



## **Extracorporeal Life Support Organization (ELSO)**

### **Guidelines for Neonatal Respiratory Failure**

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#### **Introduction**

This guideline describes prolonged extracorporeal life support (ECLS, ECMO), applicable to **newborn infants with respiratory failure**.

These guidelines describe useful and safe practice, prepared by ELSO and based on extensive experience. The guidelines are approved by the ELSO Steering Committee and are considered consensus guidelines. The guidelines are referenced to the ELSO Red Book which includes evidence based guidelines where available. These guidelines are not intended to define standard of care, and are revised at regular intervals as new information, devices, medications, and techniques become available.

The background, rationale, and references for these guidelines are found in “Extracorporeal Life Support: The ELSO Red Book, 5<sup>th</sup> Edition, 2017” published by ELSO and Seminars in Perinatology 2018. Contributing authors include: Anne Ades, MD, Thane Blinman, MD, Rachel Chapman, MD, Jim Connelly, RT, Kathryn Fletcher, MD, John Flibotte, MD, Theresa Grover, MD, Holly Hedrick, MD, Lindsay Johnston, MD, Aditi Kamdar, MD, Sarah Keene, MD, Roxanne Kirsch, MD, Daniel Licht, MD, Burhan Mahmood, MD, Nan Lin, MD, Dave Munson, MD, Eugenia Pallotto, MD, Debra Newton, RN, Leslie Raffini, MD, Sue Williams, RN.

These guidelines address technology and patient management during ECMO.

Equally important issues such as personnel, training, credentialing, resources, follow up, reporting, and quality assurance are addressed in other ELSO documents or are center- specific.

The reference is:

ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support  
Extracorporeal Life Support Organization, Version 1.4 December 2017  
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# Neonatal Respiratory ECMO

## **I. Patient Condition**

### **A. Indications**

As of July 2017, over 87,366 patients have been treated with ECMO worldwide including 35,598 neonates.<sup>1</sup> Most neonatal cases treated with ECMO have a primary respiratory diagnosis (78%), with the remainder of cases having a primary cardiac diagnosis. Approximately 4% of cases underwent extra-corporeal cardiopulmonary resuscitation (ECPR). The latest ELSO registry data demonstrates that the volume of neonatal ECMO cases is trending down and currently accounts for <10% of total annual ECMO runs.

Neonates, term or late preterm (34 0/7–36 6/7 weeks of gestation) with severe respiratory and/or cardiac failure refractory to maximal medical management, with a high likelihood of mortality and a potentially reversible etiology are considered for ECMO therapy.

Congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS) and persistent pulmonary hypertension (PPHN) are the most common neonatal diagnoses, accounting for almost 75% of all neonatal respiratory ECMO cases. Additional diagnostic categories reported to the ELSO registry include sepsis (10%), respiratory distress syndrome (5%) and “other” (9%).<sup>1</sup>

ECMO may be indicated in the following settings:

1. Oxygenation Index > 40 for > 4 hours  
Oxygenation Index:  $\frac{\text{Mean Airway Pressure} \times \text{FiO}_2}{\text{Post ductal PaO}_2} \times 100$
2. Failure to wean from 100% oxygen despite prolonged (> 48h) maximal medical therapy or persistent episodes of decompensation
3. Severe hypoxic respiratory failure with acute decompensation (PaO<sub>2</sub> <40) unresponsive to intervention
4. Severe pulmonary hypertension with evidence of right ventricular dysfunction and/or left ventricular dysfunction
5. Pressor resistant hypotension

<sup>1</sup>International Summary of ELSO Registry Report. Extracorporeal Life Support Organization (ELSO). January and July 2017, Ann Arbor, Michigan

### **B. Contraindications:**

Contraindications for neonatal respiratory ECMO include 1. lethal chromosomal disorder (includes trisomy 13, 18 but not 21) or other lethal anomaly 2. irreversible brain damage 3. uncontrolled bleeding and 4. Grade III or greater intraventricular hemorrhage.

Relative contraindications include 1.irreversible organ damage (unless considered for organ transplant) 2. <2 Kg<sup>1</sup> 3. <34 weeks post-menstrual age because of the increased incidence

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<sup>1</sup> Revenis ME, Glass P, Short BL: Mortality and morbidity rates among lower birth weight infants (2000 to 2500 grams) treated with extracorporeal membrane oxygenation. J Pediatr 1992, 121(3):452-458.

of increased intracranial hemorrhage<sup>2</sup> and 4. mechanical ventilation greater than 10-14 days. A fifth relative contraindication is in patients with disease states with a high probability of a poor prognosis. In patients with congenital diaphragmatic hernia (CDH), the absence of an initial response to resuscitation with preductal saturation >85% and a PCO<sub>2</sub> < 65 mmHg are strongly associated with worse prognosis attributable to pulmonary hypoplasia and constitutes relative exclusion criteria for ECMO in some centers.

When there is concern to the appropriateness of ECMO, the specific issues should be discussed with the relevant medical subspecialists prior to cannulation. This allows an in-depth discussion as to the risks of the procedure vs. the potential benefits. There will, however, be situations where time does not allow for a complete evaluation of the full prognosis. In these cases, discussions should occur shortly after cannulation. If ECMO support is not in the patient's best interest, it should be discontinued.

## **II. Extracorporeal Circuit**

### **A. Criteria for selecting circuit components**

The circuit is planned to be capable of total support for the patient involved.

#### **1. Blood flow for cardiac support**

Access is venoarterial. Goal ECMO blood flow is about 100 mL/kg/min (80-140 mL/kg/min) in neonates. The best measure of adequate systemic perfusion is venous saturation greater than 70%, so flow should be adjusted to reach this goal accordingly. Achieving a desired flow is determined by vascular access, drainage tubing resistance, pump properties, intravascular volume, and systemic vascular resistance.

#### **2. Blood flow and gas exchange for respiratory failure (VA or VV)**

The membrane lung and blood flow should be capable of oxygen delivery and CO<sub>2</sub> removal at least equal to the normal metabolism of the patient (i.e. an oxygen delivery of 6 mL/kg/min for neonates). This will usually equate to VV blood flows of 120 mL/kg/min for neonates. Oxygen delivery capability is determined by blood flow, hemoglobin concentration, inlet hemoglobin saturation, and membrane lung properties. Carbon dioxide removal always exceeds oxygen delivery when the circuit is planned for full support.

### **B. Circuit components**

The basic circuit includes a blood pump, a membrane lung, and conduit tubing. Depending on the application, additional components may include a heat exchanger, in-line pressure compliance reservoir (bladder), monitors, and alarms.

### **C. Pump**

The pump should be able to provide full blood flow for the patient, as defined above. Any pump which meets the specifications can be used (modified roller with inlet pressure

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<sup>2</sup> [Hardart GE, Hardart MK, Arnold JH](#). Intracranial hemorrhage in premature neonates treated with extracorporeal membrane oxygenation correlates with conceptional age. [JPediatr](#) 2004, 145(2):184-9.

control; centrifugal or axial rotary pump with inlet pressure control). However, there is variation amongst centers regarding the use of roller vs. centrifugal for neonates. Many centers have made the transition from roller pumps to centrifugal models, but some centers have encountered unacceptable levels of hemolysis with centrifugal pumps, causing them to revert to roller pumps. Other centers have not experienced this level of hemolysis with centrifugal pumps. Rigorous data regarding choice of pump type in neonates is lacking, so pump choice is based on expertise and preference of each center.<sup>1,2</sup>

<sup>1</sup>Shade BC, Schiavo K, Rosenthal T, Connelly JT, Melchior RW. A single singlecenter's conversion from roller pump to centrifugal pump technology in extracorporeal membrane oxygenation. *Perfusion*. 2016 Jun 5.

<sup>2</sup>Lou, et al. Hemolysis in pediatric patients receiving centrifugal-pump extracorporeal membrane oxygenation: prevalence, risk factors, and outcomes. *Crit Care Med*. 2014 May;42(5) 1213-20.

### **Inlet (suction) pressure**

With the inlet line occluded, the suction pressure should not exceed -350 mmHg. The inlet pressure can be very low (-325 mmHg) when the venous drainage is occluded (chattering), which causes hemolysis. Inlet pressure in excess of -350 mmHg can be avoided by inherent pump design or through a servocontrolled pressure sensor on the pump inlet side.

### **Outlet pressure**

With the outlet line occluded the outlet pressure should not exceed 325 mm/Hg (inherent in the pump design or by a servocontrolled system).

### **Power failure**

The pump should have a battery capable of at least one hour of operating time and a system to hand crank the pump in the event of power failure. The pump and circuit should have a mechanism to alarm for or **prevent reverse flow** (arterial to venous in the VA mode) if the power fails.

## **D. Membrane Lung (Oxygenator)**

The gas exchange material in membrane lungs may be solid silicone rubber, a microporous hollow-fiber (polypropylene for example), or a solid hollow-fiber membrane (PMP, polymethyl pentene for example). Membrane surface area and mixing in the blood path determine the maximum oxygenation capacity (the rated flow).

When used for total support, the membrane lung should provide full O<sub>2</sub> and CO<sub>2</sub> exchange for the patient as defined in II. A. The gas exchange capability of a specific membrane lung is described as “rated flow” or “maximal oxygen delivery.” These are two ways of describing the amount of desaturated (75%) blood that can be nearly fully saturated (95%) per minute.

**Rated flow** is the flow rate at which venous blood (saturation 75%, Hb 12 mg) will be fully saturated (95%) at the outlet of the membrane lung. **Maximal O<sub>2</sub> delivery** is the amount of oxygen delivered per minute when running at rated flow. This is calculated as outlet minus inlet O<sub>2</sub> content (typically 4-5 ml/dL, same as the normal lung) times blood flow. For example, a specific device has a rated flow of 2 L/min, (max O<sub>2</sub> 100 ml/min). If the blood flow required for total support of a patient is 1 L/min (O<sub>2</sub> about 50 ml/min) this membrane lung will be adequate. Biomedical device companies offer oxygenators of smaller sizes that allow lower

priming volumes for neonates. The published rated flow for these devices should be consulted prior to use in order to assure that the chosen oxygenator will allow enough flow per patient size.

In venovenous mode, recirculation of infused blood may occur, raising the inlet saturation well above 75%. In this situation, the outlet-inlet O<sub>2</sub> difference per unit of blood flow is decreased, and lower blood flow, cannula repositioning, increased patient volume or higher hematocrit is/are required to provide the desired amount of O<sub>2</sub> delivery.

#### **E. Sweep gas**

For most applications, the sweep gas will initially be 100% oxygen at 0.1 L/min. Increasing the sweep flow will increase CO<sub>2</sub> clearance but will not affect oxygenation.

**Avoiding air embolism** via the membrane lung. Air or oxygen bubbles can pass through the membrane into the blood if the sweep gas pressure exceeds the blood pressure or if the blood pressure is subatmospheric (this occurs when there is no blood flow or blood pressure and blood drains from the membrane lung into the tubing by gravity, entraining air through the membrane lung). This is a specific problem with microporous hollow fiber devices but can also occur with silicone or polymethylpentene (PMP) lungs due to very small holes in the membrane which can allow air entrainment. Prevention is achieved by maintaining the blood side pressure higher than the gas side pressure. This is accomplished by including a pressure pop-off valve or pressure servo regulation control in the sweep gas supply and by keeping the membrane lung below the level of the patient, so that if the pump stops, the risk of entraining air from the room will be minimized. Even with silicone and PMP lungs, it is safest to maintain the membrane lung below the level of the patient.

