CLINICAL DECISIONS
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Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Man with Severe Acute Respiratory Distress Syndrome

Michael Y. Mi, M.D.

Mr. Jackson is a 36-year-old man whom you are caring for in the intensive care unit (ICU). Before this hospitalization, he was healthy and took no medications. He has never smoked, and he drinks three or four beers every week. A week ago, a couple of coworkers in his office had respiratory illnesses, and a day later, he started having fever, chills, cough, and generalized weakness. Two nights ago, he presented to the emergency department with confusion and rapidly progressive dyspnea; urgent endotracheal intubation was performed because of acute respiratory failure. Testing for influenza virus A was positive.

In the ICU, you have been treating him for severe acute respiratory distress syndrome (ARDS) caused by influenza pneumonia. After initial lung-protective ventilation, worsening hypoxemia developed. Despite neuromuscular blockade with deep sedation and prone positioning for the past 24 hours, his respiratory status has continued to deteriorate rapidly.

His heart rate is 124 beats per minute, and his blood pressure is 92/58 mm Hg. His height is 178 cm, and he weighs 75 kg. He is currently receiving ventilation with volume-assist control at a tidal volume of 400 ml (5.5 ml per kilogram of predicted body weight), a respiratory rate of 32 breaths per minute, positive end-expiratory pressure (PEEP) of 15 cm of water, and a fraction of inspired oxygen (F_{IO_2}) of 1.0. The measured plateau pressure is approximately 30 cm of water. For the past 4 hours, he has had persistent hypoxemia, with arterial oxygen saturation between 80 and 82%. The most recent arterial blood gas measurement shows a pH of 7.22, partial pressure of oxygen (P_{AO_2}) of 50 mm Hg, and partial pressure of carbon dioxide (P_{ACO_2}) of 62 mm Hg. You know that venovenous extracorporeal membrane oxygenation (ECMO) is an option for patients like Mr. Jackson who have severe ARDS, but its use has been controversial, and you are not sure whether it will be beneficial.

TREATMENT OPTIONS

Which one of the following approaches would you recommend for this patient? Base your choice on the published literature, your own experience, guidelines, and other sources of information, as appropriate.

1. **Recommend initiation of venovenous ECMO.**
2. **Continue current treatment with other therapies.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

Disclosure forms provided by the author are available at NEJM.org.

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OPTION 1

Recommend Initiation of Venovenous ECMO

Michael A. Matthay, M.D.

This 36-year-old man has very severe ARDS caused by influenza pneumonia. His Pao_2 is only 50 mm Hg, with an Fio_2 of 1.0 and PEEP of 15 cm of water, and his arterial oxygen saturation is 80 to 82%. He has moderately severe acidosis, with a pH of 7.22 and a $Paco_2$ of 62 mm Hg. He meets the criteria for the use of rescue therapies because he has severe hypoxemia and acidosis despite treatment with lung-protective low tidal volume ventilation, neuromuscular blockade with deep sedation, and prone positioning. What additional interventions could we offer him?

Inhaled nitric oxide can improve oxygenation, although sustained benefit is difficult to achieve and there is no evidence that it results in a reduction in the risk of death. Another option would be to reduce his tidal volume to 4 to 5 ml per kilogram of predicted body weight, but he already has a $Paco_2$ of 62 mm Hg, probably because of a high dead-space fraction.[1] In addition, lowering the tidal volume will most likely worsen his respiratory acidosis. He could be treated with recruitment maneuvers, but one recent trial raises concerns about this approach,[2] and in the case of Mr. Jackson in particular, it may not be advisable since his plateau airway pressure is already 30 cm of water. Increasing PEEP higher than the current 15 cm of water may also raise the plateau airway pressure above 30 cm of water, which could cause lung overdistention that could aggravate his lung injury.[3] Another approach would be diuresis, but his systemic hypotension (blood pressure of 92/58 mm Hg) would most likely limit this option. Renal-replacement therapy could potentially reduce pulmonary edema and correct acidosis. However, his acidosis is primarily respiratory in origin, and he does not appear to have marked volume overload. In addition, evidence for the possible value of renal-replacement therapy derives mainly from one single-site study.[4] Glucocorticoids could be tried, but they may cause harm in a patient with influenza pneumonia.[5]

