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Review Article

The role of extracorporeal membrane oxygenation in COVID-19

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An extracorporeal membrane oxygenation (ECMO) program is an important component in the management of patients with COVID-19, but it is imperative to implement a system that is well-supported by the institution and staffed with well-trained clinicians to both optimize patient outcomes and to keep providers safe. There are many unknowns related to COVID-19, and one of the most challenging aspects for clinicians is the lack of predictive knowledge as to why some patients fail medical therapy and require advanced support such as ECMO. These factors can create challenges during a time of resource scarcity and interruptions in the supply chain. In the current environment, in which resources are limited and an ongoing pandemic, healthcare practitioners need to focus on evidence-based best practice for supportive care of patients with COVID-19 in refractory respiratory or cardiac failure. with As experience is gained, a greater understanding will develop in this cohort of patients regarding need and timing of ECMO. As this pandemic continues, it will be important to compile and analyze multicentered data pertaining to patient-specific outcomes to help guide clinicians caring for patients with COVID-19 undergoing ECMO support. In this paper, the authors demonstrate the strategies utilized by a major quaternary care center in the utilization and management of ECMO for patients with COVID-19.

Key Words: COVID-19; ECMO; Extracorporeal Membrane Oxygenation; Healthcare Worker Safety; ICU; Patient Safety

COVID-19, CAUSED BY the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a pandemic with more than 4 hundred fifty million confirmed cases worldwide as of 2022. While the exact number of patients is not known, large studies have demonstrated that almost 40% of patients admitted to the hospital with COVID-19 in 2020 required ICU admission and mechanical ventilation for respiratory failure secondary to acute respiratory distress syndrome.¹ A subset of these patients continue to have refractory respiratory failure despite traditional measures of low-tidal-volume ventilation, prone ventilation, neuromuscular blockade,^{2,3} and inhaled pulmonary vasodilators.⁴ For this subset of patients with COVID-19, venovenous extracorporeal membrane oxygenation

SVC, Superior Vena Cava; PAT, Pulmonary Acceration Time ¹Corresponding author.

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(ECMO) may be utilized as a rescue therapy to support pulmonary function long enough to allow for lung recovery.^{5,6} An even smaller subset of admitted patients with COVID-19, approximately 3%-to-4%, have presented with cardiogenic shock.⁷ In late 2020, the U.S. Food and Drug Administration issued a policy for ECMO as a rescue therapy during the COVID-19 pandemic.⁸ While there are insufficient data to strongly recommend ECMO support for patients with COVID-19, a brief review of prior viral pandemics and ECMO suggested that it is at least a reasonable rescue strategy $^{9-13}$ (Table 1). Previous respiratory viral outbreaks, such as the Middle East respiratory syndrome coronavirus in 2012 and the influenza A virus subtype hemagglutinin 1 neuraminidase 1 in 2009, were treated with ECMO; ECMO in these settings exhibited promising potential, with survival ranging from 65%-to-77%.¹⁴ ECMO in the COVID-19 era is different for several reasons including but not limited to: high risk of contagious 2

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Table 1
Extracorporeal Membrane Oxygenation Utilization in Prior Viral Respiratory Outbreak

