Extracorporeal Life Support Organization (ELSO)

Guidelines for Adult Respiratory Failure
August, 2017

Introduction

This guideline describes prolonged extracorporeal life support (ECLS, ECMO), applicable to adult patients with respiratory failure. These Guidelines are based on the general Guidelines for all ECMO patients. Anyone undertaking ECMO for adult respiratory failure should be thoroughly familiar with the general guidelines before proceeding to adult respiratory ECMO. The general guidelines are repeated where appropriate.

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, 5th Edition, 2017" published by ELSO. These guidelines address technology and patient management during ECLS. 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:

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I.   Patient Condition (Chapters 36, 37)

A.   Indications

1.   In hypoxic respiratory failure due to any cause (primary or secondary) ECLS should be considered when the risk of mortality is 50% or greater, and is indicated when the risk of mortality is 80% or greater.

50% mortality risk is associated with a PaO2/FiO2 < 150 on FiO2 > 90% and/or Murray score 2-3[1], AOI score 60[2], or APSS score [3]

80% mortality risk is associated with a PaO2/FiO2 < 100 on FiO2> 90% and/or Murray score 3-4 (1), AOI >80 (2), APSS 8 (3) despite optimal care for **6 hours or less** The best outcome in ECMO for adult respiratory failure occurs when ECMO is instituted early after onset (1-2 days)

1) MurrayJF, Matthay MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome [published erratum appears in Am Rev Respir Dis 1989 Apr; 139(4):1065]. American Review of Respiratory Disease 1988, **138:**720-723.

2) Dechert RE, Park PK, Bartlett RH: Evaluation of the oxygenation index in adult respiratory failure. J Trauma Acute Care Surg 2014; 76:469–473

3) Villar J, Ambrós A, Soler JA, et al; Stratification and Outcome of Acute Respiratory Distress Syndrome (STANDARDS) Network: Age, Pao2/ Fio2, and Plateau Pressure Score: A Proposal for a Simple Outcome Score in Patients with the Acute Respiratory Distress Syndrome. Crit Care Med 2016; 44:1361–1369

2. CO_2 retention on mechanical ventilation despite high Pplat (>30 cm H_2O)

3.   Severe air leak syndromes

4.   Need for intubation in a patient on lung transplant list

5.   Immediate cardiac or respiratory collapse (PE, blocked airway, unresponsive to optimal care)

B.   Contraindications
There are no absolute contraindications to ECLS, as each patient is considered individually with respect to risks and benefits. There are conditions, however, that are associated with a poor outcome despite ECLS, and can be considered relative contraindications.

1.   Mechanical ventilation at high settings (FiO2 >.9, P-plat >30) for7 days or more. Many centers do not consider time on ventilation a contraindication.

2. Major pharmacologic immunosuppression (absolute neutrophil count <400/mm3)

3. CNS hemorrhage that is recent or expanding

4. Nonrecoverable comorbidity such as major CNS damage or terminal malignancy

5. Age: no specific age contraindication but consider increasing risk with increasing age

C. Specific Patient Considerations (Chapter 36)

1. Primary causes of respiratory failure:
Infection: Viral, bacterial, fungus, PCP.
Primary lung disease: Cystic fibrosis, hemorrhagic auto immune diseases. Idiopathic fibrosis, sickle cell crisis, primary pulmonary hypertension
Chest trauma, post pneumonectomy
Posttransplant: acute, chronic (Bronchiolitis obliterans)
Chronic respiratory failure bridging to transplant

2. Secondary causes of respiratory failure:
ARDS due to shock, trauma, sepsis, ischemic tissue, DIC, reinfusion reaction, anaphylaxis
Cardiac failure with pulmonary edema
Fluid over load

3. Pulmonary embolism

4. CO_2 retention syndromes
Acute airway obstruction, asthma, COPD in exacerbation

II. Extracorporeal Circuit (Chapters 4, 5)

A. Criteria for selecting circuit components
Modern ECMO is usually conducted with integrated devices designated ECMO machines. These machines include all of the basic components listed below. For adult respiratory failure the largest size ECMO machine is used which includes large conduit tubing, a blood pump capable of at least 5 L/min, and an oxygenator with rated flow over 5 L/min. The specific commercial ECMO machines are described in Chapter 5. Smaller ECMO machines are used for selective CO_2 removal. Commercial CO_2 removal machines can be used or small ECMO machines designed for infant ECMO can be used for adult CO_2 removal.

The circuit is planned to be capable of total support for the patient involved, unless the intent is specifically partial support (i.e. CO_2 removal for asthma).

1. Blood flow for cardiac support

Access is always venoarterial. The circuit components are selected to support blood flow 3 $L/m^2/min$ (neonates 100 cc/kg/min; pediatrics 80 cc/kg/min; adults 60 cc/kg/min.) The best measure of adequate systemic perfusion is venous saturation greater than 70%. Achieving a desired flow is determined by vascular access, drainage tubing resistance, and pump properties.

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_2 removal at least equal to the normal metabolism of the patient (i.e. an oxygen delivery of 6 cc/kg/min for neonates; children 4-5 cc/kg/min; adults 3 cc/kg/min), This will usually equate to VV blood flows of 120 ml/kg/min for neonates down to 60-80 ml/kg/min for adults. 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.

If the circuit is planned for CO_2 removal only, access can be venoarterial, venovenous, or arteriovenous. Typical blood flow is approximately 10-25% of cardiac output, which is sufficient to remove the CO_2 produced by metabolism (3-6 cc/Kg/min). CO_2 removal is determined by the blood flow and the sweep gas rate, the inlet PCO_2 and the membrane lung properties.

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, 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 control; centrifugal or axial rotary pump with inlet pressure control; peristaltic pump).

1. Inlet (suction) pressure

With the inlet line occluded the suction pressure should not exceed minus 300 mmHg. The inlet pressure can be very low (minus 300 mmHg) when the venous drainage is occluded (chattering) which causes hemolysis. Inlet pressure in excess of minus 300 mmHg can be avoided by inherent pump design or through a servocontrolled pressure sensor on the pump inlet side.

2. Outlet pressure

With the outlet line occluded the outlet pressure should not exceed 400 mm/Hg (inherent in the pump design or by a servocontrolled system).

3. Power failure

The pump should have a battery capable of at least one hour operation, 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.

4. Hemolysis

The plasma hemoglobin should be less than 10 mg/dl under most conditions. If the plasma hemoglobin exceeds 50 mg /dl, the cause should be investigated.

D. Membrane lung (often called the Oxygenator) (Chapters 4, 5)

The gas exchange material in membrane lungs may be solid silicone rubber, a microporous hollow-fibre (polypropylene for example), or a solid hollow-fibre 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_2 and CO_2 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_2 delivery** is the amount of oxygen delivered per minute when running at rated flow. This is calculated as outlet minus inlet O_2 content (typically 4-5 cc/dL, same as the normal lung) times blood flow. For example, a specific device has a rated flow of 2 L/min, (max O_2 100 ccO_2/min). If the blood flow required for total support of a patient is 1 L/min (O_2 about 50 cc/min) this membrane lung will be adequate. If the blood flow required for total support is 4 L/min, this membrane lung is not adequate and the circuit will need two of these membrane lungs in parallel, or a larger membrane lung rated at 4 L/min.

In venovenous mode, recirculation of infused blood may occur, raising the inlet saturation well above 75%. In this situation, the outlet-inlet O_2 difference per unit of blood flow is decreased, and higher blood flow, cannula repositioning, increased patient volume or higher hematocrit is/are required to provide the desired amount of O_2 delivery.

E. Sweep gas

For most applications, the sweep gas will be 100% oxygen or carbogen (5% CO_2, 95% O_2) at a flow rate equal to the blood flow rate (1:1). Increasing the sweep flow will increase CO_2 clearance but will not affect oxygenation. Water vapor can condense in the membrane

lung resulting in poor CO_2 clearance, and may be cleared by intermittently increasing sweep gas flow to a higher flow.

