to leave the hospital. The development of renal failure and multiorgan dysfunction were considered risk factors for death. There are few case reports that described successful use of ECLS in BMT and stem cell transplant patients secondary to different etiologies [63]. The decision to offer ECLS in this patient population should be on a case-by-case basis. Providers should take into consideration the overall patient prognosis from the underlying illness, assess the presence of multiorgan dysfunction and understand the family wishes for their loved ones before considering ECLS as an option.

VA support has been for many years the mode of choice for pediatric respiratory ECLS [57]. It is still the predominant mode found in the ELSO registry. The utilization of VV ECLS is gaining popularity in pediatrics [26, 44, 46, 64, 65••, 66]. In 2011, VV ECLS cases outnumbered VA ECLS cases in pediatric respiratory indications. Now, in 2017, VV ECLS is considered the standard of care in pediatric patients with severe respiratory failure unresponsive to conventional therapies. Pettignano et al. [64] reported the early successful use of VV ECLS for this patient population. Eighty patients received ECLS in his center over a period of 11 years (1991–2002). Sixty-eight patients received VV ECLS with a survival rate of 81% compared to 14 VA ECLS patients with a survival rate of 64%.

The cannulation techniques for VV ECMO in pediatrics have also evolved over the last 10 years. Multisite venovenous cannulation was the preferred method used in pediatric respiratory ECLS. The continued advancement of VVDL, especially in the late 2000's when the bicaval wire-reinforced catheters was approved by the food and drug administration, single-site cannulation using these cannulas became a common practice [65••, 67]. In 2011, VVDL cannulation for VV ECLS represented 71% of the total cannulation. The use of VVDL cannulas have provided improved VV ECLS pump performance with evidence suggesting reduction of the risk of recirculation traditionally related to the multisite approach. These cannulas can be inserted percutaneously, but need to be performed under imaging guidance to avoid the risk of atrial perforation or disruption to the hepatic vein [68, 69]. Using

fluoroscopy, ultrasonography, or a combination of both is recommended.

## Adult ECLS

ARDS in adults is well described in the literature with high rates of morbidities and mortality that can exceed 60%. Many conventional methods were studied to minimize this risk with mixed results [70]. ECLS use in adults with ARDS was first described in 1972 with Dr. Hill's experience. This was followed by the first multicenter randomized trial of the use of ECLS in adults with ARDS conducted by Zapol et al. [71] at the National Institute of Health (NIH) in 1979. The results were disappointing as the mortality rate was >90%. This put the brakes on using ECLS for adult population for two decades. In 2004, Dr. Bartlett and colleagues [72] described their experience at the University of Michigan in the largest retrospective study discussing the use of ECLS in 255 adult patients with ARDS between 1989 and 2004 with a survival rate of 52%. A protocol-driven algorithm was used in their institution since 1989 guiding the treatment of severe ARDS including the use of ECLS. While on ECLS, lung rest strategies, minimal anticoagulation, and optimization of oxygen delivery were the key factors. These results were encouraging, and ECLS was perceived again as a viable and successful option for adults with ARDS not responsive to maximum conventional therapy. This regained confidence in adult respiratory ECLS was boosted by the encouraging results of the CESAR trial (efficacy and economics assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure) by Peek and colleagues in the UK [73]. This study showed improved survival rate without disability at 6 months after discharge from the hospital (63 vs 47%; RR=0.69; CI 0.05–0.97,  $P = 0.03$ ) in adult patients with ARDS transferred to ECLS center. Sixty-eight patients were supported by ECLS of whom 43 (63%) survived.

As considered by many, the real rebirth of adult respiratory ECLS occurred in 2009. This milestone was driven by two major events: the 2009 influenza A (H1N1) pandemic and by the availability of adult-size bicaval dual-lumen cannula. These cannulae are inserted percutaneously using Seldinger technique under ultrasound or fluoroscopy in the right IJV and positioned to allow drainage of venous blood from the venae cavae and reinfusing to the RA.