Study	Virus	Study Population	Study Outcomes	Comments
Patroniti et al. ¹¹	Influenza A virus subtype hemagglutinin 1 neuraminidase 1	153 ICU patients, 60 received ECMO. Source: Italian extracorporeal membrane oxygenation Network	Survival to Hospital Discharge for ECMO patients: 68%; Survival among patients receiving ECMO within 7 days of intubation was 77%	Consistent with consensus/agreements that ECMO needs to be considered early in acute respiratory distress syndrome.
Pappalardo et al. ¹⁰	Influenza A virus subtype hemagglutinin 1 neuraminidase 1	Prospective multicenter cohort of 60 patients in the Italian ECMO net dataset	Survival: 68%; Predictors of death: length of stay prior to ECMO initiation, bilirubin elevation, creatinine elevation, anemia, and shock	Consistent with prior experience: ECMO should be considered early, progressive organ dysfunction may signal futility. Consideration for ECMO should preferentially include patients with single organ dysfunction (pulmonary) if resources are limited.
Zangrillo et al. ¹³	Influenza A virus subtype hemagglutinin 1 neuraminidase 1	Systemic Review of literature: 266 patients out of 1,357 with confirmed/suspected Influenza A virus subtype hemagglutinin 1 neuraminidase 1 received extracorporeal membrane oxygenation.	Large variation in mortality (8% to 65%) dependent on co-morbidities. Estimate of overall in-hospital mortality of 28%. Most cases required prolonged (> 1 week) of support and multiorgan dysfunction or significant co- morbidities were associated with an increased risk of mortality.	So far this is consistent with outcomes in COVID-19 in relation to comorbidities. Presence of these co- morbidities should influence selection criteria for ECMO candidacy, particularly as resources are limited in a pandemic setting.
Sukhal et al. ¹²	Influenza A virus subtype hemagglutinin 1 neuraminidase 1	Systemic Review of literature: 494 patents who received ECMO for presumed Influenza A virus subtype hemagglutinin 1 neuraminidase 1 infection.	Overall Mortality 37.1%. Mean Duration of ECMO support: 10 days; Mean Duration of Mechanical Ventilation: 19 days; Mean ICU Length of Stay: 19 days	The decision to implement ECMO should include the knowledge that it will require a prolonged utilization of ICU resources and in the resource limited setting of a pandemic requires significant planning.
Alshahrani et al. ⁹	Middle East Respiratory Syndrome Coronavirus (MERS-CoV)	Retrospective review from 5 ICUs in Saudi Arabia: 17 patients on ECMO, 18 patients with conventional management. ECMO not initially available (first 18 patients). Patients had similar baseline characteristics	ECMO group: lower in-hospital mortality (65% v 100%), longer ICU stay (25 v 8 days), less norepinephrine use	Patient characteristics are similar to current outbreak: higher proportion of male patients, diabetes, and hypertension

spread from patient to provider, allocation of dwindling resources, and challenges with appropriate anticoagulation.¹⁵

Indications for ECMO in patients with COVID-19

According to the 2020 Extracorporeal Life Support Organization guidelines, patients with COVID-19 with refractory hypoxia who fail conventional treatment options (standard lungprotective ventilation, optimal positive end-expiratory pressure, and prone ventilation) should be considered for venovenous ECMO. Specifically, if their partial pressure of oxygen-to-fraction of inspired oxygen ratio is greater than or equal to 150 mmHg and pH < 7.20 (from 7.25 in prior guidelines) with partial pressure of carbon dioxide greater than 80 mmHg (from 60 mmHg in prior guidelines) for greater than 6 h.⁶ Guidelines also recommend the use of venovenous extracorporeal membrane oxygenation if a patient's partial pressure of oxygen-tofraction of inspired oxygen ratio is less than 60 mmHg for greater than 6 h or partial pressure of oxygen-to-fraction of inspired oxygen ratio is less than 50 mmHg for greater than 3 h.⁶ Indications for venoarterial extracorporeal membrane oxygenation in patients with COVID-19 is similar to patients without COVID-19; however, there have been increased reports of myocarditis and thromboembolism directly related to COVID-19, leading to cardiovascular collapse requiring venoarterial extracorporeal membrane oxygenation support.⁷ Prior to COVID-19, some institutions, including the authors' own, Masschusetts General Hospital, developed an extracorporeal cardiopulmonary resuscitation program. Yet the use of such support in COVID-19-positive patients is controversial given the high risk of contamination during an aerosol-generating procedure such as chest compressions and intubation. Taking into consideration provider safety and long-term outcomes of patients who suffer cardiac arrest, healthcare practitioners currently do not offer extracorporeal cardiopulmonary resuscitation service to patients with COVID-19. A more comprehensive list of contraindications, both relative and absolute, are included in Fig. 1.

