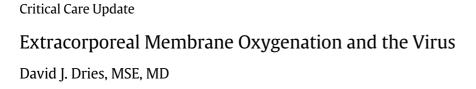Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Critical Care Update

Extracorporeal Membrane Oxygenation and the Virus

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DellaVolpe J, Barbaro RP, Cannon JW, et al. Joint Society of Critical Care Medicine-Extracorporeal Life Support Organization Task Force position paper on the role of the intensivist in the initiation and management of extracorporeal membrane oxygenation. *Crit Care Med.* 2020;48:838-846.

Prekker ME, Brunsvold ME, Bohman JK, et al. Regional planning for extracorporeal membrane oxygenation allocation during coronavirus disease 2019. *Chest.* 2020;158: 603-607.

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Extracorporeal membrane oxygenation (ECMO) is a respiratory or cardiac life support consisting of a vascular access cannula, a blood pump, and an artificial lung that removes carbon dioxide and adds oxygen. Pressure monitoring and blood sampling are available through ports situated before and after each system component. Venovenous ECMO is typically used for various forms of critical respiratory failure, whereas venoarterial (VA) ECMO sees greater utilization in the patient with a dominant presentation of heart failure such as cardiac arrest or other clinical states in which cardiac dysfunction is a significant component of illness. Although ECMO use has expanded rapidly since 2009, the majority of ECMO centers have a relatively low volume, with a median of 15 cases per year. The clinical implication is that ECMO patients and resources may move between centers providing this specialized therapy. ECMO patients are medically complex, at risk for complications, and

resource intensive. Medical transportation will be necessary to optimally match gravely ill patients with life-sustaining treatment.

Potential adverse events occurring in adults receiving ECMO may be categorized by events related to the patient and mechanical complications associated with the ECMO circuit. Patient complications include hemorrhage at surgical sites, bleeding into injured lungs, and intracranial hemorrhage. Central nervous system infarction and seizures are documented neurologic concerns. Cardiac complications include the episodic need for cardiopulmonary resuscitation and tamponade due to a clot in the pericardial sac. Finally, when groin access is used for ECMO cannulation, vascular complications including limb amputation may occur. Mechanical complications include malfunction of the blood pump, oxygenator, or cannula system. As critical care transport is provided, practitioners supporting transfer may encounter these complications.

In the current coronavirus disease pandemic, health systems confronting increased intensive care unit demand must equitably distribute resources to maximize benefit for critically ill patients during periods of resource scarcity. Triage may be necessary to allocate mechanical ventilation and resource-intensive therapy such as ECMO. For example, the Minnesota Department of Health Science Advisory Team (SAT) was developed as an advisory body to the State Health Commission including clinical, policy, ethics, and public health members to create guidelines for clinical resource allocation during a crisis. The SAT has developed regional response plans for various scenarios and provides clinical decision support tools, facilitates communication among community hospitals, directs resources to those most likely to benefit, and engages clinical experts. This group acknowledged

that ECMO requires significant resource investment and may be limited to patients most likely to survive. This commonsense approach may be strained during a pandemic situation.

A decision-making framework was created by the SAT to prioritize common ECMO indications based on the likelihood of survival and the predicted duration of ECMO support. For example, presentations likely to require a short duration of ECMO (less than or equal to 5 days) with a likelihood of survival of greater than 60% include hypercarbic respiratory failure due to status asthmaticus, cardiac arrest because of accidental hypothermia requiring rewarming, neonatal meconium aspiration, or some forms of pediatric cardiogenic shock. On the contrary, patients projected with lower survival (< 30%) and requirement for ECMO support greater than 5 days include patients requiring ECMO as a bridge to lung transplantation for irreversible respiratory failure, acute respiratory failure in the setting of severe immunocompromise, and cardiovascular collapse refractory to vasopressor therapy in the setting of multiorgan failure such as septic shock. Data from the current pandemic place these patients in the category of subjects with good survival (> 60%) but a longer duration of ECMO use (> 5 days).

Another approach to ECMO allocation in the setting of pandemic respiratory illness is provided by the Department of Emergency Medicine along with the Division of Pulmonary and Critical Care Medicine at the Harvard Medical School. This group proposes guidelines for ECMO support based on physiological parameters. For example, indications for venovenous (VV) ECMO include a low pH, a Pa_{O_2}:fraction of inspired oxygen ratio less than 80 mm Hg for more than 6 hours despite optimal management, and high airway pressures despite lung-protective ventilation with no trend toward

improvement. Absolute contraindications to ECMO therapy include active malignancy, age greater than 65 years, high-grade shock despite vasoactive drug support, multiorgan failure, inability to tolerate anticoagulation needed to provide ECMO, mechanical ventilation for more than 7 days, irreversible neurologic injury, and life expectancy less than 6 months. Relative contraindications to ECMO support include thrombocytopenia with a platelet count less than 50,000/μL, neutropenia, body mass index greater than 40, total body weight greater than 180 kg, long-term chronic respiratory insufficiency, and physical incapacity such as inability to perform activities of daily living at baseline. Regardless of how a triage system evolves, advanced medical transportation will be required to match patients and scarce resources.