Looking at the ELSO registry, there were less than 200 reported cases of adult respiratory ECLS per year, with then a substantial increase in 2009 with 493 cases. This increase continued and peaked in 2015 with 2046 cases. More than 75% of the total runs in these reports are venovenous ECLS mode (VV, VVDL, and VVDL-V) with overall survival rate of 58% [22].

Patients with viral or bacterial pneumonia, asthma, and trauma are more likely to survive [74–83]. Longer duration on mechanical ventilation before ECLS, multiorgan failure, central nervous system (CNS) events, fluid overload [74, 79, 84], non-pulmonary infections, higher peak inspiratory pressures, acidosis (pH <7.15) and higher PaCO<sub>2</sub> are associated with poor outcome. Interestingly, the use of neuromuscular blockade and prone positioning before ECLS was favorable.

This initial experience of adult respiratory ECLS with H1N1-induced ARDS came from Australia and New Zealand [83] with survival rate up to 79% at the end of the study period. Other reports from other countries came out describing their experience during the H1N1 pandemic in adults with variable result, but mostly with survival rates 50–70% [76–82]. The review of these reports revealed the importance to emphasize on the fact that ECLS is a complex, high-risk, and costly technology, and it should only be conducted in centers with sufficient experience, knowledge, and expertise in managing ECLS. As a result, a position paper [85••] was published in July 2014 by an international group of physician and health care providers in order to provide physicians, care providers, hospital administrators, and policy makers a description of the optimal approach to organizing ECLS program for adults with respiratory failure to ensure safety and proficiency.

VV ECLS using the bicaval dual-lumen cannula is the most common practice in adult respiratory indications [86, 87]. ECLS flow of 4–7 L/min would be ideal to provide adequate oxygenation and ventilation for an adult with severe ARDS. Additional venous drainage cannula (usually in the femoral vein) may be warranted to achieve this goal. Arterial oxygen saturation more than 80% would be acceptable given that clinical and laboratory evidence of adequate oxygen delivery to the tissues is achieved. ECCO2R is a modality of extracorporeal support that is increasingly utilized in adult respiratory population when hypercapnia is the main drive behind the need for excessive minute ventilation and ECLS support. ECCO2R allows the use of low blood flow (0.8–2 L/min) via a pumpless device to remove CO<sub>2</sub> efficiently. This typically is achieved by AV support accessing the femoral artery on one side and the femoral vein on the other side. This approach is ideal for patients with COPD exacerbation and hypercapnia.

Once on VV ECLS or ECCO2R, patients can soon be placed on minimal ventilator settings “rest settings,” continuous positive airway pressure (CPAP), or even get extubated to protect their lungs from further injury [87–89]. Early tracheostomy provides patients with less discomfort and allows early mobilization that would be beneficial to facilitate recovery. Early mobilization and rehabilitation is considered mandatory while patients on VV ECLS as a bridge to lung transplantation [87, 90–92].

There are few contraindications for ECLS that include advanced age, severe disability (wheelchair bound), intracranial bleeding, uncontrolled coagulopathy, mechanical ventilation more than a week with high peak pressure and oxygen requirements [87].

### ECLS Use in Pregnancy and Postpartum

The use of ECLS in pregnancy is uncommon; there are significant concerns regarding bleeding, fetal demise, and thrombotic complications. Pregnant women with H1N1 infection have higher risk of mortality and morbidity compared to non-pregnant women [93]. Over the last few years, especially during the H1N1 influenza pandemic, there have been many reports of successful ECLS use in pregnancy or postpartum period related to ARDS [83, 94, 95, 96•].