For CO_2 clearance only, blood flow can be as low as 0.5 L/min/m^2. The membrane lung can be smaller than that required for full support, and the sweep gas flow is typically oxygen at 10:1 (gas:blood).

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 polymethyl-pentene 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 popoff 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 an isotonic electrolyte solution resembling normal extracellular fluid including 4-5 MEq/L potassium. The prime is circulated through a reservoir bag until all bubbles are removed. This can be expedited by filling the circuit with 100% CO_2 before adding the prime. Microporous membrane lungs are quick to prime because gas in the circuit can be purged through the micropores. The circuit can be primed at the time of use, or days before. It is not recommended to use a primed circuit after 30 days.

Before attaching the circuit to the patient, the water bath is turned on to warm the fluid. ECLS is usually instituted with crystalloid prime. Many centers add human albumin (12.5 gm) to "coat" the surfaces before blood exposure. For infants, packed RBCs are added to bring the hematocrit to 30-40. Blood is usually not included in the prime for adult respiratory failure. When blood is added to the prime, heparin is added to maintain anticoagulation (1 unit per cc prime) then calcium is added to replace the calcium bound by the citrate in the bank blood. If time allows, it is helpful to verify the electrolyte composition and ionized calcium before starting flow. For emergency cannulation, the prime can be crystalloid with dilutional effects treated after initiating flow.

G.   Heat exchanger

A heat exchanger is needed if it is necessary to control the blood and the patient temperature at a specific level. Heat exchangers and associated water baths are often not needed for adult respiratory failure. Heat exchangers require an external water bath which circulates heated (or cooled) water through the heat exchange device. In general, the temperature of the water bath is maintained <40º Celsius, and usually at 37º. Contact between the circulating water

and the circulating blood is very rare, but should be considered if small amounts of blood or protein are present in the circulating water, or if unexplained hemolysis occurs. The water in the water bath is not sterile and may become contaminated. The water bath should be cleaned and treated with a liquid antiseptic from time to time.

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 on line monitoring or batch sampling. The primary purpose of measuring blood gases (as opposed to online saturation) is to determine the inlet and outlet PCO_2 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, although some centers prefer to give infusions directly to IV lines in the patient.

I.   Alarms

Pre and post membrane lung pressure and alarms. These measurements will 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; ¼:2.5 L/min; 3/8:5 L/min; ½:10 L/min

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 clamped the bridge it is a stagnant area which can contribute to thrombosis and possibly infection. In general, if a bridge is used, it should be maintained closed during most of the ECLS run, with a system for purging the bridge of stagnant blood when it is not in use.

K.   Elective vs. emergency circuits

The characteristics of individual components are listed above. Emergency circuits should be available within minutes of the call to a patient, and should be fully primed with crystalloid and ready to attach as soon as the patient is cannulated. They should also include safety factors to prevent high negative pressure on the inlet side and high positive pressure on the outlet side to avoid errors during emergent cannulation and attachment. The emergency circuit may include a microporous membrane lung (easy to prime), and a centrifugal pump (high-pressure limited, does not require monitors or alarms during initial set up).

III.   Vascular Access (Chapters 4, 38)

Vascular access is usually achieved by cannulation of large vessels in the neck or the groin. The blood flow resistance of the venous drainage cannula 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. Variations can be used for specific patient conditions (see patient protocols).

A.   Modes of vascular access for adults

1.   Stable patients: VV is preferred for adult respiratory failure when cardiac function is adequate or moderately depressed. VA is preferred if cardiac function is moderately to severely depressed and cardiac support is also required. Patients with severe respiratory failure and secondary cardiac failure may improve on VV support alone. VV access may be by femoral and jugular veins with 2 cannulas or a double lumen cannula via the jugular vein.

2.   Selective CO2 removal: Low flow VV with a pump is used for selective CO_2 removal AV access is possible and avoids a pump. However arterial complications can occur.

3.   **Unstable patients:** If very unstable, **VA access** via IJ or femoral vein and fem artery is preferred. VAV may be used for concomitant heart and lung failure to supplement upper body oxygenation. If cardiac function recovers before lung function, access can be converted to VV.

B.   **Cannulas**

The term "cannula" refers to the catheter that goes directly into the vessel for ECLS, to differentiate that device from all other catheters. The blood flow resistance of vascular access cannulas is directly proportional to the length and inversely proportional to the radius to the fourth power. Therefore, the internal diameter of the catheter is the most important factor controlling blood flow resistance. Other factors such as side holes and tapering sections also affect resistance, and the resistance increases at higher flows, so the characteristics of each cannula must be known before cannulation. Blood flow at 100 mmHg gradient for commonly used cannulas is described in the patient -specific protocols. Cannulas are chosen to provide the desired blood flow (section II A) above.

C.   **Cannulation**

For adult respiratory failure without cardiac failure two modes of VV access are used:

Two-cannula access via the femoral vein (drainage) and internal jugular vein for reinfusion. This approach is the quickest to establish, can be done without fluoroscopy or other imaging, has minimal recirculation, and provides full support. The drainage cannula should be at the level of the renal veins, although some prefer to place it near the right atrium which has more recirculation. The disadvantage is that the femoral access may limit activity and ambulation.

Single (double lumen) cannula via the internal jugular vein.: Avalon and Origen dual lumen cannulas have a large lumen for drainage and a smaller lumen for reinfusion. The reinfusion lumen is a side hole which can be oriented toward the tricuspid valve and the drainage holes are placed as far away as practical from the reinfusion hole to minimize recirculation. The Avalon cannula is designed to be placed in the inferior vena cava. Placement requires imaging, usually fluoroscopy, so cannulation is more difficult than 2-cannula access. The advantage of single cannula access is that is easier to mobilize and ambulate the patient. The disadvantage is the need for imaging during placement, and the cannula can pull out of the IVC into the right atrium.

The mode of cannulation can be varied depending on the clinical circumstance. A patient may start on VA because of the need for support of circulation. When hemodynamics are stable it is preferred to convert to VV to avoid the risk of systemic embolization. A patient of VV with 2 cannulas may be converted to a dual lumen cannula when the patient is awake and ready for activity and ambulation.

1.   **Methods**

Cannulas can be placed via: 1) cut down, 2) percutaneously by a vessel puncture, guidewire placement, and serial dilation (Seldinger technique), 3) by a combination of cut down exposure and Seldinger cannulation, or 4) by direct cannulation of the right atrium and aorta via thoracotomy. **Cut down exposure** of the neck vessels is usually necessary in neonates and small children. **Percutaneous cannulation** is commonly used for VV-ECMO in children over two and in adults. Direct **cardiac cannulation** is usually used for patients who cannot come off CPB in the OR, using the CPB cannulas.

VV access can be gained with a double lumen cannula, or two separate venous cannulas.

2.   **Cannulation technique**

A bolus of heparin (typically 50-100 units per kilogram) is given just before cannula placement, even if the patient is coagulopathic and bleeding.

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 cause air embolus. Local anesthesia is used for the skin. Dissection exposes the vessels. 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 kilogram) and the distal vessels are ligated. The proximal vessel is occluded with a vascular clamp, 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 in the proximal edge of the vessel are very helpful. The vessel is ligated around the cannula, often over a plastic "boot" to facilitate later cannula removal. In the femoral artery a non-ligation technique can be used (see semi-Seldinger technique below) which may ensure sufficient flow past the cannula to ensure distal perfusion

Percutaneous cannulation. Cannulation is done in the ICU, OR, or cath lab with full sterile preparation. The OR team is not essential but there should be a plan for direct cutdown access if there are complications with percutaneous placement. The safest technique is to place small conventional intravascular catheters first. The position of these preliminary catheters is verified by blood sampling or measuring the blood pressure. After full sterile preparation a guidewire is passed into the small catheter and the small catheter is removed followed by serial dilators. The final large dilator acts as an obturator for the cannula itself. With current equipment, two people are necessary to do percutaneous access: one to load of the dilators on the wire and pass the dilators, and one to occlude the vessel between dilators to avoid bleeding. When using the Seldinger technique with a large dilator and cannulas, it important to check the wire after each dilator. If the wire is kinked or bent, it must be removed and replaced with a new wire. The use of the ultrasound or fluoroscopy can help with cannula positioning. The heparin bolus can be given any time after the main wire is placed.