Nuts and Bolts

Schmidt GA, ed. *Extracorporeal Life Support for Adults. Respiratory Medicine Series.* New York, NY: Humana Press; 2016.

Vuylsteke A, Brodie D, Combes A, Fowles J, Peek G, eds. *ECMO in the Adult Patient.* Cambridge, UK: Cambridge University Press; 2017.

Care for the patient preparing for transfer after cannulation for ECMO begins with examination of the circuit from end to end with rechecks on an hourly basis to assure safe operation and detect problems before the circuit is threatened. The use of a checklist is recommended. Examine the exit site of the drainage cannula for venous blood or a double-lumen cannula, if present, for signs of infection, bleeding, or visible recirculation (return of oxygenated blood to the oxygenator) while assuring that the cannula is secure. Connectors joining the cannula to the remainder of the ECMO circuit must be checked. This is particularly important if the patient has recently been cannulated in case steps were overlooked. Connectors between tubing segments should be checked for security, cracks, and clots. Tubing is then followed to the blood pump, which is checked with a light for clots. The ECMO pump should be auscultated for abnormal sounds and felt for excessive heat generation or vibration. Alarms and pressure measurements, pump speed, flow, and power supply should be verified. Ideally, the ECMO center should create a nomogram of what to expect for circuit flow at a given rpm setting on the pump.

Tubing is then followed to the oxygenator. If a VV hemofiltration machine is also connected to the ECMO circuit, inlet and outlet pressure limits for the VV hemofiltration unit should be assessed to account for the effect of this device on the ECMO circuit. The oxygenator should be examined for clots or cracks, and connections to the remainder of the ECMO circuit examined for cracks and adequate tightness. The pressure gradient across the oxygenator membrane should be measured with the referring team and compared with expected values. Membrane function should be roughly checked by noting the color of blood exiting the membrane, which should be bright red. The Pao_2 of a blood sample taken from the outlet of the oxygenator should be greater than 225 mm Hg assuming a 100% oxygen gas mixture, which is standard, as the inflow gas to the oxygenator. Falling oxygenation in a blood sample obtained from the circuit beyond the oxygenator may signal a failing oxygenator, but the ability of an oxygenator to support gas exchange is not critically impaired until the oxygenation of blood obtained at the outflow of the oxygenator falls below a Pao_2 value of approximately 110 mm Hg and patient pulse oximeter values begin to fall. Membrane life may be prolonged by increasing anticoagulation and maintaining a higher circuit blood flow.

Gas flow (oxygen) into the circuit should be verified. Condensation may accumulate in the gas phase of the oxygenator, leading to impairment of gas exchange. This can be seen as clear water dripping from the gas exhaust port and will be reflected in poor oxygen tension in blood sampled from the circuit immediately after the oxygenator. Care should be taken to prevent excessive inflow gas pressure; some centers use a safety valve on the gas inlet to prevent excessive pressure.

Blood flow in the ECMO circuit is slowly built up over several minutes until further increases in pump speed do not produce more flow. Pump speed may then be reduced by 10% to 20% to prevent excessive negative inlet pressure at the venous inflow cannula. If adequate flow (60 mL/[kg • min] in adults) cannot be rapidly achieved, the patient may be hypovolemic, or the cannula position may be suboptimal. During the initiation of ECMO, the patient may become hypotensive caused by changes in the concentration of potassium or other electrolytes. This can be avoided by priming the circuit with a balanced electrolyte solution. During the early minutes of ECMO circuit function, gas inflow may be kept low (2 L/min) in order to prevent a sudden reduction in $Paco_2$ resulting in cerebral vasoconstriction. As circuit blood flow is optimized, gas inflow can be returned to projected values, and patient support from the clinical ventilator may be reduced. Typical lung rest involves pressure-controlled ventilation with initial peak inspiratory pressures below 30 cm H_2O with reduction over the next several hours to a ventilator peak pressure of 10 cm H_2O above resting pressure or positive end-expiratory pressure. A typical value for positive end-expiratory pressure setting during this time is 10 cm H_2O with a respiratory rate of 10 breaths/min. Gas flow into the oxygenator may be adjusted to achieve a target $Paco_2$ of 30 to 45 mm Hg based on arterial blood gas results.