In the case series from Australia and New Zealand [83], they reported the use of ECLS in 10 pregnant or postpartum patients with the survival rate of 70%. Vaginal bleeding was reported in 9% of all patients included in the study. Sharma et al. [96•] performed a literature search from 2009 to 2014 looking at the use of ECLS in pregnancy and postpartum. Thirty-one reports were found, 16 reports of VA ECLS and 15 of VV ECLS with a total of 67 patients. Overall maternal survival rate was 80% while fetal survival was slightly lower than 70%. Most common indications were severe ARDS, postpartum cardiogenic shock, and amniotic fluid embolism. In one case, delivery by cesarean section was performed during ECLS; otherwise, delivery of the fetus was deferred. Anticoagulation management was conservative maintaining lower therapeutic levels of activated clotting time (ACT) and activated partial thromboplastin time (aPTT). The author recommends using ACT levels 160–180 s and aPTT 50–80 s. There were few cases with mild to moderate amounts of postpartum vaginal bleeding with one case of catastrophic hemorrhage. The most common bleeding sites were around tracheostomy and ECLS cannulation sites. The use of ECLS in pregnancy is controversial. There are no guidelines for its use in this patient population yet, however recent reports over the last 8 years showed that ECLS has been successfully used in pregnancy and postpartum patients for cardiopulmonary failure with good maternal and fetal outcomes. ECLS seems to be underutilized in this patient population. Careful patient selection and cautious anticoagulation management can reasonably minimize bleeding risk.

### ECLS in Trauma

Acute hypoxic respiratory failure and ARDS secondary to trauma is well recognized and is associated with high mortality and morbidity. Pulmonary contusions occur in 50% in

these patients. Reid et al. [97•] reported their experience over 10 years (April 2002 to April 2012) utilizing ECLS for respiratory indications in trauma patients. Fifty-two patients were included in that review with moderate to severe head injury in 30 (58%) cases. All patients had multiple traumas and most of them (77%) had rib fractures with hemothorax and pneumothorax. Thirty-one percent of these patients underwent surgical procedure while on ECLS. VV ECLS and ECCO2R were the main modes of support. Their overall survival rate was 79%. Out of the 14 patients with intracranial bleeding, 11 ended up with an external ventricular drain and three underwent craniotomies. Multiorgan failure was the major cause of mortality; only one patient suffered from catastrophic bleeding and one with severe brain damage who eventually died. Other reports [98, 99] including more recent study by Guirand et al. [100] supported the use of ECLS mostly by VV support in trauma ARDS patients with favorable outcomes.

### Cardiac ECLS and ECPR

ECLS is still considered the most common form of mechanical circulatory support in patients with cardiac failure unresponsive to conventional therapies. Cardiac ECLS has been consistently growing among different age groups over the last few years [14, 26, 32•, 33, 34]. As of July 2016, a total of 23,874 cardiac ECLS cases reported at the registry with an overall survival rate of 44.6%, with 42% in neonates, 51% in pediatrics, and 41% in adults (ELSO). Most of these patients (>95%) is supported by VA ECLS either via cervical or central cannulation, the later being more common in the immediate post-operative period in neonates. Pediatric patients with myocarditis have the best chances to survive (up to 72%). Cardiac ECLS is provided as a mean to organ recovery or as a bridge to transplant. Newer devices like ventricular assist devices (VAD) are more durable. Its use for cardiac support is growing over the last 15 years. VADs are smaller and simpler devices compared to ECLS, which allows early mobilization.

ECPR is defined as applying ECLS during cardiac arrest while performing cardiopulmonary resuscitation, or when repetitive arrest events occur without return of spontaneous circulation for >20 min [14]. As of July 2016, there are 7217 cases of ECPR reported to the ELSO registry with 1336 in neonates, 2996 in pediatrics, and 2885 in adults with overall survival rate of 37% (41% in neonates and pediatrics and 29% in adults) [22]. The use of ECPR has increased over the years [101]. Pre ECPR acidosis, prematurity, and complication during ECLS (CRRT, intracranial bleeding, persistent metabolic acidosis) are associated with increase odds of death, while cardiac disease (e.g., arrhythmias, myocarditis) and neonatal respiratory illness are associated with improved outcome [56, 102, 103•, 104, 105]. Recent reports showed the increasing

use of ECPR in adult population with a trend towards decreased survival in recent years (27%).

ECPR practice is institution dependant and it has been mainly limited to cardiac ICUs and for in-house arrest only. There have been few reports of ECPR use for out-of-hospital cardiac arrest with documented survival and intact neurological outcome [106, 107].