It also is important to consider that patients with other pathologies that require ECMO support, such as massive pulmonary embolism or myocardial infarction, also may be COVID-19 positive. In addition to primary myocarditis from COVID-19, some patients with COVID-19 develop right and/or left ventricular dysfunction related to their severe hypoxemia. These patients are managed in several ways: (1) placement of venovenous ECMO with concurrent inotropic support, (2) placement of venoarterial ECMO, (3) cannulation with a hybrid

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Extracorporeal Membrane Oxygenation Protocol For COVID-19

Extracorporeal Membrane Oxygenation Eligibility for COVID-19 Positive Patients

- All intubated patients should be screened daily for extracorporeal membrane oxygenation needs/eligibility
- Proning failure or inability to prone
- PaO /FiO ≥ 150 mmHg and pH<7.2 with PaCO > 80 mmHg for > 6 hours
- PaO /FiO <60mmHg > 6 hours and pH<7.2 with PaCO > 80 mmHg
- PaO_/FiO_<500mmHg > 3 hours and pH<7.2 with PaCO_> 80 mmHg
- Approval by ICU Director or extracorporeal membrane oxygenation Director

Absolute Contraindications

- Age >60
- Body Mass Index > 35
- Absolute Neutrophil Count <1000
- Extracorporeal cardiopulmonary resuscitation
 Acute organ failure aside from cardiopulmonary and
- renal failure
- Chronic cardiac, pulmonary, renal, or hepatic disease documented on prior hospitalizations or visits
- Unknown neurologic status
- Active malignancy
- Refusal of blood transfusions or anticoagulation
- Mechanical ventilation > 7 days

Relative Contraindications

- Immune suppression
- Secondary infections with multidrug resistant organisms
- Recent Neurosurgical procedure
- No healthcare proxy identified

Cannulation Logistics

- Cannulation to occur at ICU bedside
- Femoral vein and internal jugular cannulation only (reduced need for guided imaging)
- Introducer sheaths placed in advance of acute deterioration

Pandemic Resource Utilization

- Daily assessment by ICU and extracorporeal membrane oxygenation teams regarding need for continued support
- Resource allocation will be guided by Hospital Incidence Command System

circuit,¹⁶⁻¹⁸ such as venoarterial-venovenous ECMO, which allows for full respiratory and cardiac support, (4) palliative care in patients who fail medical therapy and have contraindications to ECMO support.¹⁹ Ultimately, the Masschusetts General Hospital institutional ECMO criteria have been modified in light of the pandemic to best deploy resources. Precisely, patients aged >60, with a body mass index >35, and patients with chronic organ failure like renal or hepatic, are excluded from consideration. A complete list of the Masschusetts General Hospital absolute and relative contraindications for COVID-19 ECMO candidacy is presented in Fig. 1.²⁰

Logistics of ECMO in the COVID-19 era

Prior to screening a patient with COVID-19 for ECMO candidacy, it is important to have continuous communication regarding availability of critical care resources, evolving triage protocols, and the status of patients already undergoing ECMO. At the Massachusetts General Hospital, this information is available in near real-time based on continuous collaboration with the hospital incident command system, individual intensive care units, and frequently updated disease projections.

The Masschusetts General Hospital COVID-19 testing and screening policy has evolved throughout the pandemic as testing becomes more available and more reliable. The current testing strategy, as of 2022, is for all patients presenting for surgery or inpatient admission to be screened for COVID-19 with nasal polymerase chain reaction testing. Patients who already are inpatients are tested once, and if they remain asymptomatic, are not subjected to additional testing. If an inpatient requires mechanical ventilation or ECMO, they will

Fig 1. Extracorporeal membrane oxygenation screening eligibility and venovenous extracorporeal membrane oxygenation cannulation workflow.

be tested concurrently for COVID-19. Once a patient has tested positive, they must have 2 consecutive negative tests prior to being considered recovered. These criteria are inclusive for all of the Masschusetts General Hospital patients undergoing ECMO.

Swift identification of potential ECMO candidates is important during this pandemic for several reasons. This goal is achieved by having frequent evaluations of critically ill patients by a core team of ECMO physicians (at Masschusetts General Hospital. This is made up of a cardiac surgeon, 2 cardiac anesthesiology intensivists, and a pulmonary and critical care physician) who review potential cases to reach a consensus of ECMO candidacy.^{21,22} Once identified as a potential candidate, the patient is followed closely for signs of deterioration to facilitate early and safe cannulation. Provider safety is paramount, and avoiding an emergent cannulation, which could compromise patient and provider safety, is to be avoided at all costs.

Unfortunately, the COVID-19 pandemic is forcing many hospitals in America to consider what previously was an unthinkable problem in American medicine: rationing of care. ECMO is a resource-intensive intervention; thus, it is important to select candidates with the highest likelihood of recovery, as even an experienced center rapidly will run out of capacity.