Semi-Seldinger technique. Performed in the ICU, OR, or cath lab under anaesthesia with aseptic precautions. The vessel is exposed by cut down but not dissected. A small (20G)

IV catheter is passed into the vessel through the skin distal to the incision. Correct placement can be confirmed by aspiration and then heparin is administered. This catheter is then used to place the large guidewire. Dilator exchanges lead to placement of the ECMO cannula. The wound is then closed over the cannula, which is then treated like a standard percutaneous cannula. The advantages of this technique over a pure percutaneous approach are speed, accurate assessment of vessel size, and flexibility of approach.

   1. **Modes:** Percutaneous access is possible in most adult patients. Ultrasound and fluoroscopy can facilitate cannulation. In the absence of imaging, the placement of conventional IV catheters first to verify position by pressure measurement can be followed by the placement of larger cannulas over a wire.

   2. **Cannulas:** A large double lumen cannula (6) or two large (23-31 Fr) venous cannulas are required: IVC via femoral vein for drainage and right atrial via the jugular (7) or opposite femoral (8) for blood return.
For selective venovenous CO2 removal 15 Fr double lumen cannulae will deliver adequate blood flow for total CO2 removal.

   3. **Management of the distal vessels:** If the <u>neck</u> cutdown access is used, the vein and artery are ligated distally, relying on collateral circulation to and from the head. Some centers routinely place cephalad venous cannulae but this is an institutional preference and is not mandatory. If the access is via the <u>femoral</u> vessels the venous collateral is adequate but the femoral artery is often significantly occluded. If distal arterial flow to the leg is inadequate a separate perfusion line is placed in the distal superficial femoral artery by direct cutdown, or in the posterior tibial artery for retrograde perfusion.

   4. **Adding or changing cannulas:** If venous drainage is inadequate and limited by the blood flow resistance of the drainage cannula, the first step is to add another venous drainage cannula through a different vein. It may be possible to change the cannula to a larger size, but removing and replacing cannulas can be difficult. If a vascular access cannula is punctured, kinked, damaged, or clotted, the cannula must be changed. If the cannula was placed by direct cutdown, the incision is opened, the vessel exposed, and the cannula replaced, usually with the aid of stay sutures on the vessel. If the cannula was placed by percutaneous access, a Seldinger wire is placed through the cannula to facilitate cannula.

IV. **Management during ECLS (Chapters 4, 5, 40,41)**

A. **Circuit related Management**

   1. **Blood flow:** Flow: 50-80 cc/drykg/min. Max initially, then lowest flow to maintain SaO2>80-85% at rest vent settings. This will typically be 50-80 cc/kg/minute when total gas exchange support is needed.

Calculate DO_2/VO_2 frequently: Circuit DO_2 (flow x outlet-inlet O_2content) plus pt lung DO_2, =total DO_2, related to VO_2 (3cc/kg/min.) Normal DO_2/VO_2 is 5. DO_2/VO_2 <2 is inadequate delivery. DO_2/VO_2 3 or more is recommended to allow some reserve.
Goal: $DO_2:VO_2$ >3 (Corresponds to SvO_2 25-30% less than SaO_2)

2.   Oxygenation: In the absence of lung function, VV access can supply all metabolic oxygen requirements. The arterial saturation is usually 80-85%, but may be 75-80% (PaO_2 45-55 This is ample oxyhemoglobin saturation for normal systemic oxygen delivery as long as the cardiac output and hemoglobin concentration are adequate to maintain DO_2 three times VO_2. However, the ICU staff may be uncomfortable with arterial saturation under 90, and education regarding oxygen delivery is important. Avoid the temptation to turn up the ventilator settings or FiO_2 above rest settings during VV support.

The mixing of two blood flows with different oxygen content is described in detail in Chapter 4.

3.   CO2 removal: (Chapter 63) Patient $PaCO_2$ is controlled by the sweep gas flow. When the circuit and blood flow are planned for oxygenation, CO_2 removal can be excessive, and the sweep gas flow is titrated to maintain PaCO2 at 40 mmHg (usually 1:1 to blood flow). For selective CO_2 removal blood flow can be as low as 1L/min and sweep gas can be up to 15L/min, titrated to maintain $PaCO_2$ at 40 mmHg.

4.   Anticoagulation (Chapters 6, 7, 8)

4a. Heparin (regular or "unfractionated "heparin, not low molecular weight heparin) is given as a bolus (50-100 units per kilogram) at the time of cannulation, and by continuous infusion during ECLS

4a1. Measuring heparin effect. Heparin infusion is regulated to keep the **whole blood** activated clotting time (ACT) at a designated level (usually 1.5 times normal for the ACT measurement system). ACT is the time (in seconds) in which whole blood clots in response to a fibrin activating reagent. Each ACT device has a specific upper limit with normal blood (120 to 140 seconds for most systems). ACT is measured hourly and more frequently if the ACT is changing. ACT is measured at the bedside (not sent to the laboratory) because heparin dosing decisions are often required immediately.

Partial thromboplastin time (PTT) is the time (in seconds) in which calcium-free **plasma** clots in response to a fibrin activating reagent combined with calcium. PTT is more convenient than ACT because it can be measured in the laboratory. However, it is less reliable than whole blood ACT as a measure of the time to clotting because it is measured in plasma and platelets, and blood cells can affect the activity of heparin. For a normal person, 10 units of heparin per kilogram per hour will result in ACT approximately 1.5 times normal. However, ECLS patients are not normal and there is no standard dose of heparin, and no standard concentration of heparin in the blood during ECLS. If the patient has a high platelet

or white cell count, or is "hypercoagulable," a large amount of heparin may be required to maintain the target ACT. If the patient is thrombocytopenic, in renal failure, or has circulating fibrin split products, a small amount of heparin may be required.

Heparin concentration can be measured indirectly as "**anti-Xa**." This provides a measure of heparin blood concentration, so can be used to titrate the dose to achieve a desired level of heparin concentration (typically 0.5 units/ml). When using anti-Xa to titrate heparin it is important to realize that factors other than heparin also affect blood clotting.

Thromboelastography (TEG) uses a device to record the time and density of clot formation in response to a stimulus (typically kaolin). The measurement is in whole blood so the time to clotting is the ACT. The density of the clot is affected by clotting factors, platelets, and fibrinolysis, so TEG provides more information than ACT. TEG can be done with and without an agent which inactivates heparin, so the anticoagulant effect of heparin can be separated from other factors. TEG can be done at the bedside on fresh blood or in the laboratory in calcium-free blood (adding calcium to the activator).

4a2: Heparin acts by "activating" a plasma molecule called **antithrombin** (usually called AT3). If the AT3 concentration in plasma is low, clotting can occur even when large doses of heparin are given. AT3 levels should be maintained in the normal range (80-120% of control). Low AT3 can be treated by giving fresh frozen plasma, cryoprecipitate, or recombinant AT3. AT3 assay is not available in all hospital laboratories. If clotting occurs in the circuit despite a normal or high dose of heparin, and AT3 assay is not easily available, give fresh frozen plasma to replace AT3 (inexpensive) or give recombinant AT3 (very expensive) until clotting is controlled. Circuit clotting can progress to a consumptive syndrome similar to DIC. The treatment of circuit clotting is to change to a new circuit.

4a3 HITT. There is a rare condition called heparin induced thrombotic thrombocytopenia, characterized by multiple white arterial thrombi and platelet count less than 10,000. A simple assay for HITT is available, but it has a high false positive rate. ECLS patients are all on heparin and all are thrombocytopenic for many reasons. The HITT assay is often positive in these patients, although they do not have the rare disease of heparin induced thrombocytopenia. If an ECLS patient has true HITT, the platelet count will be consistently less than 10,000 despite platelet infusions. In such a case, if there are no other explanations for thrombocytopenia, it is reasonable to use a different anticoagulant than heparin. Direct thrombin inhibitor (argatroban or bivalirudin) is the alternative.