#### **F. Priming the circuit**

The assembled circuit is primed under sterile conditions with a crystalloid prime solution resembling normal extracellular fluid containing 4-5 mEq/L potassium. The prime is circulated through a reservoir with the degassing port opened on the oxygenator. All connections, pigtails and stopcocks are degassed (vented) to ensure an airless bubble-free circuit. The circuit can be crystalloid primed for immediate use or stored for 30 days prior to use. Most centers will discard a crystalloid primed circuit after 30 days due to local infection prevention and control policy.

Before attaching the circuit to the patient, the heat exchanger water bath is turned on to warm the fluid. ECMO is usually instituted with only a crystalloid prime in adults, but in neonates, most centers follow a “recipe” to reconstitute banked blood products into a priming solution that is more bio-compatible. Many centers add human 25% albumin (12.5 gm) to “protein coat” the tubing surfaces before blood exposure. RBCs are routinely added to “chase” the crystalloid solution and achieve a goal hematocrit of 30-40%. When blood is added to the prime, heparin is added to initiate anticoagulation (100 units of heparin per unit of PRBC) followed by a buffer solution, typically sodium bicarbonate. Only when the prime is circulating through the priming reservoir is calcium gluconate added to replace the calcium bound by the citrate in the bank blood. Sweep flow is added to assure gas exchange via the oxygenator and is assessed against the patient CO<sub>2</sub>. It is desirable to attempt to match as closely as possible the pH and CO<sub>2</sub> of the prime with the most recent patient blood gas. If time allows, it is helpful to verify the electrolyte composition and ionized calcium before starting flow.

## **G. Heat exchanger**

The heat exchanger is integrated with the oxygenator and controls the blood temperature at a desired temperature (typically 37 degrees Celsius) by utilizing an external circulating water bath. Water heaters are standard practice in ECMO, as opposed to more cumbersome heater/coolers used in cardiopulmonary bypass. The water reservoir should be inspected regularly for clarity. Contact between the circulating water surrounding the oxygenator and the circulating blood path is very rare, but should be considered if small amounts of blood or protein are present in the water bath or if unexplained hemolysis occurs. All manufacturers have specific recommendations for routine maintenance and disinfection of their device. These recommendations should be followed and documented appropriately.

## **H. Monitors**

Monitors are designed to measure circuit function and to alarm the operator of abnormal conditions. Most circuits will include:

1. Blood flow is commonly monitored by direct measurement of blood flow using an ultrasonic detector or can be calculated based on pump capacity and revolutions per minute for a roller pump using standardized tubing.

2. Pre and post membrane lung blood pressure measurements can include maximum pressure servo regulation control to avoid over pressuring.

3. Pre pump venous drainage line pressure (to avoid excessive negative suction pressure by the pump) can be used as a servo regulation system to prevent excessive suction.

4. Pre and post membrane lung oxyhemoglobin saturation measurements: The venous oxyhemoglobin saturation is a valuable parameter for managing and monitoring both circuit and patient factors related to oxygen delivery and consumption. The post membrane lung saturation monitor will determine if the membrane lung is working at rated flow and if function is deteriorating. Blood gases are measured from pre oxygenator and post oxygenator sites either by continuous inline monitoring or batch sampling. The primary purpose of measuring blood gases (as opposed to inline saturation) is to determine the inlet and outlet PCO<sub>2</sub> to evaluate membrane lung function and blood pH to determine metabolic status.

5. Circuit access for monitors, blood sampling, and infusions: luer connectors and stopcocks provide access to the blood in the circuit. The number of access sites should be minimized, but at least two are necessary (pre and post membrane lung). Blood access sites should be avoided between the patient and the inlet of the pump because of the risk of entraining air. It is acceptable to use the circuit for all blood sampling and infusions. The one exception is the lipid infusion. This should be infused via a peripheral iv to avoid clot formation in the circuit.

## **I. Alarms**

Pre and post membrane lung pressure and alarms determine the transmembrane lung pressure gradient. Clotting in the oxygenator is represented by increasing membrane lung pressure gradient.

Many centers use a bubble detector on the blood return line. Pressure and bubble detector alarms can be used to clamp lines and turn the pump on or off to automate these safety factors.

#### **J. Blood tubing**

Tubing length and diameter will determine the resistance to blood flow. Tubing is chosen to allow free venous drainage, and avoid high resistance pressure drop on the blood return side. The blood flow through 1 meter of tubing at 100 mmHg pressure gradient for common internal diameter in inches is: 3/16:1.2 L/min; 1/4:2.5 L/min; 3/8:5 L/min; 1/2:10 L/min. Quarter inch tubing is used routinely in neonatal patients.

A “bridge” between the arterial and venous lines close to the patient is a useful circuit component, particularly for periods off bypass during VA access, during weaning, or during an emergency. However, when the bridge is clamped, it is a stagnant area that can contribute to thrombosis requiring a system for purging the bridge of stagnant blood every 15 minutes.

An in-line compliant reservoir (bladder) may be added in the pre pump venous drainage line. This acts as a compliance chamber to help prevent excessive negative pressure that might cause cavitation. Non-invasive pressure measurements can also be obtained from this chamber, and this can be tied to a servo regulator system in the circuit. Use of a bladder is not required for centrifugal ECMO and is program-dependent.

### **III. Cannulation**

Vascular access is achieved by cannulation of the neck in neonates with respiratory failure. The blood flow resistance of the venous drainage cannula and intravascular volume status of the patient will determine the amount of total blood flow that can be delivered by the circuit. The resistance of the blood return cannula will determine the pressure in the post membrane lung blood return line, related to blood flow.

#### **A. Modes of ECMO**

- 1. Venoarterial** (provides cardiac and respiratory support)
- 2. Venovenous** (no hemodynamic support, preferred for respiratory support because it avoids using a major artery, avoids potential systemic embolism and provides oxygenated blood directly to the pulmonary circulation)

#### **B. Cannulas**

The term “cannula” refers to the catheter that goes directly into the vessel for ECMO to differentiate that device from all other catheters. The blood flow resistance of a vascular access cannula is directly proportional to the length and inversely proportional to the radius to the

fourth power. Therefore, the internal diameter of the cannula is the most important factor controlling blood flow resistance. Resistance also increases at higher flows. Cannula size is limited by patient and vessel size.

Appropriate cannulas for the majority of neonates:

1. VA: Single Lumen Venous (8 Fr, 10 Fr, 12 Fr or 14 Fr) + Arterial (8 Fr or 10 Fr)
2. VV: Double Lumen (13 Fr, 16 Fr)
3. Cephalad: A cannula can be placed in the cephalic IJ for improved drainage and to decrease venous congestion. 8 Fr or 10 Fr cannulas can usually be placed. The larger cannulas are preferred for improved drainage and decreased stasis. An arterial cannula is recommended as the drainage catheter due to the absence of side ports.<sup>1,2</sup>

<sup>1</sup>Skarsgard ED, Salt DR, Lee SK; Extracorporeal Life Support Organization Registry. Venovenous extracorporeal membrane oxygenation in neonatal respiratory failure: does routine, cephalad jugular drainage improve outcomes? *J Pediatr Surg* 2004 May;39(5):672-6

<sup>2</sup>Roberts J, Keene S, Heard M, McCracken C, Gauthier TW. Successful primary use of VVDL+V ECMO with cephalic drain in neonatal respiratory failure. *J Perinatol* 2016 Feb;36(2):126-31

## C. Cannulation

### 1. Methods

Cut down exposure of the neck vessels is usually necessary in neonates for both VA and VV support, although some centers with particular expertise have been successful with percutaneous VV cannulation.

### 2. Cannulation technique

In most situations, cannula selection occurs after cut down with direct inspection of the vessels. Some centers perform bedside ultrasound of the right neck vessels prior to cannulation to estimate the vessel size and guide selection. Some vasospasm can be expected, so a cannula with a diameter (size in Fr divided by 3.14) that is 80% of the diameter of the vessel can reliably be chosen. Additionally, some neonates are born with insufficient right neck vessels to accommodate the appropriately sized cannula to achieve desired flow. This is most common in patients with dextrocardia and left SVC or right congenital diaphragmatic hernia. If insufficient right neck vessels are identified, then the left neck can be used for cannulation. *In rare cases, peripheral cannulation is not possible.*

A bolus of heparin (typically 50-100 units per kg) is given directly to the patient prior to cannula placement.

**Direct cut down cannulation.** Cannulation is usually done in the ICU with full sterile preparation and OR team. Deep sedation/anesthesia with muscle relaxation is essential to prevent spontaneous breathing which can lead to an air embolus. Local anesthesia is used for the skin. Dissection exposes the vessels, and the artery is typically cannulated first, as it is the deeper of the two vessels in most cases. Direct handling of the vessels is minimized as much as possible to avoid spasm. Topical lidocaine or papaverine is helpful to avoid spasm. Ligatures are passed around the vessels above and below the cannulation site. Heparin is given IV (50-100 units per kg) directly to the patient, and the cephalic end of the vessels are ligated. The cardiac end of the vessel is occluded with a vascular clamp or forcep, the vessel opened, and the cannula placed. If the vessels are very small, if there is difficulty with cannulation, or if

spasm occurs, fine stay sutures placed in the proximal edge of the vessel are very helpful. The vessel is ligated around the cannula, often over a vessel loop “boot” or “bumper” to facilitate later cannula removal. Chest x-ray should be obtained to verify cannula tip location after ECMO support is initiated, and minor cannula position adjustments can be made. Echocardiography can be used in addition to assess position of the cannula tip in the right atrium or in the IVC for bicaval dual-lumen cannula.<sup>1</sup> Echocardiography can be particularly useful during dual-lumen cannula placement, as Doppler flow can guide accurate reinfusion jet flow across the tricuspid valve. In cases of VV ECMO, a vessel loop can be left around the pre-dissected common carotid artery, in case the patient must be converted to VA ECMO later.

<sup>1</sup>Irish MS, O'Toole SJ, Kapur P, et al. Cervical ECMO cannula placement in infants and children: recommendations for assessment of adequate positioning and function. *J Pediatr Surg* 1998 Jun;33(6):929-31

**Percutaneous cannulation.** Some centers have employed percutaneous cannulation techniques for VV ECMO in neonates, but it is not standard of care and has been met with increased risk of cardiac perforation during cannulation. Overall, it is not recommended in this patient group and should be conducted with extreme caution and only under imaging guidance with ECHO or fluoroscopy.

### **3. Venous drainage**

If venous drainage is inadequate, a separate drainage cannula may be required. The cephalic end of the jugular vein is most common. Some centers routinely place a cephalad venous cannula, but this is an institutional preference and is not mandatory. The femoral veins are usually insufficiently sized, but they may be assessed on a case by case basis.

### **4. Vessel reconstruction at decannulation**

Once the decision has been made to decannulate the patient, the decision must be made whether to ligate or reconstruct the neck vessels. Common carotid artery reconstruction has theoretic advantages and disadvantages. Carotid artery reconstruction should be considered in complex cardiac patients who may require future reconstructions for congenital cardiac disease or heart transplant for myocarditis. Additionally, some centers routinely reconstruct the artery and have found acceptable patency rates in the short term after repair. However, no study has shown a difference in long-term neurological outcomes when comparing those with and without carotid repair.<sup>1</sup> Thus, this decision can be left to the specific center and surgeon. Jugular venous repair is also not routinely performed, but it may be useful in a complex cardiac patient who may require a recurrent ECMO course in the future.