Cannulation strategy

The goal of any ECMO cannulation is to minimize complications and to be as efficient as possible. This is especially pertinent for patients with COVID-19. To facilitate efficient cannulation, any patient who is an ECMO candidate and has rapidly progressive respiratory failure necessitating prone ventilation has venous sheaths placed in their right internal jugular vein and right common femoral vein prior to being placed in the prone position. Patients in cardiogenic shock have femoral venous and femoral arterial sheaths placed under ultrasound guidance to avoid a difficult cannulation under duress (Fig. 1).

In this pandemic, there is the additional consideration regarding protection of healthcare staff, conservation of limited equipment, decontamination of nondisposable equipment, and limitations on safe patient transport. Masschusetts General Hospital has elected to perform all cannulations at the bedside with the most experienced physicians, a cardiothoracic/intensive care-trained anesthesiologist, and a cardiothoracic surgeon; during the COVID-19 pandemic, this often was performed by operators with at least 3 years of experience in cannulation. Ultrasound guidance is used for all vascular access to improve first-pass success. Ultrasound views during cannulation focus on guidewire and cannula position. For transesophageal echocardiography, this is achieved with a midesophageal bicaval view, and for transthoracic echocardiography, a subcostal inferior vena cava view is performed. Transesophageal echocardiography is the preferred and routinely used method for bedside cannulation in patients without COVID-19 at Masschusetts General Hospital; however, for patients with COVID-19, removing a potentially aerosol-generating procedure is of interest and only a portable transthoracic ultrasound is used for cannula positioning and venous wire confirmation. To further improve the safety of cannulation, 2 single =-lumen venous cannulae placement is preferred as opposed to a dual-lumen cannula to minimize need for fluoroscopy or transesophageal echocardiography guidance. This cannulation strategy also allows for maximum flow and to minimize recirculation.

The additional advantages of using a portable transthoracic ultrasound compared to a transesophageal echocardiography machine is the smaller footprint at the bedside, as well as the ability to thoroughly wipe down and clean the machine, leading to less risk of cross-contamination (Fig. 2). However, utilizing transthoracic echocardiography instead of transesophageal echocardiography often can be hindered by body habitus or patient positioning, leading to inadequate imaging windows. Other imaging modalities, such as fluoroscopy, can be helpful during cannulation, but all patients with COVID-19 are cannulated at the bedside, which hinders the ability to use larger equipment like portable fluoroscopy. In the spirit of reducing cross-contamination across the hospital, the risk/benefit of using portable fluoroscopy in routine cannulations deems this imaging modality less desirable.

The authors also have noted, from literature review and experience, that patients likely will require prolonged mechanical support for respiratory failure and near-total pulmonary support necessitating high flow rates (flow goal > 60% of cardiac output).⁶ To reliably achieve this, the authors are placing cannulae that can reliably flow up to the maximum flow tolerated by the oxygenator. For patients cannulated for venoarterial extracorporeal membrane oxygenation, the authors are advising concurrent placement of an appropriately-sized distal limb reperfusion cannula under ultrasound guidance to reduce the likelihood of needing further bedside procedures.

Management of patients undergoing ECMO

ECMO patients present specific challenges for management at all levels of their care. Intensive care teams need to be familiar with the specifics of ECMO to help troubleshoot circuit complications.²³ At Masschusetts General Hospital, every attempt is made to cohort patients undergoing ECMO into intensive care units with prior ECMO experience, as this has led to improved outcomes.²¹ In addition, the cardiac intensive care team is available 24 h a day, 7 days a week for any patient who is in an atypical location. Due to the potential of caring for these patients outside of these units, health practitioners at Masschusetts General Hospital have increased the cross-training of nursing staff to increase familiarity with patients undergoing ECMO. This training includes online refresher courses and online guiding documents. Despite these measures, as stated by the Extracorporeal Life Support Organization, training new staff or centers for ECMO during this pandemic is not ideal.

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Fig 2. Portable ultrasound used for COVID-19 extracorporeal membrane oxygenation cannulation.