4a4 Reversing heparin. Heparin effect can be reversed by protamine. This is routinely done in cardiac surgery where the effect of heparin must be maximal during operation, but minimal after coming off bypass. During ECLS, protamine reversal is almost never indicated because precise protamine dosing is difficult and circuit clotting can occur if heparin is reversed to normal coagulation status.

4b. Direct thrombin inhibitors. DTIs are used in HITT patients, and many centers are using DTIs as the primary anticoagulant. DTI effect is measured by ACT, PTT, or TEG.

DTI dose is titrated to clotting time 1.5 times normal, as with heparin.   DTI does not depend on AT3, so AT3 monitoring or replacement is not necessary.   There is no reversal medication but the half life is a few hours so overdose is not long lasting.

4c. Thrombocytopenia (platelet count less than 150,000) is common in ECLS patients. It may be a consequence of the primary disease, drugs, and other treatment, or caused by blood surface exposure. 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. If the platelet count is less than 20,000 spontaneous bleeding can occur. The usual practice is to transfuse platelets to keep the count greater than 80,000. Even though the platelet count is over 80,000, platelet function may be impaired. A kallikrein inhibitor (aprotinin or tranexamic acid) may improve platelet function if bleeding is a problem (see bleeding IVB).

4d. Fibrinogen. Even though fibrin formation is inhibited by anticoagulants, fibrinogen can become depleted during ECLS. Fibrinogen levels are measured daily and maintained within the normal range (250 to 300 mg/dl) by infusion of fresh frozen plasma or fibrinogen. The primary disease, or clots in the circuit, may cause fibrinolysis resulting in circulating fibrin split products. These molecules act as anticoagulants and can add to the risk of bleeding. If fibrin split products are detected and/or if bleeding is excessive, fibrinolysis can be inhibited with anti-fibrinolytics (see bleeding).

4e. Surface coatings. Extracorporeal circuits and devices are available with surface heparin coating or coating with other polymers intended to minimize blood surface interaction. These modified surfaces may decrease blood surface interaction somewhat, but systemic anticoagulation is still required when using the surface coatings currently on the market. It is possible to manage ECMO without systemic anticoagulation if bleeding cannot be controlled by other measures. During ECLS with no systemic anticoagulation blood flow should be maintained high, and a primed replacement circuit should be available if the circuit clots.

5.   **Circuit monitors, alarms, and safety (Chapters 4, 5)**

5a. High pressure. The higher the perfusion pressure, the higher the risk of leak or blowout. 400 mmHg is typically the highest safe level. If the post pump pressure is greater than 300 mmHg at the desired flow rate, the cause might be high systemic blood pressure in the patient (in VA mode), high resistance in the blood return access cannula, high resistance in the conduit tubing from the membrane lung to the cannula, or high resistance in the membrane lung. If the pressure suddenly increases setting off the high- pressure alarm, the cause is usually temporary occlusion of the infusion tubing or cannula. If this occurs stop the pump, then gradually return flow while determining the cause of the sudden increase in resistance

5b. Air in the circuit might be seen directly or detected by a bubble detector. If air is detected in the circuit stop the pump, clamp the lines near the patient, and put the patient on support settings. Because the patient is often totally dependent on ECLS, it is necessary to find

and repair the cause of air in the circuit very quickly. The most common cause is aspiration of air into the venous drainage line at the site of cannulation or through a connector or open stopcock. Another common cause is air bubbles in the intravenous infusion lines going into the patient. When air is entrained on the drainage side it is usually as small bubbles, and usually is caught in the membrane lung or bubble trap before getting into the patient. Air on the infusion side is a much more serious problem. The most common cause is air entrainment in the membrane lung. This can occur if the membrane lung is higher than the patient and if the blood side pressure drops below the gas side pressure.

5c. Clotting in the circuit is detected by careful examination, using a flashlight to go over all the extracorporeal circuit. Clots are seen as very dark nonmoving areas on the surfaces. Every circuit will have some small clots at the site of connectors, infusion lines, or in areas of low flow in the pre-pump bladder or the membrane lung. These clots are in the range of 1 to 5 mm, do not require circuit changes, and are simply observed. Clots larger than 5 mm or enlarging clots on the infusion side of the circuit (post membrane lung) should be removed by removing that section of the circuit or by changing the entire circuit if there are many such clots. Platelet/fibrin thrombi appear as white areas on the circuit at connectors and stagnant sections. These are clots which have not accumulated red cells, usually because they are in areas of very high flow. As with dark clots, no intervention is necessary unless the white thrombi are greater than 5 mm or growing.

5d. Electrical power failure. The circuit should be designed to automatically switch to battery operation if the main source of electricity is lost. An alarm should sound when the circuit switches to battery operation. The battery will operate the circuit for 30-60 minutes while the cause of the problem is being identified. The major power requirement is the water bath for the heat exchanger. When operating on battery power, it is wise to turn off the water bath. If the electrical circuit and the battery fails, the alarm will be a low flow alarm or alarms attached to the patient (saturation or blood pressure). In that case it will be necessary to crank the pump by hand.

5e. Decannulation is a life-threatening emergency identified by major bleeding at the cannulation site, air in the drainage circuit (if the drainage cannula is coming out) and loss of volume and perfusion pressure if the infusion cannula is lost. Decannulation is prevented by securing the cannulas to the skin in at least two locations, and checking the position of the cannulas and cannula fixation at frequent intervals and adequately sedating the patient. If decannulation occurs, come off bypass immediately by clamping the lines close to the patient, control bleeding by direct pressure, and reinsert the cannula as soon as possible.

5f. Hemolysis is suspected if the urine has a pink tinge (which could be due to bladder bleeding, not hemolysis) and verified by plasma Hb measurement. Normally plasma hemoglobin should be less than 10 mg/dl. Higher plasma hemoglobin can be caused by a condition primary to the patient, or by circuit components. The pump itself will not cause hemolysis unless inlet (suction) pressures are greater than minus 300 mmHg, which can happen if the pump suction exceeds the blood drainage. The pump can also cause hemolysis if there are clots in the pump chamber (which can occur in centrifugal pumps). Hemolysis can

occur if blood is flowing at a high rate through a very small orifice. This can occur if the blood return cannula has a very high resistance, or if there is a high level of occlusion in the post pump circuit. Hemolysis can also occur if a hemofilter or plasmapheresis device is attached to the circuit and run at high flows. If hemolysis occurs, the source should be found and corrected.

5g. Emergency drills addressing all these problems should be conducted by the team at regular intervals

5h. Safety. ECMO is a technology dependent therapy utilized in critically ill patients. A successful outcome is highly dependent on repetitive safe practices by a diverse team (physicians, ECMO specialists, perfusionists, nurses, etc). Policies that support a safe ECMO program include: regular emergency skills lab sessions, team training, using a pre-procedure "time out" to verify key elements and post-ECMO debriefings.

6.   Component and circuit changes

It may be necessary to stop ECLS (come off bypass) to remove and replace small components such as stopcocks and connectors, large components such as the pump chamber or membrane lung, or the entire circuit. If the patient is totally dependent on ECLS, this can be done in less than one minute as follows: Put the patient on maximal ventilator and drug support settings. Get at least one helper and assemble all the clamps and components. Clamp the lines near the patient, and clamp the lines above and below the component to be changed. With sterile technique, cut out the component and insert the new component, filling the tubing with saline and eliminating all bubbles. When changing or adding a membrane lung, the lung must be primed with crystalloid solution before attaching to the circuit.