Systemic oxygenation is dependent on the amount of cardiac output directed through the ECMO circuit. If circuit flow is adequate, it should be possible to discontinue other oxygenation rescue therapies. Ventilator oxygen delivery settings can be reduced as long as ECMO circuit flow and gas exchange membrane function are adequate. A typical goal arterial saturation is 80%. Another goal is to reduce the fraction of inspired oxygen provided by the ventilator to 30% over the first day. If ventilator oxygen cannot be reduced in this way, the ECMO circuit may be inefficient because of poor internal blood flow through the oxygenator or poor cannula function. Another explanation is high cardiac output from the patient and inadequate capture of cardiac output by the ECMO circuit, resulting in a shunt of venous blood with low oxygen content to the arterial side of the circuit. Solutions to this problem may involve cannula adjustment or mild cooling to reduce oxygen consumption by the patient.

Hemodynamic stability is usually rapidly achieved in patients receiving VV ECMO because these individuals typically have acceptable cardiovascular function. If VA ECMO is used, the initiation of pump flow usually results in rapid improvement in blood pressure and other measures of perfusion. In either case, the use of vasoactive drugs can be reduced as long as intravascular volume is adequate. ECMO should augment systemic oxygenation, permit lower ventilator pressures, and allow the reduction of hemodynamic support that was required before ECMO initiation. VA ECMO may be necessary for patients with refractory shock.

A bolus of heparin is typically administered during cannulation, typically 50 to 100 U/kg. An activated clotting time (ACT) is drawn to confirm the effectiveness of the heparin bolus, and unfractionated heparin is infused at 10 to 15 U/(kg • h) to maintain an ACT of 160 to 220 seconds.

The need for multiorgan support is common in ECMO patients. These individuals are at high risk for delirium, and standard management approaches are recommended including the control of pain, frequent interruption of sedation, provision of spontaneous

breathing trials, and early mobilization (out of bed). Maintaining a sleep-wake cycle is also an important goal. Cardiac function is evaluated with echocardiography to rule out a contribution of underlying heart disease to pulmonary dysfunction. ECMO patients are good candidates for gut-based nutrition. Intravenous nutrition may be used if necessary. Continuous VV hemofiltration for continuous renal replacement therapy may be used in combination with ECMO if necessary. In addition to the support of kidney function, titration of continuous VV hemofiltration settings may be used to gradually reduce the accumulation of excess fluid, which is commonly observed in the ECMO patient.

Anticoagulation is a critical component of ECMO therapy. Heparin is typically used to maintain necessary anticoagulation based on ACT for the circuit. As noted previously, the usual target ACT is between 160 and 220 seconds. Different ECMO programs may modify these recommendations. The theoretical goal is to prevent clotting in the circuit without causing bleeding complications in the patient. Another complication of anticoagulation in these patients is heparin-induced thrombocytopenia, leading some centers to use argatroban instead of heparin as the anticoagulant of choice for the circuit. Although there is no consensus regarding an optimal hemoglobin in these patients, a value of 7 to 10 g/dL is generally accepted. It is important to remember that the maintenance of tissue oxygen delivery at low hemoglobin concentrations requires an increase in cardiac output (or pump flow). In some cases, this may be challenging for both patient and circuit management. If the patient on ECMO requires surgery or has bleeding complications, antifibrinolytics such as tranexamic acid can be useful. Other commonly used procoagulant products include fresh frozen plasma, cryoprecipitate, and platelets with goals of an international normalized ratio < 1.5, fibrinogen > 200 mg/dL, and a platelet count $> 150 \times 10^3/mm^3$. These goals can be relaxed if the patient is not bleeding.

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Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. *JAMA.* 2020;323:2249-2251.

O'Callaghan KP, Blatz AM, Offit PA. Developing a SARS-CoV-2 vaccine at warp speed. *JAMA.* 2020;324:437-438.

Virus Update: Pathophysiology and Treatment

An excellent recent review reinforces the observation that coronavirus disease 2019 (COVID-19) binds to an angiotensin-converting enzyme receptor through which access to target cells, typically in the respiratory tract, is accomplished. Compromise of lymphocyte production follows with adverse effects on both humeral and cell-mediated immunity. As infection progresses, barrier integrity involving the epithelium and endothelium is affected. Although the lung may be the starting point for symptoms, endothelial disease progresses in severe cases with activation of coagulation and consumption of clotting factors. This leads to a significant incidence of thrombotic complications such as deep vein thrombosis, pulmonary embolism, limb ischemia, stroke, and myocardial disease including infarction.