<sup>1</sup>Duggan EM, Maitre N, Zhai A, et al. Neonatal carotid repair at ECMO decannulation: patency rates and early neurologic outcomes. *Journal Pediatr Surg* 2015 Jan;50(1):64-8

## **IV. Management during ECMO**

### **A. Circuit related**

#### **1. Blood flow**

After cannulation, blood flow is gradually increased to mix the circulating blood with the prime; then, blood flow is increased until optimal flow is achieved. Cardiac stun can be avoided with slow increases in pump flow. For VA ECMO, flow is increased until the patient is well saturated (pre-ductal) and has an adequate blood pressure with SVO<sub>2</sub> 65–80%. For VV access, adequate support is defined as arterial saturation greater than 80%. The physiologic goals (mean arterial pressure, arterial and venous saturation) are set and blood flow is regulated to meet the goals.

	<b>VA ECMO</b>	<b>VV ECMO</b>
<b>SVO<sub>2</sub></b>	65-80%	N/A (trend)
<b>SpO<sub>2</sub></b>	> 90%	80 – 90%
<b>PaO<sub>2</sub></b>	60 – 80 mmHg	40 – 60 mmHg
<b>PaCO<sub>2</sub></b>	35 – 45 mmHg*	35 – 45 mmHg

*\*in select patients such as those with congenital diaphragmatic hernia or chronic lung disease, PaCO<sub>2</sub> goal may be 45 –55 mmHg*

The ventilator may be reduced to 'rest settings' once on adequate pump flow. The FIO<sub>2</sub> may be reduced to 21%. Some centers keep the FIO<sub>2</sub> at 30% to optimize perfusion of coronaries.

Readiness for decannulation is assessed differently for VV and VA ECMO. For VV ECMO, the patient is placed on full ventilatory support and the ECMO lung is isolated by weaning FiO<sub>2</sub> or stopping flow. For VA ECMO, flow is reduced to a minimum while on full vent support. In some cases, a clamp trial is performed for a short period of time, i.e. less than 30 minutes.

## **2. Oxygenation**

Oxygenation of the tissues is affected by blood flow and hemoglobin. Excessive PaO<sub>2</sub> can be seen with high flow VA bypass. The negative effects of unnecessary hyperoxia are well described in neonates of all gestational ages. Hence, adjusting flow and/or sweep gas to keep the PaO<sub>2</sub> under 100 mmHg should be considered. Cardiac tamponade should be ruled out if the PaO<sub>2</sub> of the patient's blood gas is the same as the post lung gas.

Critically ill newborns placed on VA ECMO are often on high dose inotrope infusions. A rapid increase in blood pressure may occur with initiation of ECMO flow, which can place neonates at increased risk for intracranial hemorrhage. Inotrope infusions should be titrated aggressively to maintain blood pressure in the goal range. Inotrope infusions may be required on ECMO if the systemic perfusion pressure is inadequate (low urine output, poor perfusion, elevated lactate). Systemic vasodilatation requiring pressor drugs is common in patients in septic shock.

If systemic oxygen delivery is not adequate (venous saturation less than 65% with elevated blood lactate levels) on VA ECMO, the pump flow can be increased until perfusion is adequate. Hemoglobin of 13-14, will optimize oxygen carrying capacity.

### 3. CO<sub>2</sub> clearance

CO<sub>2</sub> clearance is controlled by the sweep gas flow rate. CO<sub>2</sub> transfer across the membrane lung will exceed oxygen transfer. CO<sub>2</sub> clearance is incredibly efficient. Blood gas must be assessed soon after initiating flow to avoid hypocarbia. Sweep gas flow rates are often equal to blood flow rates. The sweep gas is weaned with clinical improvement. In VA ECMO, if limited by sweep flow meter calibration (i.e. < 0.1 L/min) or large oxygenator size, CO<sub>2</sub> may need to be added to the sweep gas to maintain CO<sub>2</sub> within the desired range. Water vapor can condense in the membrane lung resulting in poor CO<sub>2</sub> clearance, and it may be cleared by intermittently increasing sweep gas flow to a higher flow. This is referred to as "sighing the lung".

If the patient had subacute/chronic hypercarbia, the PaCO<sub>2</sub> should be normalized over a longer period of time rather than immediately in order to avoid swings of cerebral perfusion related to CO<sub>2</sub> and pH.

### 4. Anticoagulation

Although most pediatric centers have developed institutional guidelines for anticoagulation based on their experience, published literature, and ELSO guidelines, a survey of ELSO-registered ECMO centers demonstrated significant practice variation regarding dosing, monitoring, and titration of heparin.<sup>1</sup> It is important to note that anti-Xa, ACT, and PTT levels vary greatly from one laboratory to another due to differences in the reagents and coagulation analyzers used to perform the assays.

<sup>1</sup>Bembea, M.A., G. Rycus, P. Oldenburg, G. Berkowitz, I. Pronovost, P. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey. *Pediatric Critical Care Med* 14, e77 (2013).

#### 4a. Anticoagulation Monitoring

The whole blood **activated clotting time (ACT)** is the time (in seconds) in which whole blood clots in response to a fibrin activating reagent. Each ACT device has different upper limits with normal blood (120 to 140 seconds for most systems). Goal ACT levels are usually 1.5 times normal for the ACT measurement system, i.e. 180 - 220. ACT levels measured frequently in most centers, i.e. every 1-2 hours and prn. ACT is measured at the bedside. In addition to heparin, coagulation factors, thrombocytopenia, infection, and temperature also affect the ACT level.

**Partial thromboplastin time (PTT)** is affected by heparin, coagulation factor and antithrombin levels. The normal range for the aPTT is age-related, and neonates have higher values than older children and adults. In neonates, the PTT levels do not correlate well with anti-Xa or ACT levels. Additionally, the PTT is falsely prolonged in patients with elevated CRP and falsely decreased with elevated factor VIII levels.<sup>1</sup>

<sup>1</sup>Teruya J. Coagulation tests affected by acute phase reactants such as CRP and factor VIII. Paper presented at: International conference on hematology and blood disorders; September 23-25, 2013

The **anti-Xa assay** measures the anticoagulant effect of the heparin-AT3 complex or simply the heparin concentration, depending on the assay used to assess anti-Xa level. Various assays are used at different institutions and are not well standardized. Anti-Xa levels of 0.3-0.7 IU/mL or even up to 1.0 IU/mL used in older patients may be excessive for neonates given their decreased concentration of clotting factors and decreased thrombin. Levels 0.25-0.5 IU/mL may be more appropriate for the neonatal population, but there is little evidence to support this strategy. Additionally, anti-Xa levels can be falsely lowered by hyperlipidemia, hemolysis, and hyperbilirubinemia, which occur frequently in critically ill neonates.

**Thromboelastography (TEG)** measures the time to form a clot and the density/strength of the clot. TEG may be of particular value when used to evaluate a bleeding patient in order to distinguish between an underlying coagulopathy and surgical bleeding.

**Antithrombin (AT3)** inhibits coagulation. Heparin acts by binding and “activating” antithrombin. If the AT3 concentration in plasma is low, clotting can occur even when large doses of heparin are given. Low plasma concentrations of AT3, which are physiologically normal in neonates, may also contribute to heparin resistance.

The normal range for AT3 levels is considered 80-120% of control, however, it is important to note that term neonates have an antithrombin level of approximately 60% of adult values.<sup>1</sup> Low AT3 can be treated by giving fresh frozen plasma or recombinant AT3.

<sup>1</sup>Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. American Journal of Pediatric Hematology/Oncology. 1990;12(1):95-104.

**Thrombocytopenia** (platelet count less than 150,000) is common in ECMO patients. It may be a consequence of the primary disease, critical illness, medications, and/or caused by blood surface exposure and consumption. Circulating platelets adhere to the plastic surfaces, and undergo a “release reaction” which attracts other platelets. These aggregates of “effete” platelets circulate in the blood and are removed by the liver and spleen.

The usual practice is to transfuse platelets to keep the count greater than 80,000 or 100,000. Even though the platelet count is over the desired target, platelet function may be impaired. In neonates, a platelet transfusion of 10 ml/kg should increase the platelet count by 50,000-100,000/ $\mu$ l. Many centers keep the platelet count > 100,000 for the first 3 days of the ECMO run, the time when the risk of IVH is greatest.

**Fibrinogen.** Even though fibrin formation is inhibited by anticoagulants, fibrinogen can become depleted during ECMO. Fibrinogen levels are measured daily and maintained within the normal range (>150 mg/dl) by transfusion of fresh frozen plasma or cryoprecipitate. Cryoprecipitate is derived from FFP and contains fibrinogen, factor VIII, von Willebrand factor (vWF), and factor XIII.

#### 4b. Anticoagulants

1. **Heparin** (unfractionated heparin or UNFH) is given as a bolus (50-100 units per kilogram) at the time of cannulation followed by a continuous infusion during ECMO. Given that premature infants are at higher risk for IVH, the cannulation bolus dose is often 50 units/kg.

The neonatal ECMO circuit prime is generally anticoagulated with 100 units of heparin per unit of packed red blood cells (PRBC) for the neonatal circuits with ¼ inch tubing. UNFH infusion rates in neonates on ECMO usually start at 28-30 U/kg/hr. Neonates may require higher doses of UFH due to their low plasma concentrations of ATIII. Note: Heparin Induced Thrombocytopenia (HITT) is extremely rare in neonates.

2. **Direct thrombin inhibitors (DTIs).** Argatroban and bivalirudin are examples of DTIs. They may be used as an alternative to heparin in HITT patients. Some centers are using DTIs as the primary anticoagulant. They do not require ATIII for action and unlike heparin, DTIs can inhibit clot-bound thrombin, which may be an advantage. DTI dose is titrated to PTT 1.5 - 2 times normal. It may be difficult to monitor the effect of DTIs on anticoagulation if the patient has an abnormal PTT level prior to initiating ECMO. It is important to note that DTIs do not provide any inhibition of the contact pathway.

## 5. Circuit monitors, alarms, and safety

**5a. High pressure.** Pressure in an ECMO system is monitored and servo-regulated for safety. One of the multiple pressures routinely monitored should be the inlet pressure of the blood entering the oxygenator. These alarm limits are pre-set to alert for over-pressurization, which can manifest as a contributor to hemolysis due to high resistance in the system. The high resistance pressure is most commonly related to the size and position of the arterial (or return) cannula, or uncommonly resulting from a blood leak from connectors and components. While the burst pressure is over 500 mmHg, pressures exceeding 350 mmHg may contribute to patient complications. Modern oxygenators are very low resistance and are only a contributor to high pressure alerts when clot burden has caused a flow obstruction at the inlet. This is confirmed when compared to the outlet oxygenator pressure. A widening transmembrane gradient confirms the assessment of a failing oxygenator that requires mechanical remediation or replacement.

**5b. Air in the circuit** might be seen directly or detected by a bubble detector. Any air detected post-oxygenator is at risk to enter the patient's circulating blood volume and requires an immediate response, especially on VA support. The first response is to stop the blood pump and clamp the arterial (infusion) line. If possible, restart blood flow through a bridge line to shunt the air to the venous portion of the circuit, examine the circuit for air, and identify the source of air introduction into the circuit. Remove any residual air and repair or replace the source of the entrainment. Potential causes should be examined from the venous cannula and progress through the entire circuit, looking for loose tubing connections, stopcocks and/or air in infusion lines pre-oxygenator. Much of this type of air intrusion is trapped by the oxygenator. Post-oxygenator air is an emergency on VA support due to the significant risk for the air to enter the patient's circulating blood volume. Potential causes are a gas to blood leak in the oxygenator due to over pressurization of the gas phase, a loose infusion port/stopcock, or inadvertent air entrainment from an infusion post-oxygenator. Once visible air is extracted from the circuit, circulate flow through the bridge, examine the circuit reaccumulation, and resume support when corrected.