7.   Traveling (Chapter 61)
Traveling poses risks. Do procedures in the ICU whenever possible.

In hospital. It may be necessary to travel to radiology, the operating room, or the cath lab as follows. Be sure that the battery is fully charged and the hand crank is available for the pump. Turn off the water bath to save electricity. Use a small full tank of oxygen for the sweep gas. Switch the circuit to battery power and portable oxygen before moving the patient from the bed. Before moving the patient, switch the patient monitors to a portable monitor for EKG, blood pressure, and $Sa0_2$. Minimize the number of intravenous infusions as much as possible. Bring an Ambu bag, separate oxygen tank, and emergency drugs. Plan the trip before leaving the ICU. Hold elevators, clear hallways, and be sure the receiving unit is ready. When moving the patient and the ECLS cart, one person is assigned to keep one hand on the gurney and the other on the cart to reduce tension on the tubing.

Hospital to hospital. In addition to all the details listed above, the transport team must be totally self-contained for hospital to hospital transfer. This includes spare parts for all components, a variety of cannulas and sizes, operating instruments, and medications. Arrange for hospital privileges in the referral hospital. Send instructions to the referral hospital

regarding family, consent, and blood, platelets, and plasma preparation, OR team if necessary, etc.

B.   Patient Related Management (Chapter 40,41)

1.   Hemodynamics: On VA support, SvO_2 can be used to guide hemodynamic management as discussed in the general guidelines. On VV support there is no direct hemodynamic support provided by the extracorporeal circuit. The patient should be managed with inotropes, vasodilators, blood volume replacement etc. as if the patient were not on extracorporeal support. Echocardiography is an excellent tool to assess hemodynamic function and help guide management during VV ECLS.

If cardiac failure occurs during VV support the patient can be converted to VA by adding arterial access to the femoral or subclavian artery.

During **VA support** hemodynamics are controlled by the blood flow (pump flow plus native cardiac output), and vascular resistance. Because the pulse pressure is low the mean systemic arterial pressure will be somewhat lower than normal pressure (40 to 50 mmHg for a newborn, 50 to 70 mmHg for a child or adult). In addition, patients placed on ECLS for cardiac support are on high doses of pressors when ECLS is begun. 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 SaO_2 is over 95% venous saturation greater than 70% indicates systemic oxygen delivery is adequate even though the pressure may be low. If systemic oxygen delivery is not adequate (venous saturation less than 70%) increase the pump flow until perfusion is adequate. If extra blood volume is required to gain extra flow, consider the relative advantages of blood and crystalloid solution.

Cardiac failure may be due to pulmonary hypertension causing right ventricular strain or overload. In that case VV can be converted to RA to PA via thoracotomy or via a cannula designed to reinfuse via the PA.

2.   Ventilator management: Patients are on high FiO_2 and ventilator settings during cannulation. The goal of ventilator management on ECLS is to use FiO_2 <0.4, and non-damaging "rest settings (PPlat<25)" In many patients the lung may proceed to total consolidation before recovery occurs, but this might be avoided by maintaining some inflation pressure as high pressures are decreased, and by supplying nitrogen to prevent adsorption atelectasis. Each patient is different, but a general algorithm for ventilator management is:

2a.   First 24 hours: moderate to heavy sedation.

Pressure controlled ventilation at 25/15, I:E 2:1, rate 5, FiO_2 50% ,FiN_2 50% . Positive pressure is continued to maintain some lung inflation, but PPlat over 25 can cause ongoing lung damage. PEEP can be as high as tolerated (avoiding inhibition of venous return) CO_2 is controlled by the ECMO circuit so ventilation is not necessary. If initial $PaCO_2$ >50, increase sweep slowly to bring PaCO2 down slowly, 10-20 mmHg/hour

2b.   After 24-48 hours: (Stable hemodynamics off pressors, fluid balance underway, sepsis Rx underway) moderate to minimal sedation.

Pressure controlled vent at 20/10. I:E 2:1, rate 5 plus spontaneous breaths, FiO_2 .2-.4, FiN_2 60-80% (rest settings).

2c.   After 48 hours Minimal to no sedation.

PCV as above or CPAP20 plus spontaneous breathing. Trach or extubate within 3-5 days

2d.   CO2 clearance mode: If the primary goal is CO_2 clearance (asthma, COPD exacerbation, avoiding high P in ARDS, bronchopleural fistula, weaning from severe ARDS)

VV access, DLC via IJ preferred. Cannula can be smaller size, but should allow.5 to 1 L/min flow. Recirculation is acceptable. Sweep flow is typically 5 to 10 times blood flow. Ventilator settings are rest settings as above.

2e.   Recruiting trials: None until significant aeration on CXR and > 4 cckg/ min tidal volume.

After aeration is established conduct a Cilley test. (increase FiO_2 to 1.0 with no other changes). A positive test is rapid increase to SaO_2 100%. If the Cilley test is positive, , start recruitment: CPAP with spontaneous breathing at 25cm H_2O. OR PSV at 25/10 rate 5, I:E 3:1 , 10 min/hr. then return to rest settings. Readjust blood and sweep flow if recruitment is successful. Repeat at intervals, expecting decreasing ECLS support as native lung function improves.

2f.   Airway access. Initiating ECLS, all patients are intubated endotracheally. If the patient is on VA-ECLS for cardiac support, and lung function is adequate, the patient can be extubated and managed awake with spontaneous breathing.

If the patient has respiratory failure, the airway is managed by continuing endotracheal intubation at rest settings as above. Maintaining safe positive pressure can maintain existing lung inflation, and may improve lung function as lung recovery begins. Tracheostomy avoids the discomfort of intubation and decreases the risk of nosocomial pneumonia. However, tracheostomy has the risk of bleeding in anticoagulated patients, so the technique is important (see B10).

Since the gas exchange is totally supported with ECLS, patients can be extubated and managed without mechanical ventilation. This facilitates activity and ambulation and is often used for patients bridging to lung transplantation.

2g. **Managing gas exchange with the ECLS circuit.** Patient arterial blood **gases** are the result of infusion blood **mixing** with the native blood in the aorta (VA) or right atrium (VV). The infusion blood is typically PCO_2 40 mmHg, PO_2 500mmHg, saturation 100%, oxygen content 22 ccO_2/dL.

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_2 41, PO_2 40, sat 80%, content 17ccO_2/dL in the pulmonary artery. If there is no native lung function, this will be the composition of gases in the arterial blood. It is important to realize that systemic arterial saturation around 80% is typical during VV support. As long as the hematocrit is over 40% and cardiac function is good, systemic oxygen delivery will be adequate at this level of hypoxemia. (Don't increase vent settings from rest settings because of hypoxemia.) Any native lung function will increase oxygenation over 80% sat.

In **VA mode** infusion blood mixes with blood in the aorta. The ratio of infusion to native aortic blood flow is typically 8:1 (near total bypass). If native lung function is normal (i.e. in cardiac support) and the FiO_2 is 0.2, this results in PCO_2 40, PO_2 200, sat 100%, content 21 ccO_2/dL.

If there is no native lung function this mixing results in PCO_2 40.5, PO_2 100, sat 98%, content 20 ccO_2/dL. NOTE: The forgoing is true if infusion blood goes to the aortic root (as in subclavian, carotid, or direct arch perfusion). If the infusion blood is going into the femoral artery and flow is retrograde, the mixing will occur somewhere in the mid aorta, the higher the flow rate, the higher the level of mixing. During severe respiratory failure, at typical VA flow rate (80% of full cardiac output) this can result in desaturated blood from the left ventricle perfusing the aortic arch and coronaries and fully saturated infusion blood perfusing the lower 2/3 of the body. This can occur in large children and adults. This can be managed by including SVC blood in the venous drainage, or by infusing some infusion blood into the right atrium (VVA). See patient specific protocols for further discussion.

3. **Sedation (Chapter 40,41)**
The patient should be thoroughly sedated to the point of light anesthesia during cannulation and management for the first 12 to 24 hours. The purpose is to avoid spontaneous breathing which might cause air embolism during cannulation, to minimize the metabolic rate, to avoid movement which might make cannulation difficult, and for patient comfort. It is rarely necessary to paralyze the patient, except to avoid spontaneous breathing during venous cannula placement.