Epidemiology studies continue to support the role for droplets expelled during face-to-face exposure as the most common mode of transmission. Exposure to an infected person within 6 feet for at least 15 minutes or a shorter exposure time to individuals who are symptomatic (cough) are associated with greater transmission risk. Transmission can occur from inanimate surfaces. Preclinical data suggest that viral load persists at higher levels on surfaces such as stainless steel and plastic as opposed to cardboard. The virus can be identified on impermeable surfaces for up to 3 to 4 days after contact.

The viral load in the upper respiratory tract appears to peak at the time of symptom onset with shedding of the virus beginning approximately 2 to 3 days before the appearance of symptoms. Asymptomatic and minimally symptomatic carriers clearly can transmit disease. In screening for patients based on symptoms, the most common findings in hospitalized patients are fever, dry cough, and shortness of breath. Fatigue, muscle aches, and gastrointestinal symptoms are less common. Complications in hospitalized patients include acute respiratory distress syndrome, acute liver injury, myocardial injury including infarction, thromboembolic events as described earlier, and acute kidney injury.

Thus far, the most commonly used and reliable test for COVID-19 detection has been the reverse transcription polymerase chain reaction targeting a variety of genes of the virus. This test is likely to be positive with samples obtained from a variety of respiratory sources or stool within the first week of symptom onset. A swab of the nasopharynx may detect infection as early as day 1 of symptoms. Reverse transcription polymerase chain reaction samples from sputum or stool may be positive after a nasal swab is negative. A second testing strategy identifies

infection indirectly by measuring the host immune response through the detection of antibodies to the virus. Antibody detection occurs during the second week of infection and is likely to continue beyond the first 2 weeks of illness. Antibody identification is also important to help understand the extent of COVID-19 in the community and identify individuals who could be immune and protected from becoming infected. Immunoglobulin M and immunoglobulin G are the typical antibodies targeted in diagnostic antibody assays.

Supportive care continues to be the standard for management of the hospitalized patient. The vast majority of COVID-19 patients will require oxygen therapy. Noninvasive ventilation advancing to lung-protective ventilation through an endotracheal tube is a subsequent step upward in care. Prone positioning has also proven useful. The short-term use of neuromuscular blocking agents may facilitate oxygenation. Advanced respiratory dysfunction in patients affected by COVID-19 is treated using strategies developed earlier for acute respiratory distress syndrome. Secondary infection with bacteria or fungus is common. Overall, hospital mortality from the virus is approximately 15% to 20% but up to 40% among patients requiring intensive care unit admission. Among patients younger than 40 years, hospital mortality is reported at less than 5%, whereas mortality in patients aged 70 to 79 years is 35% and greater than 60% for patients aged 80 to 89 years.

The most recent development of interest in the management of COVID-19 is vaccination. A number of vaccine types are under development. For example, messenger RNA (mRNA) or mRNA-based vaccines deliver mRNA coded for COVID-19 to patient cells, leading to an immune response without the danger of actual virus exposure. Another strategy is to deliver a live but attenuated virus for which replication remains intact, without other complications of viral exposure, as another means to trigger an immunologic response in a patient. This strategy has been used successfully in the development of an Ebola vaccine. A third approach under investigation is the delivery of a virus, which is unable to replicate, as a vaccine. Again, immune response is triggered, but the spread of infectious complications is prevented. Additional information regarding these newer treatment strategies should become available in the coming months.

Summary Points

- ECMO remains a salvage strategy for patients most severely affected by COVID-19. Transportation agencies will become involved in the care of these patients

because many ECMO centers can accommodate relatively few patients. Patients may be cannulated for ECMO at outside hospitals before transport to an ECMO center. Because the use of ECMO is resource intensive, epidemiologic and clinical criteria are under development to determine which patients may be candidates for this therapy in the era of COVID-19.

• A transport agency taking responsibility for a newly cannulated ECMO patient should carefully evaluate the circuit and the patient for obvious problems in order to complete patient transfer successfully. Details in recently published works describing ECMO practice may be used for programs beginning the development of an ECMO management protocol for use during patient transfer.

• Sophistication is growing as additional diagnostic tests for COVID-19 are developed, and treatment therapies including vaccines advance to clinical trials. However, at present, the essence of hospital care begins with careful support of oxygenation. Avoidance of infection through the use of masks and social isolation, where appropriate, remain the foundation of COVID-19 management in the general population.

Acknowledgments