Clinical Research Response Apr 14, 2020

Extracorporeal Membrane Oxygenation (ECMO) for the Management of COVID-19 Patients

Hayes Viewpoint:

On the basis of past experience in treating acute respiratory distress syndrome, extracorporeal membrane oxygenation (ECMO) has been explored for use in severe COVID-19–related respiratory failure. However there is very limited published evidence to inform decisions regarding the use of ECMO in this patient population. Unprecedented acuity levels in many hospitals may hamper widespread adoption of ECMO as a life-saving intervention owing to the expense; demand on personnel; inexperience of staff; and the potential for severe complications, including hemorrhage and infection.

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At A Glance

Technology
Extracorporeal membrane oxygenation (ECMO)

Manufacturer
Various manufacturers are involved in the design and manufacturing of ECMO circuits.

Focus of Report
This report is focused on the evidence regarding the clinical outcomes in severe COVID-19 patients who require extracorporeal life support (ECLS) using ECMO compared with those maintained with standard mechanical ventilation.

Literature Summary
There was very limited clinical evidence regarding the use of ECMO for this patient population. A single small (n=8), retrospective, observational study was selected for inclusion in this report. Expert opinion and review articles were excluded.

Regulatory Status
ECMO is a procedure and therefore not subject to Food and Drug Administration (FDA) regulation. However, any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.

Viewpoint
ECMO has been used for acute respiratory failure in adults, children, and neonates. On the basis of this experience, ECMO has been explored in the treatment of respiratory failure associated with severe COVID-19 infection. However, there is very limited published evidence to inform decisions regarding the use of ECMO in this patient population. Unprecedented acuity levels in many hospitals may hamper widespread adoption of ECMO as a life-saving intervention owing to the expense; demand on personnel; inexperience of staff; and the potential for severe complications, including hemorrhage and infection. In the absence of conclusive evidence regarding clinical benefit and safety, the use of ECMO for severe respiratory failure in COVID-19 patients may well exceed the capacity of many healthcare facilities.

Health Technology

Health Problem

Coronaviruses are a large group of viruses known to infect birds and mammals, including humans, causing respiratory and systemic symptoms.

COVID-19, also known as SARS-CoV-2, is caused by a novel coronavirus, first detected in December 2019. COVID-19 infections spread rapidly, resulting in the current global pandemic.

Most COVID-19 patients suffer minor symptoms, including cough, fever, shortness of breath, and fatigue. Patients generally receive home care and recover over time without incident. Some patients can develop severe respiratory symptoms, including pneumonia, respiratory distress, and acute respiratory distress syndrome (ARDS) requiring hospitalization and, in some cases, intensive care therapy, respiratory support, and mechanical ventilation (ELSO, 2020).

Technology Description

Mortality in COVID-19 patients who require mechanical ventilation is high. When mechanical ventilation and optimal medical management fail to improve hypoxemic respiratory failure, extracorporeal membrane oxygenation (ECMO) may be employed as a lifesaving intervention to support cardiopulmonary function. ECMO, capable of providing total cardiopulmonary support, is provided with a specially designed circuit that removes blood from the body and circulates it through an artificial membrane lung to add oxygen and remove carbon dioxide. The ECMO system consists of a blood pump, a membrane lung (the oxygenator), conduit tubing, and, if needed, a heat exchanger, monitors, and alarms. The membrane lung is intended to deliver oxygen and remove carbon dioxide equal to normal metabolism. (ELSO, 2017)

ECMO is very resource intensive, requiring specially trained staff and may only be available in high-volume facilities. This costly life-saving strategy also has a potential for significant complications, including hemorrhage and infection (MacLaren et al., 2020).

Additional information about ECMO may be found in the Position Statements and Guidelines and Online Resources sections.

Intended Use

ECMO is intended to provide life-saving cardiopulmonary support in the presence of respiratory failure.

Research Summary

Research Question

Is there published evidence comparing clinical outcomes for extracorporeal membrane oxygenation (ECMO) with standard respiratory life support (e.g., mechanical ventilation) in the management of acute respiratory distress syndrome (ARDS) in patients with COVID-19?

Viewpoint

ECMO has been used for acute respiratory failure in adults, children, and neonates. On the basis of this experience, ECMO has been explored in the treatment of respiratory failure associated with severe COVID-19. However, there is very limited published evidence to inform decisions regarding the use of ECMO in this patient population. Unprecedented acuity levels in many hospitals may hamper widespread adoption of ECMO as a life-saving intervention owing to the expense; demand on personnel; inexperience of staff; and the potential for severe complications, including hemorrhage and infection. In the absence of conclusive evidence regarding clinical benefit and safety, use of ECMO for severe respiratory failure in COVID-19 patients may well exceed the capacity of many healthcare facilities.

Search Strategy

Abstracts reviewed for this report were obtained from a robust search in the PubMed database, as shown in Table 1.