After the patient is stable on ECLS, all sedation and narcotics should be stopped long enough to allow a thorough neurologic examination. Then sedation and analgesia may be resumed depending on patient's level of anxiety and discomfort. The primary reason for

sedation during the VV-ECLS is to tolerate endotracheal intubation. Conversion to tracheostomy should be considered early in the course in patients over 5 years of age to allow decreasing sedation. Sedation should be minimal, but it is important to be sure the patient does not pull on cannulas and tubes running the risk of decannulation or occluding the perfusion line. If the venous blood drainage is limited for any reason, blood flow may not be adequate to support systemic perfusion or gas exchange. This is often the case if the patient is anxious, moving about, or coughing. Sedation should be sufficient to avoid increasing the native metabolic rate, and systemic paralysis and cooling may be necessary if venous drainage cannot be achieved. Holding sedation and analgesia long enough to do a neurologic exam should be done daily (a daily drug holiday).

For adult patients the Richmond Agitation-Sedation Score (RASS) score is a good way to manage sedation. The scoring system and choice of sedative drugs is discussed in Chapter 40.

4.   Blood volume, fluid balance and hematocrit (Chapters 8, 41,)

As with any critically ill patient, the ultimate goal of management is adequate hematocrit, normal body weight (no fluid overload), and normal blood volume. During ECLS the **blood volume** is increased by the volume of the extracorporeal circuit. Because 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 crystalloid solution (perhaps with red blood cells in infants) and the priming solution will equilibrate with the native blood volume during the first several minutes of ECLS. 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 blood volume should be maintained at a level high enough to keep right atrial pressure in the range of 5-10 mmHg. This will assure adequate volume for venous drainage, as long as the resistance of the drainage cannula is appropriate

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 causes lung and myocardial failure, adding to 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 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, continuous hemofiltration is added to the extracorporeal circuit to maintain fluid and electrolyte balance.

The amount of oxygen delivered during ECMO depends on the blood flow and the hemoglobin concentration. The higher the hemoglobin the lower the flow requirement. The lower the hemoglobin the higher the flow requirement. Both high flow and transfusion have

risks. The tradeoff is in favor of normal hemoglobin (15 g%) allowing lower flows. This is discussed in Chapter 4.

5.   Temperature

Temperature can be maintained at any level by adjusting the temperature of the water bath. Temperature is usually maintained close to 37° C. If the patient was cannulated under conditions which could lead to hypoxic ischemic brain injury, it is reasonable to maintain mild hypothermia (32 to 34°) during the first 24 to 72 hours to minimize brain injury. Hypothermia will require sedation or paralysis to avoid shivering, and may exacerbate bleeding. Hyperthermia (from fever or inflammation) is controlled with the heat exchanger to avoid hypermetabolism.

6.   Renal and nutrition management (Chapters 4, 41, 62)

As mentioned above spontaneous or pharmacologic diuresis should be instituted until patient is close to dry weight and edema has cleared. This will enhance recovery from heart or lung failure and decrease the time on ECLS. If renal failure occurs, it is related to the primary disease and is treated by continuous hemofiltration (CVVHD). As with all critically ill patients, full caloric and protein nutritional support is essential.

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 ECLS. Bacteremia during ECLS 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.   Positioning

Patient positioning should be as mobile and normal as possible depending on the primary condition. There is a tendency to allow the patient to be anesthetized and lay supine for days at a time. In older children and adults, this will lead to posterior lung compression and atelectasis and should be avoided. If the primary problem is respiratory failure, posterior consolidation can be prevented and even treated by prone positioning for several hours each day. An alternative is a sitting position, although it may be difficult to maintain ECLS flow in the sitting position. If the patient is on ECLS for cardiac support it is often possible to extubate and allow the patient to move about spontaneously in bed. Obviously this is not recommended for patients with trans-thoracic cannulation and an open chest.

9.   Bleeding (Chapter 7)

Bleeding is the most common complication during ECL S because of systemic anticoagulation, thrombocytopenia, and thrombocytopathia. **Prevention** of bleeding is important throughout the ECLS course. Care providers may forget that simple venipuncture,

fingersticks, endotracheal suctioning, passage of a catheter through the nose or urethra, can lead to uncontrollable bleeding. Because of ample blood access there is very rarely any need for needle punctures in ECLS patients. Suctioning and passage of catheters should be done with caution, and only after assuring that the anticoagulation status is optimal (low ACT, adequate platelet counts). If invasive procedures are necessary, appropriate preparation is essential. Management of anticoagulation is discussed in section IV.A.4 above. Particular attention should be paid to fibrinogen and AT3 level if the patient is on heparin.

Management of bleeding begins with **returning coagulation status to normal** as much as possible. This involves decreasing the anticoagulant infusion until the ACT or PTT is 1.4 to 1.5 times normal, transfusing platelets until the platelet count is greater than 100,000, and giving antifibrinolytics if fibrinolysis is documented or suspected (particularly after a recent major operation). Fresh frozen plasma or specific clotting factors may be indicated if deficiencies are demonstrated. Often these maneuvers will stop bleeding. If not, it is reasonable to turn the anticoagulant off altogether; however, this may result in major circuit clotting and should not be done until and unless **site specific** measures (below)are completed. Using a thromboresistant coated circuit may allow withholding heparin for a longer period of time with less risk of clotting complications.

Cannulation site. This is the most common site of bleeding, particularly if access has been gained by direct cutdown. Bleeding can be minimized by doing the dissection without systemic heparin, then waiting a few minutes before cannulation if patient condition permits. Bleeding at the cannulation site may be an indication that the cannula is loose or pulling out. The possibility of decannulation should always be considered. Usually cannula site bleeding is slow oozing related to disruption of small vessels in the skin or subcutaneous tissue. Topical pressure will often control the bleeding, although care must be taken to avoid compressing the cannula. If bleeding persists after direct cutdown access the wound should be reexplored

Recent operation. When the platelet count, ACT, and other medications are optimal, the operative site should be reexplored for active bleeding. When an operative site is explored for bleeding it is best to leave the site open with active drainage and a plastic seal closure, rather than surgical closure of the skin. (Cutdown cannulation site is an exception.) Reexploration may be necessary many times before bleeding is controlled. There is a moderate risk of wound infection, but that risk is much lower than the risk of ongoing bleeding. See patient specific guidelines for post cardiotomy and other conditions.

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 is indicated to determine if the tube is in the parenchyma of the lung. If it is the tube should be removed, but thoracotomy will probably be need to control the bleeding and air leak. If not all the steps outlined above may stop the bleeding. If not thoracotomy is indicated (either via thoracoscopy or directly). Even if bleeding is controlled

by operation it often recurs within days. Because of this, it is wise to pack the chest open which permits frequent bedside reexploration until the patients is off ECMO

Mucous membranes. Bleeding from the nasopharynx, mouth, trachea, rectum, or bladder commonly occurs with minor trauma associated with patient care. It is difficult to control bleeding in these areas by direct pressure but full nasal packing or traction on a Foley catheter with a large balloon in the bladder may stop major bleeding.

Uterus. Women in the childbearing years may experience a menstrual period during ECLS (although that is rare in critically ill patients). However, uterine bleeding is usually not severe and subsides spontaneously. When ECLS is used in a recent postpartum patient, uterine bleeding can be a significant problem. After ruling out retained products of conception, the bleeding may be controlled by oxytocin, or creating a balloon tamponade within the uterus. Very rarely hysterectomy may be necessary.

GI bleeding can occur from esophagitis, gastritis, duodenal ulcer, or other sources. It is important to determine the site of bleeding by endoscopy or angiography. If the site of bleeding can be reached by an endoscope or arterial catheter, local measures should be attempted. The decision to operate to control bleeding or excise the bleeding organ is the same as in any patient with GI bleeding and a systemic coagulopathy. The coagulopathy is corrected as much as possible, and then operation is indicated if uncontrolled bleeding persists. The same is true for spontaneous bleeding into other solid organs (liver, kidney, retroperitoneal tissue) or bleeding into the thorax or peritoneal space.