**5c. Clotting in the circuit** is detected by careful visual examination of the circuit using a strong light source. Clots are dark (red, brown, black) non-moving areas seen on the circuit, typically in areas of alterations in flow (reservoir, oxygenator, and connectors). Small pre-oxygenator clots of this type may not require intervention other than continuing observation and monitoring. Should the characteristics change or become partially mobile, further intervention may be considered. Light colored thrombi (white, cream) consisting of platelets and fibrin, are often observed in areas of turbulent flow such as at tubing/connector ends. Typically, no intervention is required unless a significant change is observed in color, size, or mobility causing concern for dislodgement. Intervention regarding clot burden within the circuit ranges from isolated component changes versus consideration to change the entire circuit.

**5d. Electrical power failure.** Every ECMO system should have an integrated battery backup in the event of power failure. An audible and visual alert should accompany a loss of power and transition to battery power. A battery system should be capable of maintaining power to the pump for a minimum of sixty minutes. It is not advisable to use battery power to maintain water bath heat due its extreme amperage requirements. The water bath should be disconnected from the battery power, and alternate forms of temperature maintenance should be instituted. Should the battery power fail, pump flow can be maintained by use of a manual pump cranking system

**5e. Unplanned decannulation** is a life-threatening emergency identified by major bleeding at the cannulation site, visible air in the venous drainage area of the circuit (if the drainage cannula is coming out), and loss of volume. Decannulation is prevented by securing the cannulas to the skin in at least two locations and checking the position of the cannulas on CXR and cannula fixation at frequent intervals, i.e. daily, PRN, and after patient repositioning and transport.

**5f. Hemolysis** is defined in the ELSO Registry as free hemoglobin in the blood plasma in concentrations exceeding  $> 50$  mg/dL. Normally plasma hemoglobin should be less than 10 mg/dl. Hemolysis may be suspected if the urine is dark and urinalysis shows large blood, but no red cells. Hemolysis is verified by elevated plasma hemoglobin level. There may also be increased conjugated bilirubin, anemia, and increased haptoglobin. Higher plasma hemoglobin can be caused by negative pressure generated by centrifugal pumps, partial circuit or component thrombosis, malocclusion of roller pump, high shear stresses related to turbulent flow, and chattering of the venous lines. Hemolysis results in increased free circulating hemoglobin that causes nephrotoxicity, increased vascular resistance, increased thrombin generation, platelet dysfunction, and clotting disorders.

## **6. Component and circuit changes**

It may be necessary to temporarily clamp off ECMO to remove and replace clotted components or replace the entire circuit. The patient should be placed on increased ventilator settings and 100% oxygen, and they should be sedated to avoid air embolus. When changing a membrane lung, the lung must be primed with crystalloid solution before attaching to the circuit.

Patients may experience a SIRS response following a circuit change. Lasix and SCUF are usually held for 6-12 hours. Steroids have not been found to be helpful in ameliorating the SIRS response.

## **7. Traveling**

Traveling poses risks, however, it may be necessary to travel to radiology, the operating room, or the cath lab. Verify that the battery is fully charged and the hand crank is available for the pump. Turn off the water bath, switch the circuit to battery power, and switch the sweep to a portable oxygen tank. When moving the patient and the ECLS cart, one person is assigned to keep one hand on the bed and the other on the cart to reduce tension on the tubing.

### **B. Patient related management**

#### **1. Hemodynamics**

During **VV support** the patient is dependent on his own hemodynamic physiology. Appropriate medications and infusions are used to control cardiac output, blood pressure and resistance.

During **VA support** hemodynamics are controlled by the blood flow (pump flow plus native cardiac output) and vascular resistance. Since the pulse pressure is low, the mean systemic arterial pressure will be somewhat lower than normal pressure (40 to 50 mmHg for a newborn). In addition, patients placed on ECMO for cardiac support are typically on significant inotropes prior to ECMO initiation. As these drugs are titrated down, resistance falls and systemic pressure falls proportionately. If the systemic perfusion pressure is inadequate (low urine output, poor perfusion), pressure can be increased by adding blood or low doses of pressor drugs. Systemic vasodilatation requiring pressor drugs is common in patients in septic shock. Although the mean arterial pressure may be low, systemic perfusion may be completely adequate. Systemic perfusion is best measured by mixed venous blood saturation. Assuming a SaO<sub>2</sub> over 95% and a venous saturation greater than 65% indicates systemic oxygen delivery is adequate even though the pressure may be low. If systemic oxygen delivery is not adequate (venous saturation less than 65%), increase the pump flow until perfusion is adequate. If extra blood volume is required to gain extra flow, consider the relative advantages of blood products and crystalloid solution.

#### **2. Ventilator management**

Once the patient is stabilized on ECMO support, either VV or VA mode, the ventilator settings are typically weaned to allow the lungs to rest during the acute inflammatory phase of illness, commonly referred to as “rest settings.” Current ELSO guidelines recommend a peak inspiratory pressure (PIP) of 15-22, a positive end-expiratory pressure (PEEP) of 5-8, a rate of 12-20, an inspiratory time of 0.5 seconds, and a FiO<sub>2</sub> of 0.21-0.30. Many centers use PIP 20, peep 10, I-time 1, rate 10, FiO<sub>2</sub> 0.21. Some centers use APRV (airway pressure release

ventilation) with continuous positive pressure and occasional pressure release or CPAP with spontaneous breathing. Using high PEEP levels, however, may inhibit venous return and have the usual negative effect on hemodynamics when the patient is managed in the VV mode.

A RCT published by Keszler et al. in 1992, showed a PEEP of 12-14 to be associated with a shorter ECMO run and increased lung compliance.<sup>1</sup> High- versus low-PEEP ventilation during ECMO is patient- and diagnosis-dependent.

<sup>1</sup> Keszler M, Ryckman FC, McDonald JV, et al. A prospective, multicenter, randomized study of high versus low positive end-expiratory pressure during extracorporeal membrane oxygenation. *J Pediatr.* 1992;120(1):107-113.

**Air Leak.** In patients with air leak syndrome, positive pressure should be limited to avoid worsening of the air leak. In some patients, CPAP may be warranted. In the event of tracheal damage or continued air leak, the patient may be extubated while on ECMO. This allows the lungs to be re-recruited with negative pressure instead of positive pressure. Anton-Martin, et al. published a case series in 2014 showing that extubation while on ECMO was feasible and did not increase mortality.<sup>1</sup> Impaired pulmonary clearance of secretions and atelectasis are the main problems with managing neonates extubated on ECMO.

If the patient develops a pneumothorax, placement of a chest tube needs to be considered carefully. An enlarging pneumothorax or a pneumothorax causing hemodynamic compromise requires external drainage. This could be a small catheter placed by Seldinger technique or a surgical thoracostomy with placement of a chest tube. (See procedures, section 9 below). Weaning the heparin infusion prior to chest tube placement limits bleeding complications. A small pneumothorax with no hemodynamic compromise is best treated conservatively. Placing even a small tube may result in significant bleeding ultimately requiring thoracotomy.

<sup>1</sup> Anton-Martin P, Thompson MT, Sheeran PD, Fischer AC, Taylor D, Thomas JA. Extubation during pediatric extracorporeal membrane oxygenation: a single-center experience. *Pediatr Crit Care Med.* 2014 Nov;15(9):861-9.

**Managing gas exchange with the ECMO circuit.** Patient arterial blood gases reflect a combination of ECMO circuit infusion blood (ideally an oxygen saturation of 100% with normal PCO<sub>2</sub>) mixed with native cardiac output. Oxygen content should be adequate to achieve metabolic needs by achieving adequate hemoglobin levels.

**In VV mode,** infusion blood mixes with systemic venous return blood. At typical blood flow, the ratio of infusion blood to deoxygenated right atrial blood is usually around 3:1. This results in PCO<sub>2</sub> 41, PO<sub>2</sub> 40, saturation 80%, content 17ml O<sub>2</sub>/dL in the pulmonary artery. If there is no native lung function, this will be the composition of gases in the arterial blood. VV ECMO gas management depends on the patient's oxygen consumption, systemic O<sub>2</sub> delivery, adequate cardiac function, and normal hematocrit. Venous drainage and sweep flow diffusion gas exchange via the membrane lung adjustments will yield a systemic arterial saturation around 80% during VV support. This degree of hypoxemia (PaO<sub>2</sub> 40-60, SaO<sub>2</sub> 70-90) will maintain normal oxygen delivery during VV support. It is not recommended to increase ventilator settings from baseline settings due to perceived hypoxemia. Native lung function will increase oxygenation saturation over 80%.

**In VA mode**, infusion blood mixes with blood in the aorta. Being mindful of the ideal characteristics of circuit blood, typical management of gas exchange related to the circuit is to alter pump flow to achieve a goal PaO<sub>2</sub> and to alter sweep flow to affect PaCO<sub>2</sub>. To increase oxygenation, increase pump flow. To increase carbon dioxide removal, increase sweep flow. Again, it is not advisable to alter ventilator settings from baseline during ECMO support until it is deemed recommended to begin weaning procedures in preparation for trial off and decannulation.

### 3. Sedation

Neonates are initially managed on narcotic and benzodiazepine intermittent dosing. Many infants require narcotic infusions. Some neonates may also require benzodiazepine infusions. Patients are given muscle relaxants during cannulation, decannulation, and circuit change at times due to the risk of air embolism. Some institutions hold sedation and analgesia for a neurologic exam (a daily drug holiday).

### 4. Blood volume, fluid balance, and hematocrit

During ECMO support, the **blood volume** is increased by the volume of the extracorporeal circuit. Since the extracorporeal circuit is not compliant, this doubling or tripling of the blood volume has no hemodynamic effect; each milliliter of blood removed is immediately replaced by an identical volume. The extracorporeal circuit is primed with red blood cells in neonates. The priming solution will equilibrate with the native blood volume during the first several minutes of ECMO. This will dilute blood cells, platelets, and proteins depending on the ratio between the native blood volume and the extracorporeal prime. This dilution is caused by an increase in the crystalloid component of the plasma which will equilibrate into the extracellular space causing edema.

The goal of fluid management is to return the **extracellular fluid volume** to normal (dry weight) and maintain it there. The reason is that edema caused by critical illness or iatrogenic crystalloid fluid infusion contributes lung and myocardial failure, compounding the primary problem. Achieving normal ECF status can be difficult in a patient who is septic and has active capillary leakage from the plasma into the extracellular space. During the acute inflammatory stage early in ECLS, capillary leak will occur and is exacerbated by excessive crystalloid infusion. When the patient is hemodynamically stable (typically 12-48 hours), diuretics are instituted and continued until dry weight is achieved. If the diuretic response is not sufficient to achieve negative fluid balance or if the patient is in overt renal failure, hemofiltration is added to the extracorporeal circuit to maintain fluid and electrolyte balance.

### 5. Temperature

The desired blood temperature within an ECMO circuit matches the normal patient average body temperature (typically 37 degrees Celsius). This temperature is a set point on the water bath of the heat exchanger. If there is a concern for hypoxic ischemic brain injury and there is a desire to maintain mild hypothermia (32 to 34°) during the first 24 to 72 hours in line with an institutional hypothermia protocol, it is possible to decrease the water bath temperature and adjust it along with a cooling blanket to maintain optimal hypothermia. Of note, a hypothermia protocol may require sedation or paralysis to avoid shivering and may exacerbate bleeding. Hyperthermia (from fever or inflammation) may be masked due to the water bath set point on the ECMO circuit. Therefore, it is advantageous to closely assess for infection using laboratory values (WBC, CBC shifts, acidosis, blood cultures) to avoid hypermetabolism and recognize potential infection.