### ELSO

The Extracorporeal Life Support Organization (ELSO) was founded in 1989 (<https://www.elseo.org>). It is an international non-profit consortium of health care centers and individuals who are dedicated to the development, evaluation, and improvement of ECLS. ELSO maintains the world's largest registry of data on ECLS patients, with voluntary submission of this data. It provides ELSO centers with biannual reports on center-specific as well as worldwide number of cases, outcomes, and complications. Other functions of ELSO include providing data for quality assurance and research, which has been growing. There are just fewer than 10,000 ECLS publications listed in PubMed as of January 2017. It also publishes the ELSO Redbook, which is considered the definitive reference for ECLS. ELSO has been partnering with its global chapters (EuroELSO, Asia-Pacific ELSO, Latin American ELSO, and South and West Asia ELSO) to advance ECLS support internationally. There are published guidelines that are available for public describing useful and safe ECLS practice; these guideline are revised regularly.

### Complications

Bleeding is still a major complication during ECLS. Forty-six mechanical and patient related complications are recorded through the registry every year. Oxygenator failure is the most common mechanical complication. Table 1 summarizes the most common events reported to ELSO as of July 2016 [22].

### Patient Management During ECLS

ECLS patient management is complex. It starts with patient selection and initiation of ECLS. This is a large topic to cover in this context, so for that reason; we will briefly cover four major areas: ventilator management, anticoagulation, fluid and nutrition, and neurological management.

### Ventilator Management

Understanding the role of ECLS in respiratory indications is the key. It is important to mention that ECLS is a support



**Table 1** Mechanical and patient-related complications in respiratory ECLS

ECLS respiratory complications—percent reported (% survival)			
Complication	Neonates	Pediatrics	Adults
Mechanical			
Oxygenator failure	5.7 (53)	10.6 (43)	9.1 (47)
Pump malfunction	1.6 (65)	2.2 (47)	1.5 (40)
Oxygenator clots	16.7 (63)	11.1 (52)	13.6 (57)
Cannula problem	11.5 (65)	15.3 (54)	5.9 (47)
Cannula site bleeding	7.9 (63)	18.3 (54)	13.2 (51)
Patient related			
Seizures, clinical–EEG	8.7 (60)–1.4 (49)	4.8 (36)–1.6 (37)	1.1 (42)–0.4 (43)
CNS infarcts	6.8 (53)	4.2 (34)	2 (29)
CNS hemorrhage	7.6 (43)	6.4 (22)	3.9 (21)
Dialysis required	3.1 (39)	11.1 (33)	9.9 (43)
CAVHD required	2.2 (42)	8.9 (40)	11.8 (45)
Culture proven infection	5.8 (51)	16.8 (48)	17.5 (48)

EEG electroencephalogram, CAVHD continuous arteriovenous hemodialysis

modality not a cure. It provides efficient gas exchange using an artificial lung, allows time for ECLS providers to treat the underlying lung disease and prevent further iatrogenic lung injury.

Gentle ventilation is a very important principle in respiratory ECLS. Using high pressures trying to “open the lungs” is a dangerous maneuver that can lead to further lung injury and poor outcomes [71]. Applying lung “rest settings” on the ventilator should occur within the first few hours after initiation of ECLS [108•]. This can be achieved in many formats. Conventional ventilation using synchronized intermittent mandatory ventilation (SIMV) pressure control (PC) with pressure support (PS) is one way. Minute ventilation will be brought down to a minimum. PC of 5 cmH<sub>2</sub>O above positive end expiratory pressure (PEEP) with a rate of 5, PEEP of 5–15 cmH<sub>2</sub>O and PS of 5–10 is acceptable as long as the peak inspiratory pressure (PIP) stays below 20 and never exceeds 25 cmH<sub>2</sub>O. In addition to being protective of further iatrogenic lung injury, the use of this mode allows the providers to prevent any swings in PIP that may occur using a volume control mode and enable them to objectively calculate the dynamic compliance of the lung as a measure of daily progress.