Anticoagulation of patients with COVID-19 undergoing ECMO

There are concerns regarding potential dysregulation of coagulation in patients with COVID-19, and close management of anticoagulation is essential.²⁴ Patients can experience disseminated intravascular coagulation, with decreases in platelet count and antithrombin and increases in fibrin degradation products and D-dimer.²⁵ Increases in inflammatory mediators (interleukin-2, interleukin-6, and tumor necrosis factor) and perturbances in the coagulation cascade have led to upsurges in both thrombotic and hemorrhagic complications.²⁶ Cerebrovascular complications and myocardial ischemia have been seen in young and otherwise healthy patients infected with COVID-19.²⁶ This is amplified even further for patients on ECMO, as the continuous contact between the circuit and patients' blood leads to further disturbances in the inflammatory and coagulation response, creating difficulties in deciding a proper anticoagulation strategy.⁶ While some patients on ECMO are experiencing thromboembolic complications and systemic hypercoagulability, others are suffering from increased bleeding complications like intracranial hemorrhage, as evident by institutional data showing rates of intracranial hemorrhage close to 30%.²⁰ For patients without COVID-19 on ECMO, some centers use thromboelastography or thromboelastometry to gain insight into the coagulation profile of the patient and direct their anticoagulation strategy, but data are limited in patients with COVID-19. The guiding principle of the authors' anticoagulation strategy is the use of an unfractionated heparin infusion (Supplemental Appendix 1) (Table 2). If heparin-induced thrombocytopenia is suspected or heparin cannot be used, then bivalirudin is used or no anticoagulation in venovenous ECMO if appropriate.

Table 2 Guiding Principle of Anticoagulation with ECMO in COVID-19 Patients

	Venovenous ECMO	Venoarterial ECMO	
Partial Thromboplastin Time (PTT)	40 to 50 s	70 to 100 s	
Anti-Xa	0.15 to 0.29 IU/mL	0.15 to 0.29 IU/mL	
Lab Draws and Timing	 The PTT is drawn 2 h post cannulation, followed by q6h draws with titrations until goal PTT or Anti-Xa is reached. Two consecutive draws resulting in no change in the heparin infusion result in labs being drawn q12h rather than q6h. 		
emorrhagic and- In instances of circuit thrombosis or patient hemorrhage, the PTT/Anti-Xa goal is ad discretion of the treating clinician.Xa Adjustments- In instances of circuit thrombosis or patient hemorrhage, the PTT/Anti-Xa goal is ad discretion of the treating clinician.		tt hemorrhage, the PTT/Anti-Xa goal is adjusted at the	

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Anesthesia and COVID-19 ECMO

In the interest of minimizing provider exposure and conserving valuable intensive care unit resources, the number of elective surgical procedures has substantially decreased. However, patients on ECMO with COVID-19 will develop conditions necessitating procedural or surgical intervention, and will require the expertise of anesthesiologists. It is, therefore, important that anesthesiologists are familiar with some common issues that develop on ECMO.²⁷

Decannulation

Patients on venovenous ECMO for COVID-19 tend to require longer support (20-to-40 days) compared to patients without COVID-19, based on initial reports out of China.²⁸

The Masschusetts General Hospital institutional data, which included stricter patient inclusion criteria, displayed a median duration of support of 12 days.²⁰ Compared to pre-COVID-19 data, patients on venovenous ECMO for COVID-19 at Masschusetts General Hospital were younger, with a median age of 47 years old.²⁰ The rate of successful decannulation from venovenous ECMO was 67%.²⁰ Masschusetts General Hospital existing weaning protocols have not formally changed for COVID-19, as there always has been a desire to liberate patients from mechanical support as expeditiously as possible (Appendix 3. Supplementary material). This is a balanced approach, as avoidance of a second cannulation is imperative given the increase in mortality associated with additional cannulations.²⁹