## 6. Renal and nutrition management

Pharmacologic diuresis is typically started once the acute SIRS response has cleared and there are no ongoing issues with decreased venous return and cutting out. This will enhance recovery from heart or lung failure and decrease the time on ECMO. SCUF (slow continuous ultrafiltration) can be used to remove fluid. Solutes are not cleared to any significant degree. SCUF volumes must be managed closely. It is easy to pull off enough fluid in a short period of time to develop renal failure. Hence, a basal SCUF rate is not recommended in neonates. If renal failure occurs for any reason, it may be treated by continuous hemofiltration (CVVHD).

Neonates are not typically fed while on ECMO. Some institutions will do trophic feeds. However, it is difficult to assess the infant's tolerance to feeds with the common gasless appearance on abdominal x-ray. Further, neonates with congenital diaphragmatic hernia have a sump to suction prior to repair and are kept NPO. Total parenteral nutrition is provided with fluid restriction and calories approximately 80 kcal/kg/day. Lipids must be run through a peripheral intravenous line to avoid lipid precipitation and thrombosis in the circuit.

## 7. Infection and antibiotics

The cannula sites are cleaned frequently with antiseptic solution and may be covered with an antiseptic cream or ointment. Appropriate antibiotics should be given for documented infection. There is no standard policy regarding prophylactic antibiotics simply because the patient is on ECMO. Bacteremia during ECMO may be related to bacterial growth on a component of the circuit but is usually related to another source in the patient. Unlike suspected “line sepsis” in the usual critically ill patient, it is usually not possible to change the access cannulas if contamination is suspected, and it may be dangerous to change the circuit. If all other sources of bacteremia have been ruled out, the entire circuit up to the cannulas can be changed expeditiously.

## 8. Bleeding/Clotting

**Clotting.** The most common mechanical complications for neonatal respiratory and cardiac ECMO support are due to clots in the circuit (oxygenator, bridge, bladder, hemofilter, or other). These are seen more commonly with respiratory than cardiac ECMO runs.

**Bleeding.** Bleeding at the ECMO cannula site, surgical site bleeding, and CNS hemorrhage rates have shown an increased frequency since 2000. Bleeding into the head or brain parenchyma is the most serious ECMO complication. It can be extensive and fatal. Head ultrasounds should be performed every 24 hours for at least the first 3-5 days in stable neonates on ECMO and then per institution protocol.

Although head ultrasound (HUS) is available as a bedside tool, it is not always sensitive enough to detect ICH. In one study, HUS missed 15 of 16 (94%) minor hemorrhages and 1 of 3 (33%) major hemorrhages. The missed major hemorrhage was located in the right parieto-temporal cortex and subcortical white matter. HUS missed all minor infarctions and 3 of 8 (38%) major infarctions.<sup>5</sup> Further, 50% of patients with normal HUS had an abnormal brain MRI post-ECMO.<sup>4</sup> Infarctions, diffuse edema, and atrophy are often detected on CT scan and MRI in children with normal HUS studies.<sup>1-3</sup>

If the patient is unstable from a hemodynamic or coagulation standpoint, daily HUS should be considered. If bleeding is detected, the degree of bleeding will guide therapy. If available,

portable CT scan may provide additional information on severity and progression of hemorrhage without the added difficulty of transporting the patient. For a small bleed, coagulation status will need to be optimized and HUS repeated 2 times per day to detect any extension. For extending bleeds or bleeds that are moderate, measures to optimize cardiorespiratory support should be undertaken to allow the patient to be weaned from ECMO. For severe intraparenchymal hemorrhage, withdrawal of ECLS may be indicated.

1. Bulas, G.A. Taylor, R.M. O'Donnell, B.L. Short, C.R. Fitz, G. Vezina. Intracranial abnormalities in infants treated with extracorporeal membrane oxygenation: update on sonographic and CT findings. *Am J Neuroradiol*, 17 (2) (1996), pp. 287-294
2. E.L. Lazar, S.J. Abramson, S. Weinstein, C.J. Stolar. Neuroimaging of brain injury in neonates treated with extracorporeal membrane oxygenation: lessons learned from serial examinations. *J Pediatr Surg*, 29 (2) (1994), pp. 186-190
3. D. Bulas, P. Glass. Neonatal ECMO: neuroimaging and neurodevelopmental outcome. *Semin Perinatol*, 29 (1) (2005), pp. 58-65
4. Bembea MM, Felling R, Anton B, Salorio CF, Johnston MV. Neuromonitoring during Extracorporeal membrane oxygenation: A systematic review of the literature. *Pediatr Crit Care Med*. 2015 Jul;16(6):558-64
5. Wien MA, Whitehead MT, Bulas D, Ridore M, Melbourne L, Oldenburg G, Short BL, Massaro AN. Patterns of brain injury in newborns treated with extracorporeal membrane oxygenation. *AJNR Am J Neuroradiol*. 2017 Apr;38(4):820-826

**Bleeding post chest tube placement.** Bleeding is a common complication even if all appropriate steps are taken during tube placement. It may occur early or after days. Accumulated blood should be evacuated, even if this requires a lower, more posterior tube. Evacuating the blood quantifies the rate of bleeding and decreases the risk of a hemothorax and later organized clot. A CT scan may be indicated to determine if the tube is in the parenchyma of the lung. If it is in the parenchyma, the tube should be removed, but thoracotomy will probably be need to control the bleeding and air leak. If less invasive measures do not stop the bleeding, thoracotomy is indicated to find and control the source. Even if bleeding is controlled by operation, it may recur within days. In this case, it is wise to pack the chest open, permitting frequent bedside re-exploration until the patient is off ECMO.

**Mucous membranes.** Bleeding from the nasopharynx, mouth, trachea, rectum, or bladder commonly occurs with minor trauma associated with patient care. Patients should not have rectal temperatures, rectal suppositories, or receive intramuscular medications. Bladder catheterizations should be avoided if possible.

**GI bleeding** can occur from gastritis from sump placement/local irritation at the gastric mucosal level. The addition of acid suppression medication is often adequate, although gastric lavage with saline may be indicated to evaluate for ongoing bleeding. Topical agents such as Carafate and Mylanta should be avoided due to an unacceptably high aluminum content.

## 9. Procedures

Procedures on ECMO, ranging from chest tube and PICC placement to CDH repair, all require special consideration for hemostasis in anticoagulated patients. The heparin infusion is often decreased with ACT goals decreased in the range of 160-180 and anti-Xa in the rage of 0.3-

0.5 IU/mL. Platelet levels are also increased to >100,000 and fibrinogen > 150. Many centers routinely add an aminocaproic acid infusion perioperatively to minimize bleeding for CDH repairs on ECMO.

If bleeding occurs and persists post procedure despite decreased heparin and product replacement, it is reasonable to stop anticoagulation altogether until the bleeding stops. The half-life of heparin is 45 minutes. This may stop the bleeding, but may also result in clotting in the circuit. Therefore, it is good practice to have a primed circuit immediately available when anticoagulation is turned off.

## 10. Neuroimaging

**Head Ultrasound (HUS).** Head ultrasound is an essential neuroimaging technique for the care of an ECMO patient. Brain parenchyma that has experienced ischemic, hemorrhagic, or white matter injury may appear echogenic; however, at times, these lesions can be difficult to differentiate by HUS alone. Ultrasound is not a sensitive tool for reliably detecting small hemorrhages and ischemic lesions. HUS is able to detect changes in ventricular size. Advantages of HUS include ease of use, bedside portability, low cost, efficiency, and no exposure to radiation. Furthermore, since this study is done in “real time,” results are available readily for medical decision-making.

Although this varies by institution, a common imaging protocol includes obtaining a baseline pre-ECMO ultrasound followed by daily monitoring HUS for the first week of cannulation, the period during which the incidence of ICH is highest.<sup>1,2</sup> Subsequent HUS monitoring is typically performed every other day for the duration of the ECMO run. Additional ultrasounds may be obtained based upon clinical indications, such as new onset seizures, sudden drop in hemoglobin, or other clinical concerns.

In addition, in the ECMO population, there is growing concern for discrepancy between detection of abnormalities on HUS as compared to head CT scan (HCT) or magnetic resonance imaging (MRI).<sup>3-5</sup> For example, Lazar et al showed that in a series of 74 neonatal ECMO patients, only 53% of patients with confirmed structural injury by HCT or MRI brain had signs of injury on serial HUS examinations.

HUS has not been shown to predict long-term neurodevelopmental outcomes in the ECMO population, particularly in the absence of a catastrophic bleed. In the study by Glass et al, 43% of children with severe and 67% with moderate brain injury on neuroimaging by head ultrasound were later noted to have no disability at 5-year follow-up.<sup>6</sup> Conversely, a normal HUS does not rule out future developmental impairment; Lazar et al found that 13.5% of neonates treated with ECMO had delayed neurological development even without evidence of anatomic injury on serial HUS or follow-up imaging.<sup>3</sup> Rollins et al found no association between an abnormal HUS and neurodevelopmental outcomes.<sup>5</sup> Therefore, HUS should not be used in isolation to predict neurodevelopmental outcomes.

<sup>1</sup>Khan AM, Shabarek FM, Zwischenberger JB, et al. Utility of daily head ultrasonography for infants on extracorporeal membrane oxygenation. *J Pediatr Surg* 1998;33:1229-1232.

<sup>2</sup>Biehl DA, Stewart DL, Forti NH, Cook LN. Timing of intracranial hemorrhage during extracorporeal life support. *ASAIO journal (American Society for Artificial Internal Organs : 1992)* 1996;42:938-941.

<sup>3</sup>Lazar EL, Abrahamsom SJ, Weinstein S, J.H. SC. Neuroimaging of Brian Injury in Neonates Treated with Extracorporeal Membrane Oxygenation: Lessons Learned from Serial Examinations. *Journal of Pediatric Surgery* 1994;20:5.

<sup>4</sup>Babcock DS, Han BK, Weiss RG, Ryckman FC. Brain abnormalities in infants on extracorporeal membrane oxygenation: sonographic and CT findings. *AJR American journal of roentgenology* 1989;153:571-576.

<sup>5</sup>Rollins MD, Yoder BA, Moore KR, et al. Utility of neuroradiographic imaging in predicting outcomes after neonatal extracorporeal membrane oxygenation. *J Pediatr Surg* 2012;47:76-80.

<sup>6</sup> Glass P, Bulas DI, Wagner AE, et al. Severity of brain injury following neonatal extracorporeal membrane oxygenation and outcome at age 5 years. *Developmental medicine and child neurology* 1997;39:441-448.

**Head Computed Tomography (HCT).** Head CT (HCT) can be used to detect significant structural or acute vascular changes. For neonatal ECMO, portable HCT has been used for follow up of abnormal ultrasounds for emergent evaluation that would impact immediate survival or continued ECMO candidacy. Head CT includes risk of radiation and risk of cannula movement with patient transfer to scanner.

However, multiple small studies have shown that HCT has improved sensitivity to detect intracranial pathology found on HCT that is missed by HUS, including significant intracranial hemorrhage and infarction.<sup>1-3</sup>

HCT may provide some insight into neurodevelopmental outcomes, although this has not been consistently replicated. In one study, the severity of neuroimaging findings was associated with worsened neurocognitive outcomes.<sup>4</sup> Notably, a small subset of the group (10%) without pathological neuroimaging findings was also classified as disabled.

<sup>1</sup>Bulas DI, Taylor GA, O'Donnell RM, Short BL, Fitz CR, Vezina G. Intracranial abnormalities in infants treated with extracorporeal membrane oxygenation: update on sonographic and CT findings. *AJNR Am J Neuroradiol* 1996;17:287-294.