Bleeding into the head or brain parenchyma is the most serious ECLS complication. It is usually extensive and fatal. If it is possible to take the patient off ECLS on high ventilator and drug settings, it is reasonable to operate on the skull to drain the blood, if such a procedure is indicated

If bleeding persists despite all of these procedures and maneuvers, it is reasonable to **stop anticoagulation altogether** until the bleeding stops. The best way to do this is to come off bypass on high flow high ventilator/inotrope settings if the patient's condition will permit it. Often bleeding will stop once a patient is off ECLS for several hours. If the patient will not tolerate coming off bypass, it is reasonable to stop the anticoagulation altogether and allow the ACT to return to the normal range for hours. This may stop the bleeding but may also result in clotting in the circuit, so whenever anticoagulation is turned off a primed circuit should be immediately available.

10.   Procedures (Chapter 6, 61)
Procedures from venipuncture to liver transplantation can be done with success during ECLS. When an operation is necessary, coagulation should be optimized (anticoagulation minimized) as described above. Even small operations like chest tube placement are done with extensive use of electrocautery. For the surgeon, the procedure is like operating on any coagulopathic patient.

Tracheostomy is often done in ECLS patients but the technique is different than standard tracheostomy. The trachea is exposed through a small incision, all with extensive electrocautery. The smallest opening in the trachea is made between rings, preferably with a needle, wire, and dilation technique. Do not incise a ring or create a flap. Because the patient is on ECLS support there is no urgency about gaining access or conversion from ET tube to trach tube. The operative site (and trachea) should be bloodless after operation. Subsequent bleeding (common after a few days) should be managed by complete reexploration until bleeding stops.

V   Weaning, Trials off, Discontinuing ECLS for Futility (Chapters 4, 42)

A.   Weaning
When management is carried out as described in Section IV (using the lowest flow to provide adequate support at low ventilator settings and pressor doses), weaning is automatic. Extracorporeal support is decreased as native organ function improves. When ECC support is less than 30% of total, native heart or lung function may be adequate to allow coming off ECLS, and a trial off is indicated. Note: as long as ECC support is more than 30 to 50%, there is no indication to trial off, except in special circumstances such as uncontrolled bleeding.

1.   Weaning adults from VV ECMO
Decrease flow in steps to 1L/min at sweep FiO_2 100% OR decrease flow to 2L/min then decrease sweep FiO_2 to maintain $SaO_2 > 95\%$. When SaO_2 stable on these settings, on VV, trial off by clamping sweep on vent rest settings PSV or spontaneous breathing at 50% FiO_2. If SaO_2 >95 and $PaCO_2$ <50 x 60 min, come off.

If $PaCO_2$ >50 stay on at low flow, or go to selective CO_2 clearance mode. In long cases oxygenation often improves before CO_2 clearance. However, CO_2 clearance is usually restored as the lung heals. It may be necessary to continue selective CO_2 removal with ECLS for weeks after improvement in oxygenation.

B.   Trial off
Trial off **during VV access** is very simple. Cardiac function is adequate and only native gas exchange is tested. Adjust ventilator to settings you would accept off ECLS (rate, plateau pressure, PEEP, FiO_2). Maintain blood flow and anticoagulation, stop the sweep gas, and cap off the oxygenator. Follow the patient SaO_2 and PCO_2. If lung function is adequate at acceptable ventilator settings for an hour or more the patient is ready for decannulation.

If the trial off is successful but the patient is precarious, the circuit can be cut away and access cannulas left in place in case the patient needs to be returned to ECLS support with a new circuit. In this circumstance the usual practice is to infuse low dose heparinized saline into the cannulas and reassess frequently. Access cannulas can be left in place for 24 hour or more. If there is no uncertainty about the need for further ECLS, it is better to remove the cannulae after the trial off has finished successfully.

C. Decannulation

The cannulas can be removed whenever the patient is ready, but ideally after the heparin has been turned off for 30 to 60 minutes. Cannulas placed by direct cutdown are removed by direct cutdown. The cannulae are removed and the vessels simply ligated (or occasionally repaired). If the femoral artery has been cannulated by cutdown, vascular repair will be required. Venous and arterial cannulae placed by percutaneous access can be removed directly and bleeding controlled by topical pressure.

When removing a venous cannula, air can enter the venous blood through the side holes if the patient is breathing spontaneously. This is prevented by a Valsalva maneuver on the ventilator, or by short-term pharmacological paralysis when removing the venous cannula.

D. Stopping support for futility

ECLS should be discontinued promptly if there is no hope for healthy survival (severe brain damage, no heart or lung recovery, and no hope of organ replacement by VAD or transplant). The possibility of stopping for futility should be explained to the family before ECLS is begun. The definition of irreversible heart or lung damage depends on the patient and the resources of the institution. In each case, a reasonable deadline for organ recovery or replacement should be set early in the course. For cardiac failure, for example, three to five days of no cardiac function in a patient who is not a VAD or transplant candidate is considered futile in most centers. For lung failure, for example, two weeks of no lung function in a patient who is not a transplant candidate is considered futile in many centers, although there are cases of lung recovery after 30 days of ECLS.

Fixed pulmonary hypertension leading to right ventricular failure in a patient with respiratory failure has been considered an indication of futility in the past. Recently there are many cases who have been converted to VA or RA to PA support with ultimate recovery to normal lung function. These patients may require months of support, so should be managed in facilities equipped for providing months of support. See IV B 1.

VI. Patient and Disease Specific Protocols (Chapter40,41,43,53,54,56,58,60)

A. Bronchoscopy

Bronchoscopy and airway lavage are facilitated by extracorporeal support and should be used as indicated. Lighter sedation, prone positioning, and chest PT may allow mobilization of distal secretions and may reduce the need for bronchoscopy.

B. Management of air leaks

Chest tube placement is frequently accompanied by bleeding complications and need for thoracotomy, so a conservative approach is often taken to pneumothoraces. **A small pneumothorax** (estimated 50% or less with no hemodynamic compromise and no enlargement

over time) can be managed by waiting for absorption with no specific treatment. **A symptomatic pneumothorax** (> 50%, enlarging, or causing hemodynamic compromise) should be treated by external drainage, although a small tube can be used with appropriate preparation (see section IV:9). **Massive air leak** or bronchopleural fistula (less than half of the inspired volume comes out as expired volume) can be managed by ECLS, in fact it is sometimes a specific indication for ECLS.

As in any bronchopleural fistula, the first objective is to evacuate the pleural space so that the lung contacts the chest wall, leading to adhesions with closure of the visceral pleura.

During ECLS this can almost always be managed by a single chest tube placed on high continuous suction (20-50 cm/H_2O), then limiting inspiratory pressure and volume. In some cases, it may be necessary to manage the airway by continuous positive airway pressure at 10, 5, or even 0 cm/H_2O for hours or days leading to total atelectasis. When the air leak has sealed, airway pressure is gradually added until conventional rest settings are reached.

Recruitment of the totally atelectatic lung may take one or more days.

Bronchopleural fistula with a massive air leak **directly from a bronchus or the trachea** (after lung resection or trauma for example) should be managed initially as outlined above, but direct endoscopic or thoracotomy closure is often required.

C.   Selective CO_2 removal

For status asthmaticus and other conditions in which blood $PaCO_2$ is very high, reduce the blood PCO_2 gradually to avoid acid base imbalance or cerebral complications. A suggested rate of decreasing arterial PCO_2 is 20 mmHg/hr. When selective CO_2 removal is used to treat permissive hypercarbia and to achieve rest lung settings in ARDS, CO_2 can be normalized at acceptable rest lung settings with low blood flow (20% of cardiac output). If the lung failure is severe this can result in major hypoxemia. If the cardiac output and hemoglobin concentration are adequate, arterial saturation as low as 75% is safe and well tolerated. However, increasing extracorporeal blood flow to improve oxygenation is preferable to increasing ventilator pressure or FiO2 when selective CO_2 removal is used. This is not an option with arteriovenous CO_2 removal. In choosing the cannulation approach in such patients it is important not to undersize the cannula so that the maximum flow is less than the required flow to facilitate oxygenation.