Table 1. Literature Search Strategy for Extracorporeal Membrane Oxygenation for the Management of COVID-19 Patients

Database	Date of Search	Terms	Search Limits	Rationale	Results
PubMed	April 9. 2020	***(COVID-19 OR COVID 19 OR SARS-CoV-2 OR 2019-nCoV OR SARS CoV 2) AND (ECMO OR extracorporeal membrane oxygenation)***	None	Condition and intervention	17 citations

The following types of publications were excluded: expert opinion, review articles, single-patient case reports, editorials, commentaries, articles without abstracts, and studies evaluating ECMO in patients treated for conditions other than COVID-19. After removal of all editorial articles, reviews, commentaries, and publications and articles that were not on topic for this focused report, 1 record remained.

In addition, gray literature was searched for position statements and guidelines (***see*** Table 3).

Summary of Search Results

COVID-19 has only been identified since December 2019. Therefore, it is not surprising that very limited clinical evidence regarding the use of ECMO for this patient population was identified. No studies directly addressing the research question were identified. A single small (n=8), retrospective, observational study (Li et al, 2020) evaluated outcomes of patients treated with ECMO only and did not have a standard respiratory life support (e.g., mechanical ventilation) comparator group. Data from this abstract is presented in the following table.

Multiple professional organizations have published guidance documents for COVID-19 patient management. The World Health Organization, the American Thoracic Society, Extracorporeal Life Support Organization, and Surviving Sepsis Campaign guidance from the Society of Critical Care Medicine and European Society of Intensive Care all suggest considering ECMO for select patients. All concur that this expensive, resource-intensive intervention should only be offered by facilities with expertise in the area of ECMO. While these organizations suggest considering ECMO, it should be noted that none of these are considered evidence-based guidelines.

For more details, please see the Position Statements and Guidelines and Abstracts sections.

Table 2. Study Summary Table

Key: ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; pt(s); patient(s); VA, veno-arterial; VV, veno-venous

Abstract Number Author (Study Year) Country	Study Design	Patient Population	Reported Outcomes	Conclusions
1. Li et al. (2020) China	Retrospective observational noncomparative study Data reported as of March 25, 2020	n=8 Severe COVID-19 patients n=7 received VV ECMO n=1 received VA ECMO Primary outcome: 28-day mortality	Death: n=4 Weaned from ECMO (after 22, 40, and 47 days of support) but remains on MV: n=3 On VV ECMO w/ MV: n=1 Duration of MV prior to ECMO: 4-21 days	Authors suggest that ECMO could be an integral part of the critical care of COVID-19 pts in centers w/ advanced ECMO expertise.

Ongoing Studies

An advanced search of the database at www.ClinicalTrials.gov on April 9, 2020, using the terms ***COVID*** (condition) and ***ECMO*** (intervention) yielded 2 active relevant studies.

Key: CoV, coronavirus; CVVH, continuous veno-venous hemofiltration; ECMO, extracorporeal membrane oxygenation; NCT, National Clinical Trial; SARS, severe acute respiratory syndrome; vv, veno-venous

NCT Number	Title	Status	Condition	Intervention	Study Type	Study Design
NCT04324528	Cytokine Adsorption in Severe COVID-19 Pneumonia Requiring Extracorporeal Membrane Oxygenation	Recruiting	Coronavirus COVID-19 SARS-CoV Infection Respiratory Failure Cytokine Storm	Device: vv-ECMO + cytokine adsorption (Cytosorb adsorber) Device: vv-ECMO only (no cytokine adsorption)	Interventional	Allocation: Randomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment
NCT04340414	Safety and Effectiveness of Low-flow ECMO Driving by CVVH Machine in Severe NCP	Recruiting	COVID-19 ECMO	Device: Low flow ECMO driving by CVVH machine	Interventional	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment

Limitations of the Report

The Hayes Viewpoint in the Clinical Research Response is based on a review of abstracts. No full-text articles were reviewed and a comprehensive

Health Technology Assessment was not conducted.

Regulation And Guidance

Regulation

Food and Drug Administration (FDA)

Extracorporeal membrane oxygenation (ECMO) is a procedure and therefore not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.

The FDA issued guidance to provide a policy to help expand the availability of devices used in ECMO therapy to address this public health emergency.