Protection of providers

ECMO cannulation is not by default an aerosolizing procedure, but due to the urgent nature and the risk of blood exposure and inadvertent ventilator disconnects during positioning, healthcare practitioners at Masschusetts General Hospital currently are treating it with a similar respect. Outside of every patient room prior to beginning the cannulation, there is a donning and doffing station; this includes all the disposable personal protective equipment required for cannulations, as well as hand sanitizer. All providers in the room wear an N95 or higher-quality respirator mask (or powered air purifier for those unable to wear an N95), face shields, and fluid-resistant gowns. In addition, the cannulating providers and assisting nurse wear surgical hoods, level-4 fluid-resistant gowns, shoe covers, and double-layer surgical gloves. The portable ultrasound used for vascular access and transthoracic ultrasound is completely enclosed in a sterile bag outside of the room prior to placement at the patients' bedside (Fig. 2). Before any cannulation, a preemptive huddle occurs outside the room where all surgical equipment is prepared and reviewed to reduce the need for any additional providers to enter the room; the huddle involves the intensivist, surgeon, nurse, and respiratory therapist. The equipment included and discussed in the huddle are the portable ultrasound, varying sizes of vascular cannulae, and vessel repair surgical kit. There are 2 sets of nursing staff: one inside the room assisting the cannulation, with a second directly outside of the room available to retrieve additional equipment or medications if needed. This reduces the risk of cross-contamination and the need to excessively don and doff personal protective equipment. For new staff, or staff not familiar with cannulation protective procedures, a donning and doffing video is presented prior to assuming patient care to represent these protocolsTo decrease the risk of transmission throughout the hospital and community, visitors are prohibited from entering the patient's room. Reducing the number of occasions a provider must enter and exit the patient's room also is crucial, and as such, laboratory work, imaging tests, and additional procedures are timed together. When entering a patient's room, all are required to scan the biothreats tracker, which helps with contact tracing if a provider later tests positive for COVID-19.

Along with protection of providers, the protection of patients without COVID-19 who may require ECMO during this pandemic is of paramount importance. While limited, there are data to suggest that COVID-19 does not spread through ECMO circuit membranes; so it is reasonable to use support for patients without COVID-19 even if the circuit had been used on a patient positive with COVID-19 in the past.³⁰ For added safety and protection for Masschusetts General Hospital patients without COVID-19 on ECMO, they are placed in a section of the intensive care unit different from the patients with COVID-19. The patients with COVID-19 on ECMO preferably are housed in negative-pressure rooms that contain an anteroom for donning and doffing. Additionally, the patients without COVID-19 on ECMO.

Although not common, when a circuit or oxygenator requires exchanging, this is done by an expert team of respiratory therapists and perfusionists who are well-versed in this procedure (Appendix 2. Supplemental material). For patients with COVID-19, personal protective equipment required by this team is similar to that required when initiating support.

During the decannulation procedure, staff in the room are expected to wear full personal protective equipment as was done during cannulation. Decannulation usually is performed at the bedside for venovenous ECMO, but for venoarterial ECMO, decannulation often is performed in the operating room due to the need for vessel repair. If the decannulation is to occur in the operating room, there is a singular designated operating room used that contains an anteroom for donning and doffing.

Future directions

In search of expedited and efficient care for patients with COVID-19, several extracorporeal medical devices were given expedited emergency use authorization.³¹ One device of particular interest to intensivists is a venovenous extracorporeal carbon dioxide removal device. In April 2020, the Hemolung Respiratory Assist System (ALung, Pittsburgh, PA) was issued emergency use authorization for the treatment of patients with COVID-19 and respiratory failure.³¹ This transvenous

extracorporeal system is used with or without mechanical ventilation to reduce a patient's partial pressure of carbon dioxide and pH when they are unable to correct these metabolic disturbances due to COVID-19. Advances in technology, such as venovenous extracorporeal carbon dioxide removal, will be key in battling this pandemic as well as future pandemics.

Conclusion

An ECMO program is an important component in the management of patients with COVID-19. It is imperative to implement a system that is well-supported and trained, to both optimize patient outcomes and to keep providers safe. There are many unknowns related to COVID-19, and one of the most challenging aspects for clinicians is the lack of predictive knowledge as to why some patients fail medical therapy and require advanced support such as ECMO. These factors can create challenges during a time of resource scarcity and interruptions in the supply chain.

In this evolving environment, health practitioners need to focus on evidence-based best practices for supportive care of patients in refractory respiratory or cardiac failure. As experience is gained, a greater understanding will develop in this cohort of patients regarding need and timing of ECMO. As this pandemic continues, and new pandemics arise, it will be important to compile and analyze multicentered data pertaining to patient-specific outcomes to help guide clinicians caring for patients with COVID-19 undergoing ECMO support.

Declaration of Competing Interest

The authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2022. 05.010.

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