<sup>2</sup>Babcock DS, Han BK, Weiss RG, Ryckman FC. Brain abnormalities in infants on extracorporeal membrane oxygenation: sonographic and CT findings. *AJR American journal of roentgenology* 1989;153:571-576.

<sup>3</sup>Taylor GA, Fitz CR, Glass P, Short BL. CT of cerebrovascular injury after neonatal extracorporeal membrane oxygenation: implications for neurodevelopmental outcome. *AJR American journal of roentgenology* 1989;153:121-126.

<sup>4</sup>Bulas D, Glass P. Neonatal ECMO: neuroimaging and neurodevelopmental outcome. *Semin Perinatol* 2005;29:58-65.

**Magnetic Resonance Imaging (MRI).** MR imaging is the gold standard for detection of intracranial injury and pathology, in particular, stroke and white matter injury.<sup>1,2</sup> Advantages include lack of radiation exposure as well as the high sensitivity and specificity for intracranial pathology. Disadvantages include timing. Diffusion restriction can only be seen on MRI within a window of a few minutes to 10 days post ischemic injury; outside of this window, timing of an injury can be difficult to define.

Further, the clinical significance of these findings is not always clear. Rollins et al looked at 26 neonates post ECMO with both neuroimaging data and neurodevelopmental outcomes and found no association between HUS or MRI and neurodevelopmental outcomes.<sup>1</sup> However, in an older study by Lagos et al, presence of increased cerebrospinal fluid spaces correlated with worse outcomes at 6 and 12 months of age.<sup>3</sup> This is corroborated by studies in the congenital diaphragmatic hernia population, whereby increased extra-axial CSF and intracranial hemorrhage predicted worse neurodevelopmental outcomes at one year of age as measured by the Bayley developmental scores.<sup>4</sup>

<sup>1</sup>Rollins MD, Yoder BA, Moore KR, et al. Utility of neuroradiographic imaging in predicting outcomes after neonatal extracorporeal membrane oxygenation. *J Pediatr Surg* 2012;47:76-80.

<sup>2</sup>Wien MA, Whitehead MT, Bulas D, et al. Patterns of Brain Injury in Newborns Treated with Extracorporeal Membrane Oxygenation. *AJNR Am J Neuroradiol* 2017;38:820-826.

<sup>3</sup>Lago P, Rebsamen S, Clancy RR, et al. MRI, MRA, and neurodevelopmental outcome following neonatal ECMO. *Pediatr Neurol* 1995;12:294-304.

<sup>4</sup>Danzer E, Zarnow D, Gerdes M, et al. Abnormal brain development and maturation on magnetic resonance imaging in survivors of severe congenital diaphragmatic hernia. *J Pediatr Surg* 2012;47:453-461.

## 11. Neuromonitoring

**Electroencephalogram (EEG).** Critically ill infants are at high risk for seizures and the majority of seizures tend to be electrographic only.<sup>1,2</sup> Incidence of seizures for neonates on ECMO vary between 5-30%. In one single-center study, Lin et al demonstrated not only the high incidence of seizures in neonates on ECMO at 18%, but an association between presence of electrographic seizures and worsened neurologic outcomes.<sup>2</sup> It is currently the American Clinical Neurophysiology Society recommendation for continuous EEG monitoring for critically ill children and neonates.

<sup>1</sup>Abend NS, Dlugos DJ, Clancy RR. A review of long-term EEG monitoring in critically ill children with hypoxic-ischemic encephalopathy, congenital heart disease, ECMO, and stroke. *J Clin Neurophysiol* 2013;30:134-142.

<sup>2</sup>Lin JJ, Banwell BL, Berg RA, et al. Electrographic Seizures in Children and Neonates Undergoing Extracorporeal Membrane Oxygenation. *Pediatr Crit Care Med* 2017;18:249-257.

## V. Weaning, Trial off, Discontinuing ECMO for Clinical Improvement and Futility

### A. Weaning

Extracorporeal support is decreased as native organ function improves. When VA ECMO flow is less than 30-50 ml/kg/min, native heart and lung function may be adequate to allow coming off ECMO, and a trial off is indicated. With VV ECMO, once the lungs are open, the sweep flow can be weaned down (ideally to 0.1 L/min). There is no need to wean the flow on VV ECMO.

### B. Trial off

Trial off **during VV ECMO** is simple. Cardiac function is adequate, and only native gas exchange is tested. The ventilator is adjusted. A PaO<sub>2</sub> > 60 mmHg (8kPa) with an FIO<sub>2</sub> of < 0.50 with a maximal peak pressure of 25 cm H<sub>2</sub>O suggests that the patient is ready for decannulation. Blood flow and anticoagulation are maintained while the membrane is isolated by discontinuing the sweep gas. Follow the patient SaO<sub>2</sub> and PCO<sub>2</sub>. If lung function is adequate at acceptable ventilator settings for an hour or more, the patient is ready for decannulation.

Trial off **during VA ECMO** requires either low flow (20 ml/kg/min) or clamping of the drainage and infusion blood lines and circulating blood through the circuit via the AV bridge. Ventilator settings are adjusted to acceptable levels, and infusions are converted to the patient. Echocardiography can be helpful to assess cardiac function during a trial off. Anticoagulation is continued during the trial off, and the blood lines and access cannulas are unclamped periodically to avoid clot formation. If the trial off is successful, circuit lines can be cut and access cannulas “locked” with heparinized saline, awaiting decannulation. However, it is ideal

to trial off with surgery present such that the cannulas can be removed immediately if the trial off is successful.

### **C. Decannulation**

Cannulas placed by direct cutdown are removed by direct cutdown. The cannulas are removed and the vessels ligated (or occasionally repaired). When removing the venous cannula, air can enter the venous blood through the side ports if the patient is breathing spontaneously. This can be prevented by the administration of pharmacological muscle relaxant and expeditious movement when removing the venous cannula.

### **D. Stopping support for futility**

According to the ELSO guidelines, ECMO should be stopped if there is no hope for healthy survival.<sup>1</sup> This could include severe brain injury, diagnosis of an irreversible process, or organ failure with no possibility of transplant. During the consent process prior to placing a patient on ECMO, it should be made clear that continuation of ECMO will be reassessed frequently and that ECMO may be discontinued if the patient has not shown any improvement in a reasonable amount of time. The definition of a reasonable amount of time is patient and diagnosis dependent.

<sup>1</sup> Extracorporeal Life Support Organization (ELSO) General Guidelines for all ECLS Cases. November 2013:1-24.

## **VI. Patient and Disease Specific Protocols**

### **A. Meconium aspiration (MAS)**

Since 2012, there have been 933 cases of MAS reported to the ELSO Registry. The average run time was 145 hours, and the longest run time 1111 hours. The overall survival was 92%. While meconium itself is free of bacteria, it reduces the antibacterial activity of the amniotic fluid and increases the risk of perinatal infection. Further, aspiration induces hypoxia in the neonate secondary to airway obstruction, surfactant dysfunction, chemical pneumonitis, and pulmonary hypertension. VV ECMO is the most common mode of support for MAS, even in those requiring pressor support.

### **B. Neonatal sepsis/pneumonia**

Since 2012, there have been 168 cases of sepsis reported to the ELSO Registry. The average run time was 163 hours, and the longest run time 1155 hours. The overall survival was 45%. The most common organisms involved are group B beta hemolytic streptococcus (GBS) or gram-negative organisms. There have been 41 cases with the primary diagnosis of pneumonia to the ELSO registry. The survival rate for pneumonia is 60%.

### **C. PPHN (persistent pulmonary hypertension of the newborn)**

Since 2012, there have been 885 cases of PPHN/PFC reported to the ELSO Registry. The average run time was 172 hours, and the longest run time 1908 hours. The overall survival was 73%. PPHN may be secondary to MAS, sepsis, and pneumonia. In this setting the vasculature is vasoconstricted, but normally formed. In other cases, the lung parenchyma may be normal, but the pulmonary vasculature may be remodeled. This can be seen in premature closure of the ductus,

secondary to exposure to maternal medications, i.e. SSRIs, aspirin, indomethacin and CDH. This can also be part of genetic syndromes; alveolar capillary dysplasia, surfactant protein B deficiency, and Fryns syndrome. It is common to see severe hypoxemia in the setting of relatively normal ventilation.

#### **D. Hypoxic ischemic encephalopathy (HIE)**

Patients with hypoxic ischemic encephalopathy (HIE) are at risk for abnormal pulmonary vasorelaxation and pulmonary hypertension (PPHN), which occurs in 25%.<sup>1</sup> Whole body cooling (WBC) is standard of care for these infants, but the effect of cooling in patients with HIE who also require ECMO is not definitively known. WBC has not been shown to increase the risk of PPHN, but worsening of symptoms with both cooling and rewarming has been described.<sup>1,2</sup> A randomized controlled trial of WBC in neonatal ECMO patients without a formal diagnosis of HIE showed no benefit and a trend toward harm.<sup>3</sup> However, since the evidence for WBC infants with HIE is substantial, many centers now continue cooling after ECMO initiation. Small case series have shown this to be feasible, and some patients have had a normal developmental outcome.<sup>4</sup>

<sup>1</sup>Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *The New England journal of medicine*. 2005;353(15):1574-1584.

<sup>2</sup> Shah SK, Khan AM, Cox CS, Jr. Pulmonary hypertensive crisis requiring ECMO associated with rewarming from whole body hypothermia for hypoxic ischemic encephalopathy: clinical observations from a case series. *European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery [et al] = Zeitschrift fur Kinderchirurgie*. 2010;20(3):205-206.

<sup>3</sup> Field D, Juszczak E, Linsell L, et al. Neonatal ECMO study of temperature (NEST): a randomized controlled trial. *Pediatrics*. 2013;132(5):e1247-1256.

<sup>4</sup> Massaro A, Rais-Bahrami K, Chang T, Glass P, Short BL, Baumgart S. Therapeutic hypothermia for neonatal encephalopathy and extracorporeal membrane oxygenation. *The Journal of pediatrics*. 2010;157(3):499-501, 501e491.

#### **E. Prematurity**

Late preterm (34-36 weeks) and early term infants (37-38 weeks) are at increased risk of ECMO related morbidity and mortality.<sup>1</sup> Historically, infants less than 34 weeks were thought to be at too high a risk for hemorrhage and were not typically offered ECMO, though there are a number of documented survivors.<sup>2,3</sup> ELSO registry analysis has shown that delaying the initiation of ECMO in premature infants can abrogate this risk, but unfortunately, the mortality is higher for patients in whom ECMO is employed later.<sup>4</sup>

<sup>1</sup>Ramachandrapa A, Rosenberg ES, Wagoner S, Jain L. Morbidity and mortality in late preterm infants with severe hypoxic respiratory failure on extra-corporeal membrane oxygenation. *J Pediatr*. 2011;159(2):192-8.

<sup>2</sup>Church JT, Kim AC, Erickson KM, et al. Pushing the boundaries of ECLS: Outcomes in <34 week EGA neonates. *J Pediatric Surg*. 2017

<sup>3</sup>Mehta A, Ibsen LM. Neurologic complications and neurodevelopmental outcome with extracorporeal life support. *World J Crit Care Med*. 2013;2(4):40-47

<sup>4</sup>Smith KM, McMullan DM, Bratton SL, Rycus P, Kinsella JP, Brogan TV. Is age at initiation of extracorporeal life support associated with mortality and intraventricular hemorrhage in neonates with respiratory failure? *Journal of perinatology : official journal of the California Perinatal Association*. 2014;34(5):386-391

#### **F. Trisomy 21**

Neonates with trisomy 21 (T21) deserve special mention, as they are over-represented in cases of severe pulmonary hypertension and the need for ECMO. 2.3% of neonates with T21 admitted to children's hospitals receive ECMO, and this is especially common in those with concomitant cardiac diagnoses.<sup>1</sup> Mortality is overall slightly higher than in non-T21 neonatal respiratory ECMO patients at 46%.<sup>2</sup> Prolonged hospitalization and late post ECMO hospital death are also more common in these patients.<sup>3</sup>

<sup>1</sup>Backes CH, Nicholson L, Rivera BK, Swier N, Marshall W, Cua CL. Extracorporeal Membrane Oxygenation Incidence, Characteristics, and Outcomes in Neonatal Down Syndrome Patients. *ASAIO journal*. 2016;62(4):477-481.