- Enforcement Policy for Extracorporeal Membrane Oxygenation and Cardiopulmonary Bypass Devices During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (FDA, April, 2020)

Position Statements and Guidelines

Table 3. Clinical Guidelines/Practice Statements

Name of Organization	Date Searched	Guidance Identified
Ontario Health Technology Assessment Series	April 9, 2020	No relevant guidance located.
Scottish Intercollegiate Guidelines Network (SIGN)	April 9, 2020	No relevant guidance located.
U.S. Preventive Services Task Force (USPSTF)	April 9, 2020	Not applicable (N/A)
Veteran Affairs/Department of Defense (VA/DoD)	April 9, 2020	No relevant guidance located.
Centers for Disease Control and Prevention (CDC)		
MMWR Recommendations and Reports	April 9, 2020	N/A
CDC Healthcare Infection Control Guidelines	April 9, 2020	No relevant guidance located.
National Institute for Health and Care Excellence (NICE)		
NICE Guidance	April 9, 2020	COVID-19 rapid guideline: Critical care in adults (NG159) (This guideline does not discuss extra corporeal membrane oxygenation.)
NICE Pathways	April 9, 2020	N/A

Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected (March, 2020), World Health Organization

In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients with refractory hypoxemia despite lung protection ventilation. ECMO should only be offered in expert centers with sufficient case volume to maintain expertise and can apply the IPC [infection prevention and control] measures required for adult and pediatric COVID-19 patients. (Conditional recommendation)

COVID-19: Interim guidance on management pending empirical evidence from an American Thoracic Society-led International Task Force (Wilson et al., 2020), American Thoracic Society

The task force made [consensus] suggestions based upon scarce direct evidence, indirect evidence, and clinical experience.

For patients with refractory hypoxemia due to progressive COVID-19 pneumonia (i.e., ARDS), we suggest that extracorporeal membrane oxygenation (ECMO) be considered if prone ventilation fails.

Clinical practice guidelines declined to make a recommendation for or against ECMO in ARDS and ECMO has not been studied in COVID-19 patients.

The task force acknowledged that ECMO may not be feasible during much of a pandemic because it is resource intensive, challenging from an infection control perspective, and requires frequent blood transfusions at a time when blood may be in shortage.

ELSO Guidance Document: ECMO for COVID- 19 Patients with Severe Cardiopulmonary Failure (ELSO, 2020)

ECMO is indicated in patients who have a high risk of mortality...There are several ways to measure mortality risk in ARDS. All include PaO2/FiO2 below 100, despite and after optimal care...This decision [to initiate ECMO] is a local (hospital and regional) responsibility. It is a case by case decision that should be reassessed regularly based on overall patient load, staffing, and other resource constraints, as well as local governmental, regulatory or hospital policies.

Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19) (Alhazzani et al., 2020) Society of Critical Care Medicine and the European Society of Intensive Care Medicine

In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, we suggest using venovenous (VV) ECMO if available, or referring the patient to an ECMO center (weak recommendation, low quality evidence).

The abstract of a guideline published in Chinese by the Chinese Society of Extracorporeal Life Support (CSECLS) was also identified. A link to this abstract, The Recommendations on extracorporeal life support for critically ill patients with novel coronavirus pneumonia is provided for informational purposes.

Additional Information

Publication History

Date	Title	Status
April 14, 2020	Extracorporeal Membrane Oxygenation (ECMO) for the Management of COVID-19 Patients	New

Related Hayes Reports

Chloroquine and Hydroxychloroquine for COVID-19

Convalescent Plasma for Treatment of COVID-19

Online Resources

Extracorporeal membrane oxygenation (ECMO): does it have a role in the treatment of severe COVID-19 (Hong et al., 2020), ***International Journal of Infectious Diseases***. (NOTE: this is a journal pre-proof of the full text.)

Preparing for the most critically ill patients with COVID-19: the potential role of extracorporeal membrane oxygenation (MacLaren et al., 2020), ***JAMA***.

Abstracts

1. Asaio j. 2020;Mar 30.

Extracorporeal membrane oxygenation for coronavirus disease 2019 in Shanghai, China

Li X, Guo Z, Li B, Zhang X, Tian R, Wu W, Zhang Z, Lu Y, Chen N, Clifford SP and Huang J

Severe cases of coronavirus disease 2019 (COVID-19) cannot be adequately managed with mechanical ventilation alone. The role and outcome of extracorporeal membrane oxygenation (ECMO) in the management of COVID-19 is currently unclear. Eight COVID-19 patients have received ECMO support in Shanghai with 7 with VV ECMO support and 1 VA ECMO during cardiopulmonary resuscitation. As of March 25, 2020, 4 patients died (50% mortality), three patients (37.5%) were successfully weaned off ECMO after 22, 40 days and 47 days support respectively, but remain on mechanical ventilation. One patient is still on VV ECMO with mechanical ventilation.The PaO2/FiO2 ratio before ECMO initiation were between 54 to 76 and all were well below 100. The duration of mechanical ventilation before ECMO ranged from 4-21 days. Except the one emergent VA ECMO during cardiopulmonary resuscitation, other patients were on ECMO support for between 18 to 47 days. In conclusion, ensuring effective, timely, and safe ECMO support in COVID-19 is key to improving clinical outcomes. ECMO support might be an integral part of the critical care provided for COVID-19 patients in centers with advanced ECMO expertise.

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