HFOV can also be used during ECLS. It can be advantageous in cases of severe air leak syndrome, severe pulmonary edema, and pulmonary hemorrhage. It is important to minimize the minute ventilation and bring ventilation settings (amplitude and frequency) to a minimum. Mean airway pressure should be kept below 20 cmH<sub>2</sub>O and never exceeds 25. It is uncommon to maintain patients on HFOV during ECLS course; its use could make it difficult to perform pulmonary toilet, assess tidal volumes, and patient might need heavy sedation.

Airway pressure release ventilation (APRV) or bi-level mode can be used emphasizing the same principles. P High can be set at 10–15 cmH<sub>2</sub>O as long as the total pressures stay below 20 cmH<sub>2</sub>O and never exceeds 25. T High (time allowed for P High to be delivered) can be extended (6–10 s) to guarantee further recruitment as patient can breathe spontaneously during this.

CPAP with PS is a modality that is more acceptable now especially in awake patients with or without tracheostomy. Patients, especially adults, can be extubated early in the ECLS course.

Pulmonary toilet is pivotal in managing these patients, by frequent suctioning of mucous plugs and secretion. Bronchoscopy should be used liberally for that purpose. Saline installation in the endotracheal tube can facilitate that. Other materials like pulmozyme and perfluorocarbon liquid have been used with variable results.

### Anticoagulation Management

The interaction between the blood and the biomaterials of the ECLS circuit can lead to unwarranted effects by activating platelets and coagulation factors that promotes thrombosis and consumptive coagulopathy [109]. As a result, using anticoagulation therapy is needed. The use of unfractionated heparin (UFH) has been the gold standard. It is cheap, available, has a short half-life, and can be reversed with protamine sulfate if needed. On the other hand, UFH is an indirect anticoagulant; it works by potentiating antithrombin (AT) effect to inhibit “free” thrombin; it does not inhibit clot-bound or circuit-bound thrombin. Monitoring and managing anticoagulation therapy during ECLS is challenging especially in neonates and young children. Laboratory monitoring is typically done

in vitro which does not account for the in vivo endothelial effect. Managing coagulation starts before ECLS, once a patient is considered a candidate for ECLS, basic coagulation laboratory values including platelets, aPTT, prothrombin time (PT), AT level, and fibrinogen are obtained. An attempt should be made, if possible, to correct any deficiency by replacing with platelets, fresh frozen plasma, and cryoprecipitate. This approach may facilitate UFH management after ECLS initiation.

A loading dose of UFH (50–100 units/kg) is usually given during cannulation just before placing the cannulae in the vessels.

ACT has been, for decades, the most commonly used routine whole blood test [110]. It measures how many seconds that takes a blood sample to form a clot. It is inexpensive, and can be performed quickly at bedside test, but it is not specific and provides a general idea about coagulation. For example, a prolonged ACT (>250) could indicate thrombocytopenia, platelet dysfunction, consumptive coagulopathy, excessive heparin, or a combination of these events. More detailed testing is needed to determine the next appropriate action [111]. Acceptable range is 180–220 s. That can be lower (160 s) if there are concerns about bleeding.

aPTT is a plasma-based test that measures time to fibrin formation. It has been an acceptable mean to titrate anticoagulation therapy, and there is decent experience among providers, but it could show a lot of variability, and its use in critical conditions might be questionable [112••]. Acceptable range of 1.5–2.5X patient baseline or 60–90 s is reasonable.

Anti-Xa assay (Heparin level, Heparin assay) is a plasma-based test that measures the UFH effects based on its ability to catalyze AT inhibition on Factor Xa.

Appropriate Anti-Xa levels of 0.3–0.7 unit/mL correlate well with UFH effects and showed to minimize blood sampling, blood products transfusions with less bleeding and clotting complications.

Thromboelastogram (TEG) is another whole blood point of care test that examines the clot formation, strength, and fibrinolysis. It is not widely available; there is an element of subjectivity to the results interpretation, and there is limited data on improved outcomes with its use.