<sup>2</sup>Cashen K, Thiagarajan RR, Collins JW, Jr., et al. Extracorporeal Membrane Oxygenation in Pediatric Trisomy 21:30 Years of Experience from the Extracorporeal Life Support Organization Registry. *J Peds*. 2015;167(2):403-408.

<sup>3</sup>Southgate WM, Annibale DJ, Hulsey TC, Purohit DM. International experience with trisomy 21 infants placed on extracorporeal membrane oxygenation. *Pediatrics*. 2001;107(3):549-552

## **G. ECPR**

Extracorporeal cardiopulmonary resuscitation (ECPR) is the initiation of ECMO, including cannula placement, during ongoing CPR, so that the ECMO flow itself becomes part of the resuscitation. By necessity, these patients are placed on venoarterial (VA) ECMO. For success, both timeliness of ECMO deployment and excellent CPR technique are required. This is more common in cardiac patients, but ELSO registry data shows that 17% of the neonatal eCPR patients have a respiratory diagnosis.<sup>1</sup> Survival for neonates treated with eCPR is typically 39%-45%, which is not dramatically worse for that of other neonatal cardiac patients, but it is much worse than expected for neonatal respiratory patients.<sup>1</sup>

<sup>1</sup>McMullan DM, Thiagarajan RR, Smith KM, Rycus PT, Brogan TV. Extracorporeal cardiopulmonary resuscitation outcomes in term and premature neonates. *Pediatr Crit Care Med*. 2014;15(1):e9-e16.

## **H. EXIT to ECMO**

EXIT (ex utero intrapartum treatment) may be performed for prenatally diagnosed cases of pulmonary hypoplasia (CDH, thoracic masses) with immediate placement of cannula and initiation of ECMO support before the cord is clamped at the infant is separated from placental bypass. The conceptual advantage is avoidance of clinical instability, hypoxia, and acidosis that occur and may worsen pulmonary hypertension. However published data is limited to a few case series and describe practical success, but unproven benefit.<sup>1,2</sup>

<sup>1</sup>Stoffan AP, Wilson JM, Jennings RW, Wilkins-Haug LE, Buchmiller TL. Does the ex utero intrapartum treatment to extracorporeal membrane oxygenation procedure change outcomes for high-risk patients with congenital diaphragmatic hernia? *Journal of pediatric surgery*. 2012;47(6):1053-1057.

<sup>2</sup>Kunisaki SM, Fauza DO, Barnewolt CE, et al. Ex utero intrapartum treatment with placement on extracorporeal membrane oxygenation for fetal thoracic masses. *Journal of pediatric surgery*. 2007;42(2):420-425.

## **I. Congenital diaphragmatic hernia (CDH)**

Infants born with CDH often have life threatening cardiorespiratory failure in the immediate newborn period and first weeks of life, and thus account for the most common

indication for neonatal ECMO utilization, accounting for ~28% of all neonatal ECMO use.<sup>1</sup> While survival rates exceeding 70% are possible for CDH infants overall, those requiring ECMO have a more guarded prognosis, with a survival rate of approximately 50%.<sup>2,3</sup>

The rationale for use of ECMO in these infants is that pulmonary vascular reactivity and pulmonary hypertension will improve over the first few weeks of life in many infants, and despite continued pulmonary hypoplasia, survival may improve with cardiopulmonary support.

Data from the ELSO registry demonstrated that among 7002 CDH infants, 51% of infants treated with ECMO survived to discharge, compared with 73% overall survival for neonatal ECMO for other pulmonary indications.<sup>4</sup> Since 2012, the average run time was 302 hours and the longest run time 1733 hours.

Clinical management of the infant with CDH on ECMO is complex and presents unique challenges including approach and timing of surgical repair and management of pulmonary hypertension in the presence of persistent fetal shunts. Predicting those infants most likely to improve after ECMO is challenging.

For those infants who do not survive despite ECMO therapy, the cause of death is most commonly pulmonary hypertension, respiratory failure, or complications such as hemorrhage. ECMO may be life-saving in infants with CDH, but is reserved for infants with highest risk of mortality. While no uniformly accepted criteria for ECMO initiation currently exist, most clinicians consider ECMO use for infants > 2 kg in weight and >34 weeks' gestation without other life-limiting anomalies who fail "optimal medical management". This is typically defined as some combination of the need for PIP of >28 cm H<sub>2</sub>O or MAP >17 cm H<sub>2</sub>O to maintain a preductal oxygen saturation of 85-90% or postductal oxygen saturation of 70%, a PaO<sub>2</sub> < 40 mmHg for 4 hours on FIO<sub>2</sub> of 1.00, OI > 40 for 4 hours, respiratory acidosis with pH < 7.15 despite optimal ventilator management, hypotension refractory to vasopressors, or refractory metabolic acidosis.<sup>5,6</sup> In general, those anatomic, physiologic, and clinical parameters that predict mortality also predict the need for ECMO.<sup>7</sup> Intrathoracic position of the liver is highly associated with ECMO use (80% liver up vs. 25% liver down).<sup>8,9</sup> In addition, a metanalysis of 22 studies found that LHR < 1 predicted ECMO use in CDH.<sup>10</sup>

Current clinical practice recommendations support the concept of minimizing barotrauma through limitations on peak airway pressure, and suggest that early initiation of ECMO in infants failing this strategy may prevent lung injury. EXIT to ECMO in infants with severe CDH is not currently recommended.

<sup>1</sup>International Summary of ELSO Registry Report. Extracorporeal Life Support Organization (ELSO). January and July 2017, Ann Arbor, Michigan.

<sup>2</sup>Golden J, Jones N, Zagory J, et al. Outcomes of congenital diaphragmatic hernia repair on extracorporeal life support. *Pediatr Surg Int*, 2017; 33(2): 125-131.

<sup>3</sup>Murthy K, Pallotto EK, Gien J, et al. Predicting death or extended length of stay in infants with congenital diaphragmatic hernia. *J Perinatol* 2016; 36(8): 654-9.

<sup>4</sup>Paden ML, Rycus PT, Thiagarajan R, ELSO Registry. Update and outcomes in extracorporeal life support. *Semin Perinatol* 2014; 38(2): 65-70.

<sup>5</sup>Reiss I, Schaible T, van den Hout L, Capolupo I, et al: CDH EURO Consortium. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH Euro Consortium consensus. *Neonatology* 2010; 98(4): 354-64.

<sup>6</sup>Chandrasekharan PK, Rawat M, Madappa R, Rothstein DH, Lakshminrusimha S. Congenital diaphragmatic hernia- a review. *Matern Health Neonatol Perinatol* 2017; 3, 6.

<sup>7</sup>Kays DW, Islam S, Larson SD, Perkins J, Talbert JL. Long-term maturation of congenital diaphragmatic hernia treatment results: toward development of a severity-specific treatment algorithm. *Ann Surg* 2013; 258(4): 638-44.

<sup>8</sup>Russo FM, Eastwood MP, Keijzer R, Al-Maary J, Toelen J, Van Mieghem T, Deprest JA. Lung size and liver herniation predict need for extracorporeal membrane oxygenation but not pulmonary hypertension in isolated congenital diaphragmatic hernia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017; 49(6): 704-13.

<sup>9</sup>Hedrick HL, Danzer E, Merchant A, Bebbington MW, et al. Liver position and lung-to-head ratio for prediction of extracorporeal membrane oxygenation and survival in isolated left congenital diaphragmatic hernia. *Am J Obstet Gynecol* 2007; 197(4): 422.

<sup>10</sup>Oluoyomi-Obi T, Kuret V, Puligandla P, Lodha A, Lee-Roertson H, Lee K, Somerset D, Johnson J, Ryan G. Antenatal predictors of outcome in prenatally diagnosed congenital diaphragmatic hernia (CDH). *J Pediatr Surg* 2017; 52(5): 881-888.

### **Mode of ECMO for CDH:**

While nearly one third of infants with CDH are treated with ECMO, the optimal mode of delivery for this therapy is a subject of debate. Historically, most infants with CDH were treated with veno-arterial (VA) ECMO. Some studies suggest that veno-venous (VV) ECMO may be equally efficacious for this population. Many infants with CDH require ECMO for cardiovascular compromise as a result of ventricular dysfunction, right heart overload secondary to severe pulmonary hypertension, and in some cases relative ventricular hypoplasia with pulmonary venous hypertension. One benefit of VA ECMO is the ability to off load volume from the right heart, allowing the right heart to recover in the face of persistent elevation of pulmonary vascular resistance. However, VA ECMO typically results in carotid ligation and is associated with a higher risk of complications, particularly hemorrhagic or bleeding complications, which is relevant in the setting of infants who may require invasive surgical treatment while on ECMO. VV ECMO is technically challenging in smaller infants, but may preserve pulmonary blood flow with oxygenated blood, which enhances vasodilation. It also preserves the carotid artery and, thus, is the preferred method of ECMO for CDH for some clinicians.

Over the past two decades, several studies have shown equivalent outcomes for infants treated with VA versus VV ECMO. Single center studies demonstrated no difference in ECMO duration, hospital length of stay, and neurologic or catheter complications when comparing VV to VA ECMO.<sup>1-4</sup> One center reported increased mortality and another reported increased ventilator days in the VA ECMO group, and all other reported outcomes were similar.<sup>1,2</sup> Two large analyses of ELSO data (Dimmit: 1990-99 and Guner: 1991-2006) of over 5000 infants with CDH treated with ECMO, found that VA ECMO (82-86%) was overwhelmingly the preferred modality.<sup>4,5</sup> Both studies reported equivalent survival (VA-53-54% vs VV-50-58%) when adjusted for severity of illness and gestational age at birth and found increased renal complications and need for inotropes in the VV ECMO group, but there was an increase in neurologic complications including cerebral infarction in the VA ECMO group. Conversion from VV to VA ECMO occurred in 18% of patients, and this was associated with increased mortality of 56%.<sup>5</sup> The conclusion of these studies was that VV and VA ECMO provide equivalent survival but that VV ECMO has a trend towards a lower risk profile and is considered by several authors the preferred method of ECMO for infants with CDH.

<sup>1</sup>Finer NN, Tierney AJ, Ainsworth W. Venovenous extracorporeal membrane oxygenation: the effects of proximal internal jugular cannulation. *J Pediatr Surg* 1996; 31(10): 1391-5.

<sup>2</sup>Austin MT, Lovvorn HN, Feurer ID, Peitsch J, Earl TM, Bartilson R, Neblett WW, Pietsch JB. Congenital diaphragmatic hernia repair on extracorporeal life support: a decade of lessons learned. *Am Surg* 2004; 70(5): 389-95.

<sup>3</sup>Kugelman A, Gangitano E, Pincros J, Tantivit P, Taschuk R, Durand M. Venovenous versus venoarterial extracorporeal membrane oxygenation in congenital diaphragmatic hernia. *J Pediatr Surg* 2003; 38(8): 1131-6.

