VIEWPOINT

Preparing for the Most Critically Ill Patients With COVID-19
The Potential Role of Extracorporeal Membrane Oxygenation

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The novel coronavirus has now infected tens of thousands of people in China and has spread rapidly around the globe.[1] The World Health Organization (WHO) has declared the disease, coronavirus disease 2019 (COVID-19), a Public Health Emergency of International Concern and released interim guidelines on patient management.[2] Early reports that emerged from Wuhan, the epicenter of the outbreak, demonstrated that the clinical manifestations of infection were fever, cough, and dyspnea, with radiological evidence of viral pneumonia.[3,4] Approximately 15% to 30% of these patients developed acute respiratory distress syndrome (ARDS). The WHO interim guidelines made general recommendations for treatment of ARDS in this setting, including that consideration be given to referring patients with refractory hypoxemia to expert centers capable of providing extracorporeal membrane oxygenation (ECMO).[2]

ECMO is a form of modified cardiopulmonary bypass in which venous blood is removed from the body and pumped through an artificial membrane lung in patients who have refractory respiratory or cardiac failure.[5] Oxygen is added, carbon dioxide is removed, and blood is returned to the patient, either via another vein to provide respiratory support or a major artery to provide circulatory support. ECMO is a resource-intensive, highly specialized, and expensive form of life support with the potential for significant complications, in particular hemorrhage and nosocomial infection. Recent evidence suggests that use of ECMO in the most severe cases of ARDS is associated with reduced mortality.[6] There is some evidence that outcomes from ECMO are better in higher-volume centers.[7]

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The role of ECMO in the management of COVID-19 is unclear at this point. It has been used in some patients with COVID-19 in China but detailed information is unavailable.[3] ECMO may have a role in the management of some patients with COVID-19 who have refractory hypoxemic respiratory failure.[6] However, much about the virus is unknown, including the natural history, incidence of late complications, viral persistence, or the prognoses in different subsets of patients. This uncertainty might be compared to the emergence of influenza A(H1N1) in 2009, when it was initially unclear what the role of ECMO should be.[8] However, the degree of uncertainty surrounding COVID-19 is much greater. To address this, prompt mobilization of existing registries and clinical research groups should help facilitate the systematic collection of data. For example, the Extracorporeal Life Support Organization (ELSO) Registry is being adapted to acquire new information about COVID-19 and prospective observational studies are under way.

ECMO does not provide direct support for organs other than the lungs or heart beyond increasing systemic oxygen delivery and mitigating ventilator-induced lung injury. A substantial proportion of critically ill patients with COVID-19 appear to have developed cardiac arrhythmias or shock,[3] but it is unknown how many have or will develop refractory multiorgan failure, for which ECMO may be of more limited use. To postulate about the potential benefit of ECMO in this infection, more data on the mechanism of death and disease are required. The virus may cause death through progressive hypoxic respiratory failure, septic shock, refractory multiorgan failure, or by precipitating exacerbation of comorbid diseases such as ischemic heart disease or cardiac failure, but the relative proportions of these diseases in large cohorts of patients with COVID-19 infection are unknown.

The global spread of COVID-19, although the number of cases outside of China remains small, will likely occur via many dispersed epicenters where local transmission has become established. If these epicenters occur in sophisticated health care systems with preexisting ECMO programs, this will provide vital information about the utility of ECMO and help anticipate global demand. Should the initial experience be encouraging, it is likely that non-ECMO centers will refer early to ECMO centers in anticipation of impending clinical deterioration. This will disproportionately affect hospitals with ECMO programs, even when ECMO is not required.

Furthermore, with the apparent contagiousness of this virus and the relatively high numbers of patients who require intensive care, this may prove very resource-consumptive. Countries will need to pay specific attention to the considerable investment needed to provide ECMO during this outbreak. Judgment will be needed to decide when ECMO may be worthwhile and when it may not, understanding that the risk-to-benefit ratio of performing ECMO in these circumstances is dynamic and dependent on many factors. If the mechanism of death in COVID-19 ultimately includes a substantial number of patients with septic shock or refractory multiorgan failure, then the shift away from ECMO is likely to occur earlier because

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the most severely ill patients in this cohort would be less likely to benefit. The higher the all-cause mortality, the less relevant ECMO becomes.

Regardless, ECMO is clearly a finite resource. In a large outbreak, additional limitations to providing ECMO may include a lack of ECMO consoles or disposable equipment, suitably trained staff, or isolation rooms with the requisite infrastructure. Many materials necessary to make ECMO circuitry are manufactured in China and it is conceivable that the outbreak may disrupt supply chains.

A number of different models of ECMO service provision exist worldwide, ranging from a relative lack of regulation and centralization—with many hospitals having ECMO capability but often with very low case volumes (eg, in the US or Japan)—through to regional or national coordination of ECMO referral centers with dedicated interhospital retrieval teams (eg, New Zealand, Australia, Singapore, Qatar, the United Kingdom, or Sweden). In response to influenza A(H1N1) in 2009, some countries such as Italy adopted the latter model and it is possible that COVID-19 could be addressed similarly. The advantages of such an approach include standardization of indications, management, data collection, and containment.[5,7] The disadvantage is the potential for hospitals that provide ECMO to be overwhelmed with critically ill patients unless interhospital transfers are centrally coordinated.

With the WHO recommendation for ECMO in place and the tropism of the COVID-19 virus for severe respiratory illness, the number of cases in which ECMO is used may increase over the course of this outbreak. However, there may come a tipping point. Should the case volume in any given region increase beyond the ability to provide routine care, any earlier increase in ECMO use may give way, with utilization later decreasing in proportion to the overwhelming demands on the system as a whole.

Support with ECMO is for the most critically ill patients in regions with the extensive resources required to provide this therapy. ECMO is not a therapy to be rushed to the frontline when all resources are stretched in a pandemic. In less well-resourced countries, many more lives will be saved by ensuring oxygen and pulse oximetry are widely available. Mitigation efforts to slow the outbreak are critical so that health care systems are not overwhelmed and all patients receive the correct management, whether simply confirmation of the diagnosis and appropriate quarantine, oxygen therapy alone, mechanical ventilation or, for those most likely to benefit, ECMO.

ARTICLE INFORMATION

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REFERENCES

1. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. *JAMA*. 2020. Published online January 23, 2020. doi:10.1001/jama.2020.0757

2. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected—interim guidance. Published January 28, 2020. Accessed February 11, 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. Published online February 7, 2020. doi:10.1001/jama.2020.1585

4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. Published online January 30, 2020. doi:10.1016/S0140-6736(20)30211-7

5. Brodie D, Slutsky AS, Combes A. Extracorporeal life support for adults with respiratory failure and related indications: a review. *JAMA*. 2019;322(6):557-568. doi:10.1001/jama.2019.9302

6. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc bayesian analysis of a randomized clinical trial. *JAMA*. 2018;320(21):2251-2259. doi:10.1001/jama.2018.14276

7. Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med*. 2015;191(8):894-901. doi:10.1164/rccm.201409-1634OC

8. White DB, Angus DC. Preparing for the sickest patients with 2009 influenza A(H1N1). *JAMA*. 2009;302(17):1905-1906. doi:10.1001/jama.2009.1539