Direct antithrombin inhibitors' use has been documented in ECLS in cases of heparin induced thrombocytopenia (HIT) or heparin resistance. Bivalirudin and argatroban have been used with some promising results [113, 114]. For more details on this topic, please visit ELSO website—guidelines <https://www.else.org/resources/guidelines.aspx>.

### Neurological Management: Sedation, Analgesia and Neuromuscular Blockade

Optimal sedation and analgesia during ECLS remains poorly defined. Many studies have demonstrated the need to escalate sedation requirement during ECLS [115–119]. Fentanyl and

morphine [120] are the most commonly used opioids in ECLS. Escalation of these medications have been documented and attributed to an increase in the volume of distribution, increased sequestration in the circuit tubing and oxygenator, and decreased metabolism, at least in the case of morphine use [121], to its active metabolites. The use of benzodiazepine (e.g., midazolam and lorazepam) and dexmedetomidine [122, 123] are common practices in different age groups. Dexmedetomidine is an  $\alpha$ -2 adrenergic receptor agonist that has analgesedative effects that may facilitate weaning heavy sedation. It is not uncommon for ECLS patients to be heavily sedated during the first few days. The use of muscle relaxation is commonly used in cannulation, decannulation, and during procedures. It should not be a routine practice. Non-depolarizing agents are commonly used in PICU settings including ECLS patients when necessary. These agents can be used as continuous infusion (e.g., Cisatracurium, Atracurium, vecuronium) or bolus dosing (Rocuronium, vecuronium). Cisatracurium is considered an appropriate agent to use in ECLS patients because of its reasonable recovery time once turned off (20–30 min), safety profile, and ability to use in patients with multiorgan failure. Cisatracurium is eliminated by ester hydrolysis and Hofmann elimination. It is recommended to perform regular neurological examination on heavily sedated patients early in their course once or twice a day by lifting off the muscle relaxation and possibly reducing the sedation infusion.

The goal of minimizing sedation while maintaining comfort is ideal. Non-medical maneuvers including child life support, music, playing games, reading books, and family involvement play a major role in caring for these patients with less sedation, less withdrawal, and faster recovery.

Frequent neurological examination is critical during ECLS. Intracranial complications especially during VA ECLS are serious [124–126]. Clinicians should be vigilant, performing neurological assessments daily. A sudden unilateral change in the diameter of one pupil should prompt an aggressive investigation for an acute intracranial pathology especially bleeding. Serial head ultrasound can be performed at the bedside for neonates and young infants receiving ECLS to assess for intracranial abnormalities.

### Fluids and Nutrition

Adequate nutrition is pivotal for recovery in critical illness. Enteral nutrition, even at trophic amounts, is preferred [66] to maintain gut integrity, reduce risk of bacterial translocation and risk of TPN-related cholestasis, but total parenteral nutrition can be used if needed.

Maintaining strict fluid balance in ECLS patients is crucial. Fluid overload has been associated with increased mortality [52, 127••]. It is not unusual to require large volume of fluids at the initiation of ECLS, but clinician should be proactive

instead of reactive in fluid management. The use of diuretics, concentrating medication infusion, and the judicious early initiation of ultrafiltration and CRRT has proven to reduce ECLS duration and length of stay [52, 53, 128, 129].

## Conclusion and the Future

ECLS or ECMO is an acceptable mode of support in neonates, pediatrics, and adults with acute cardiorespiratory failure unresponsive to conventional therapies with an overall survival of 58%. The use of ECLS is growing especially in adult respiratory indications, and will continue to grow. Bleeding is still one of the most challenging complications. The development of new devices over the last few years resulted in a much simpler, safer, and prolonged ECLS support. New styles of patient management including minimal sedation, spontaneous breathing, early tracheostomy, and early mobilization are becoming more common. The next generation of ECLS devices will be easier to manage by caregivers, less thrombogenic, and more durable with less or no need for systemic anticoagulation. As per Dr. Bartlett, these are the highlights of the next era in ECLS care “ECMO III.”

## Compliance with Ethical Standards

**Conflict of Interest** Omar Al-Ibrahim and Christopher M.B. Heard declare they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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