<sup>4</sup>Dimmit RA, Moss RL, Rhine WD, Benitz WE, Henry MC, VanMeurs KP. Venoarterial versus venovenous extracorporeal membrane oxygenation in congenital diaphragmatic hernia: the Extracorporeal Life Support Organization Registry, 1990-1999. *J Pediatr Surg* 2001; 36(8): 1199-1204.

<sup>5</sup>Guner YS, Khemani RG, Qureshi FG, Wee CP, et al. Outcome analysis of neonates with congenital diaphragmatic hernia treated with venovenous vs venoarterial extracorporeal membrane oxygenation. *J Pediatr Surg* 2009; 44(9): 1691-701.

### **Timing of Repair:**

The approach to the timing of repair in infants repaired while on ECMO varies greatly between centers. Some centers advocate for early repair to allow for longer pulmonary recovery, while others delay surgical repair until later in the ECMO course to minimize bleeding complications. CDH repair on ECMO does carry a higher risk profile, most notably hemorrhagic complications. Surgical site bleeding is reported in 8-14.7% of infants repaired on ECMO and up to 30% have hemorrhagic complications overall.<sup>1-4</sup> Reducing systemic anticoagulation to achieve an ACT of 140-160 (rather than 180-220) in combination with the use of Amicar resulted in decreased surgical site bleeding (8.8% of CDH infants repaired on ECMO) with no deaths attributable to hemorrhage.<sup>3</sup> Further, several studies have suggested that survival is improved if decannulation can be achieved prior to repair.

<sup>1</sup>Partridge EA, Peranteau WH, Rintoul NE, Herkert LM, Flake AW, Adzick NS, Hedrick HL. Timing of repair of congenital diaphragmatic hernia in patients supported by extracorporeal membrane oxygenation (ECMO). *J Pediatr Surg* 2015; 50(2) 260-2.

<sup>2</sup>Fallon SC, Cass DL, Olutoye OO, Zamora IJ, Lazar DA, et al. Repair of congenital diaphragmatic hernias on Extracorporeal membrane oxygenation (ECMO): does early repair improve patient survival? *J Pediatr Surg* 2013; 48(6): 1172-6.

<sup>3</sup>Dassinger MS, Copeland DR, Gossett J, Little DC, Jackson RJ, Smith SD. Early repair of congenital diaphragmatic hernia on extracorporeal membrane oxygenation. *J Pediatr Surg* 2010; 45(4): 693-7.

<sup>4</sup>Hollinger LE, Lally PA, Tsao K, Wray CJ, Lally KP. A risk-stratified analysis of delayed congenital diaphragmatic hernia repair: does timing of operation matter? *Surgery* 2014; 156(2): 475-82.

### **Survival/Outcome for CDH:**

Data suggest that prolonged ECMO runs beyond 4-6 weeks may be of limited utility, although universally accepted limits on length of treatment have not been established. Kays, et al. described survival related to length of ECMO treatment and found survival rates of 56% after 2 weeks of ECMO, 46% survival at 3 weeks, and 43% of patients at 4 weeks survived to discharge. After 5 weeks of ECMO, survival dropped to 15%, and after 40 days of ECMO support there were no survivors.<sup>1</sup>

If certain milestones such as decannulation from ECMO or surgical repair are successfully achieved, survival increases (both ~65% survival to discharge).

Overall, the reported incidence of chronic lung disease or bronchopulmonary dysplasia in survivors of CDH is 33-52%, with ECMO utilization associated with a 9-fold increase in this complication (CDH + ECMO 67% CLD vs CDH without ECMO 18% CLD;  $p=0.04$ ).<sup>2</sup> Many survivors require long term treatment of pulmonary hypertension (14% treated with sildenafil at discharge), with ECMO an independent predictor of chronic pulmonary hypertension.<sup>3</sup>

Right-sided congenital diaphragmatic hernia (R-CDH) occurs in up to 25% of all CDH cases. In one series, R-CDH was not associated with increased mortality, but it was associated with increased severity of pulmonary hypoplasia, with increased requirement of pulmonary vasodilatory therapy and tracheostomy.<sup>4</sup>

ECMO utilization in CDH survivors is associated with a 17-fold increased risk of growth failure at one year of age (OR 17; 95% CI: 1.3-849.4) and is an independent predictor of growth failure at one year of age.<sup>5,6</sup> Up to 50-80% of CDH infants are diagnosed with clinical GERD with the highest risk seen in those requiring ECMO and/or a patch repair.<sup>7</sup> The need for gastrostomy tube placement is increased in infants who survive ECMO (50% ECMO patients vs 16% no ECMO;  $p < 0.05$ )<sup>8</sup> and highest in those receiving both ECMO and patch repair (OR 12.4; 95% CI: 2-76).<sup>9</sup>

Hearing anomalies are seen in over 30% of long-term CDH survivors with an increased incidence of sensorineural hearing loss (SNHL) significantly associated with requirement for ECMO.<sup>10</sup>

CDH recurrence rate of CDH has been reported in 23% of infants treated with ECMO versus a rate of 3% in those without ECMO, with use of ECMO as an independent risk factor for recurrence (OR adj 6.3; 95% CI: 1.2-33.9).<sup>9</sup>

The risk of neurologic sequelae is significant in CDH survivors, with those requiring ECMO at the highest risk.<sup>11,12</sup> Neurodevelopmental delay, seen in about 25-35% of CDH survivors, may be present in up to 85% of those treated with ECMO,<sup>5,8</sup> despite similar rates of intracranial hemorrhage. The majority of CDH children have neurodevelopmental outcomes within the average range at 5 years of age. However, rates of borderline and extremely low IQ scores are significantly higher than in the general population. CDH survivors are also at increased risk for developing symptoms of emotionally reactive and pervasive developmental problems. Risk of autism is significantly elevated.

A contemporary look at a population of 5 year olds showed that the majority of children with CDH have neurodevelopmental outcomes within the average range.<sup>13</sup> Autism was diagnosed in 11% of this population which is significantly higher than the general population.<sup>13</sup> Further, preterm, late preterm, and near-term infants carried an increased risk of neurodevelopmental delay as compared to term infants.<sup>14</sup> These findings seem to be independent of ECMO. Regardless of the ultimate cause, CDH ECMO survivors are at risk of long-term neurologic complications, and close neurodevelopment follow-up is warranted.

<sup>1</sup>Kays DW, Islam S, Richards DS, Larson SD, Perkins JM, Tlabert JL. Extracorporeal life support in patients with congenital diaphragmatic hernia: how long should we treat? *J Am Coll Surg* 2014; 218(4): 808-17.

<sup>2</sup>Jaillard SM, Perrat V, Dubois A, Truffert P, Lequien P, Wurtz AJ, Storme L. Outcome at 2 years of infants with congenital diaphragmatic hernia: a population-based study. *Ann Thorac Surg* 2003; 75(1): 250-6.

<sup>3</sup>Wynn J, Krishnan U, Aspelund G, et al. Outcomes of congenital diaphragmatic hernia in the modern era of management. *J Pediatr* 2013; 163(1): 114-9.

<sup>4</sup>Partridge EA, Peranteau WH, Herkert L, Rendon N, Smith H, Rintoul NE, Flake AW, Adzick NS, Hedrick HL. Right- versus left-sided congenital diaphragmatic hernia: a comparative outcomes analysis. *J Pediatr Surg*. 2016 Jun;51(6):900-2.

<sup>5</sup>Bojanic K, Woodbury JM, Cavalcante AN, et al. Congenital diaphragmatic hernia: outcomes of neonates treated at Mayo Clinic with and without extracorporeal membrane oxygenation. *Paediatr Anaesth* 2017; 27(3): 314-321.

<sup>6</sup>Pierog A, Aspelund G, Farkouh-Karoleski C, Wu M, Kriger J, Wynn J, Krshnan U, Mencin A. Predictors of low weight and tube feedings in children with congenital diaphragmatic hernia at 1 year of age. *J Pediatr Gastroenterol Nutr* 2014; 59(4): 527-30.

<sup>7</sup>Cortes RA, Keller RL, Townsend T, Harrison MR, Farmer DL, et al. Survival of severe congenital diaphragmatic hernia has morbid consequences. *J Pediatr Surg* 2005; 40(1): 36-45.

<sup>8</sup>McGahren ED, Mallik K, Redgers BM. Neurological outcome is diminished in survivors of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation. *J Pediatr Surg* 1997; 32(8): 1216-20.

<sup>9</sup>Janssen S, Heiwegen K, van Rooij IA, Scharbatke H, Roukema J, de Blaauw I, Botden SM. Factor related to long-term surgical morbidity in congenital diaphragmatic hernia survivors. *J Pediatr Surg* 2017; epub. PMID: 28602525.

<sup>10</sup>Partridge EA, Bridge C, Donaher JG, Herkert LM, Grill E, Danzer E, Gerdes M, Hoffman CH, D'Agostino JA, Bernbaum JC, Rintoul NE, Peranteau WH, Flake AW, Adzick NS, Hedrick HL. Incidence and factors associated with sensorineural and conductive hearing loss among survivors of congenital diaphragmatic hernia. *J Pediatr Surg*. 2014 Jun;49(6):890-4.

<sup>11</sup>Bernbaum J, Schwartz IP, Gerdes M, D'Agostino JA, Coburn CE, Polin RA. Survivors of extracorporeal membrane oxygenation at 1 year of age: the relationship of primary diagnosis with health and neurodevelopmental sequelae. *Pediatr* 1995; 95(5Pt1): 907-13.

<sup>12</sup>Nijhuis van der sanden MW, van der Cammen-van Zijp MH, Janssen AJ, Reuser JJ, Mazer P, van Heijst AF, Gischler SJ, Tibboel D, Kollee LA. Motor performance in five-year-old extracorporeal membrane oxygenation survivors: a population-based study. *Crit Care* 2009; 13(2) R47.

<sup>13</sup>Danzer E, Hoffman C, D'Agostino JA et al. Neurodevelopmental outcomes at 5 years of age in congenital diaphragmatic hernia. *J Pediatr Surg* 2017;3;52(3):437-43.

<sup>14</sup>Danzer E, Gerdes M, D'Agostino JA et al. Younger gestational age is associated with increased risk of adverse neurodevelopmental outcome during infancy in congenital diaphragmatic hernia. *J Pediatr Surg* 2016;7;51(7):1084-90.

## **VII. Expected Results**

The overall survival to hospital discharge is 72% for patients treated with ECMO for neonatal respiratory disease. The overall survival rate to decannulation from ECMO support is slightly higher at 83%. The average ECMO run times have increased during the last 15 years to slightly more than 200 hours per ECMO run, as compared to approximately 150 hours in the 1990s.<sup>1</sup> Longer ECMO runs and lower survival suggest that ECMO is being increasingly utilized as a therapy for more critically ill patients with more associated comorbidities.<sup>2</sup>

<sup>1</sup>International Summary of ELSO Registry Report. Extracorporeal Life Support Organization (ELSO). January and July 2017, Ann Arbor, Michigan.

<sup>2</sup>Sharma J, Rimal A, Weiner J, Haney B, Pallotto EK. Neonatal Pulmonary Extracorporeal Membrane Oxygenation (ECMO) Practice Trends Based on Primary Diagnosis - Two Decade Comparison. Poster session presented at: Pediatric Academic Society (PAS); 2017 May 6-9; San Francisco, CA.

## **VIII. Simulation**

Simulation should be an integral part of any neonatal ECMO program. Simulation can be used for initial and on-going education. Simulation is particularly useful for team training and for exposure of teams to the rare emergencies that occur in ECMO where quick response and effective teamwork are essential for patient care. Training on any new piece of equipment can be optimized using simulation. Simulation can also be used for quality improvement. It can allow for identification of latent patient safety threats as well as for developing new ECMO policies and procedures.