D.   Pulmonary embolism

Many patients with primary or secondary ARDS will have small (segmental) pulmonary emboli on contrast CT or angiography. Such emboli do not require any specific treatment aside from the heparinization which accompanies ECLS. When **major or massive pulmonary embolism** is the cause of respiratory/cardiac failure, venoarterial ECLS is very successful management if cannulation and extracorporeal support can be instituted before brain injury occurs. After VA access and successful ECLS is established, document the extent of pulmonary embolism by appropriate imaging studies. Massive pulmonary emboli will usually resolve or move into segmental branches within 48-72 hours of ECLS support. Heparinization is required for the

circuit, and adding thrombolytic drugs to speed up clot lysis often results in extensive spontaneous bleeding, so it is best to avoid lytics. The patient can be weaned from ECLS then from ventilation and managed by pulmonary embolism prophylaxis. Almost all such patients are managed with placement of an inferior vena caval filter.

E.   ARDS from secondary lung injury (following shock, trauma, sepsis, etc.)
Once the patient is on ECLS support there is a temptation to be less aggressive treating the primary problem, however this is generally a mistake. The threshold for operations should be lower rather than higher despite ECLS and anticoagulation (for example pancreatic resection and drainage for necrotizing pancreatitis, fasciotomy and/or amputation for compartment syndromes and gangrene, excision and drainage of abscesses, etc.).

F.   Fluid overload
ECLS offers the opportunity to treat massive fluid overload easily. Adequate renal perfusion through native cardiac output or through VA perfusion can be assured minute to minute with appropriate management. As long as renal perfusion is adequate pharmacologic diuresis can be instituted and maintained even in septic patients with active capillary leak. Continuous hemofiltration can and should be added to the circuit if pharmacologic diuresis is inadequate. The hourly fluid balance goal should be set (typically -100 to 300 cc/hr for adults) and maintained until normal extracellular fluid volume is reached (no systemic edema, within 5% of "dry" weight). Although normal renal function can usually be maintained, the life threatening condition is respiratory failure. Even if acute renal failure follows ECLS, it will resolve to normal renal function within six months in 90% of cases.

G.   Post-ECLS recovery and management
A patient is weaned off ECLS on lung-protective ventilator settings as described in V. If respiratory function is tenuous the vascular access catheters can be left in place as described in V. Once the patient is off ECLS ventilator weaning continues per unit protocol. There is a tendency to drift into positive fluid balance, more sedation, increasing ventilator settings which should be carefully avoided. If tracheostomy was not done during ECLS it should be done as soon as anticoagulation is reversed in most cases to facilitate ventilator weaning and minimize pharyngeal airway contamination and pneumonia. Patients who experience severe lung injury from necrotizing pneumonia, or from very high plateau pressures prior to ECLS will have the physiologic syndrome of very high alveolar level dead space. This is characterized by adequate oxygenation on low FiO2 but CO2 retention, respiratory acidosis, the need for hyperventilation (either spontaneous or via the ventilator) to maintain PaCO2 under 60, and an emphysematous(honeycomb) appearance on chest x-ray or CT scan. This condition has the characteristics of chronic irreversible obstructive lung disease; however, this condition almost always reverts to normal within 1-6 weeks. It is analogous to the condition of alveolar level dead space CO2 retention that occurs in children with severe staphylococcal pneumonia leaving large bullae at the alveolar level. These conditions heal by contracture eliminating the alveolar level dead space.

Post ECMO: Be careful! 10% of post ECMO pts die in hospital Stay in the home ICU until off vent x 24 hours. Avoid return to sedation and more ventilation. Scan for DVT within 48 hours of coming off ECMO. Consider IVC filter if there are signs of DVT.

H.   Lung biopsy

The cause of severe respiratory failure may be unknown when the patient is started on ECLS. Although lung biopsy is the next step in diagnosis, it is potentially dangerous in patients on ECLS with anticoagulation. If pulmonary function rapidly improves during ECLS (the first few days) lung biopsy may be delayed until the patient is off anticoagulation. However, if pulmonary function is not improving and the primary diagnosis is not known, lung biopsy can and should be done within the first week on ECLS as early biopsy increases diagnostic yield allowing introduction of specific therapy early. Lung biopsy is best done by thoracotomy (or thoracoscopy) rather than transbronchially because of the risk of major hemorrhage into the airway with transbronchial biopsy. As with any thoracotomy during ECLS, it is best to leave the chest open covered by an adhesive plastic drape, with definitive closure after ECLS.

I.   Rare conditions

ECLS has been used for rare causes of pulmonary failure with variable success. When considering ECLS for a specific diagnosis for the first time in any given center it may be helpful to consult the ELSO registry for the worldwide experience with that condition. Examples are vasculitis, autoimmune lung disease, bronchiolitis, obliterans, Goodpasture syndrome, rare bacterial, fungal or viral infections.

VII. Expected Results (Chapter 43)

In the last ten years, hospital survival of thirteen thousand adult respiratory failure cases recorded in the ELSO Registry averages 58%. These patients were considered moribund in the ECMO centers so the value of ECMO support seems obvious. However, we do not know what the survival is in similar patients managed with conventional care in the centers reporting to the registry. If the survival of thirteen thousand similar patients without ECMO were 50% or less, the survival advantage of ECMO would be highly statistically significant.

Conducting prospective trials of ECMO has unique problems in study design, ethics, and interpretation. There have been 11 prospective trials of ECMO in severe respiratory failure; 5 of these were is adults. Two trials done decades ago show no advantage to ECMO. Three recent trials show a significant survival advantage to ECMO in adult respiratory failure.
Bartlett RH. Clinical research in acute fatal illness: lessons from extracorporeal membrane oxygenation. J Intensive Care Med 2016; 31(7):456-465. PMID: 25223826

The CESAR trial in the UK compared patients randomized to conventional care versus protocolized care including ECMO if needed. Healthy survival at 6 months was 63% in the ECMO protocol versus 47% in the conventional care group. (p=.03) 16 patients randomized to ECMO improved on the Glenfield protocol for ARDS management and were not treated with ECMO (13

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survived). Because of this the study is described as demonstrating that patients referred to the ECMO center have a better outcome than patients managed in conventional ICUs.

Peek GJ, Mugford M, Tiruvoipati R, et al; for the CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomized controlled trial. Lancet 2009 Sep 15

A matched pairs study of ECMO in H1N1 influenza patients in the UK showed 76% survival in the ECMO protocol group versus 45% survival in the matched pairs control group. Although the matching was done in 3 different ways. 6 ECMO patients could not be matched to conventional are controls.). Because of this the study is described as demonstrating that patients referred to the ECMO center have a better outcome than patients managed in conventional ICUs

Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). JAMA 2011;306:1659e1668.

A matched pairs study of ECMO in H1N1 influenza patients in France showed 65% survival in 103 ECMO patients and 66% survival in 157 similar conventional management patients. Using the matching criteria chosen, only 52 ECMO patients could be matched to a conventional care patient. The survival was 50% (ECMO) and 60% (conventional) in the 52 per group analysis. When the matching was done using the replacement method to make 103 matched pairs, the survival was 78% ECMO and 45% conventional.

Tai Pham, Alain Combes, Hadrien Roze et al, Extracorporeal Membrane Oxygenation for Pandemic Influenza A(H1N1)–induced Acute Respiratory Distress Syndrome A Cohort Study and Propensity-matched Analysis. Am J Respir Crit Care Med Vol 187, Iss. 3, pp 276–285, Feb 1, 2013

Another prospective randomized trial is underway (Combes, The EOLIA trial) This study is expected to be completed and reported by 2018.

It is likely that future trials will compare ECMO instituted early (48 hours) in the course of severe respiratory failure to current practice (typically 3-6 days after intubation).