Thus, I favor venovenous ECMO. The patient meets standard criteria for ECMO, including those in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, the results of which were published recently in the *Journal*.[6] This relatively young patient does not meet exclusion criteria for ECMO (cardiac failure, advanced chronic lung disease, cancer, severe neurologic injury, or major coexisting conditions), and he has single-organ failure. Although the randomized EOLIA trial — in which early ECMO was compared with conventional mechanical ventilation with crossover to ECMO for refractory hypoxemia — did not show a significantly lower rate of the primary end point (mortality at 60 days) in the ECMO group than in the conventional-treatment group, there was a nonsignificant indication of potential benefit (a rate of 35% in the ECMO group vs. 46% in the control group, $P=0.09$). Furthermore, the EOLIA trial may have been underpowered, especially since the trial was stopped after enrollment of only 75% of the planned 331 patients. In terms of secondary outcomes, the ECMO-treated patients had significantly more days alive and free of prone positioning and renal-replacement therapy than patients in the conventional-treatment group. In addition, a benefit in favor of ECMO was observed for the prespecified secondary outcome of crossover to ECMO (28% crossover rate) or death. With respect to adverse events, there was a numerically higher incidence of stroke in the conventional-treatment group, and there was no significant difference between the two groups in the incidence of hemorrhagic stroke. On balance, this patient is an excellent candidate for ECMO if it can be delivered in a medical center that is experienced with this therapy.

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OPTION 2

Continue Current Treatment with Other Therapies

Alan H. Morris, M.D.

The decision to use ECMO for Mr. Jackson raises difficult issues that include both physician overconfidence in ECMO and the credibility of study results. Our first obligation is to ensure safety

and protect patients from harm. We should then maximize the probability of a favorable outcome for the patient. It is clear that iatrogenic and avoidable harm is a serious medical problem. It is also clear that we lack evidence for many clinical decisions. Some researchers argue that much, if not most, of the published evidence that we bring to bear during clinical decision making is incorrect.[7]

Subjective judgment and willingness to offer unproven treatments contribute to much unwarranted variation in care.[8] Dramatic interventions are difficult to resist. After all, if the patient seems to be dying, should we not do something? The challenge is to demonstrate with confidence that the "something" does more good than harm.[9,10] This is a daunting challenge. The 2017 guideline from the American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine on mechanical ventilation for adults with ARDS states, "Additional evidence is necessary to make a definitive recommendation for or against the use of ECMO in patients with severe ARDS."[11] ECMO is invasive, costly, and dangerous, even though the technology has advanced rapidly. Until ECMO clearly produces a credible benefit that outweighs its risks in patients with ARDS, its use should be restricted to well-designed, rigorous scientific studies that will produce credible outcome results.

The EOLIA trial is the latest addition to the literature. Proponents of ECMO will conclude from the EOLIA trial that ECMO was probably beneficial (results regarding a secondary end point were better with ECMO); however, although the results with respect to the primary end point of 60-day mortality will suggest to some readers a benefit with respect to patient outcome, the difference between the groups was neither statistically significant ($P=0.09$) nor highly credible. Among the patients who were assigned to the control strategy (mechanical ventilation only), 28% were considered to have treatment failure and crossed over to receive ECMO support as rescue therapy. The introduction of ECMO in these patients was decided by the treating physician. Although some guidance was provided by the EOLIA study protocol, we cannot know how the treating physicians made these judgments; their reasoning was not captured. Since clinicians identify patients unequivocally expected to die with only approximately 85% accuracy,[12] one expects that some of these "rescued" patients in the EOLIA trial might have lived with continued mechanical-ventilation-only treatment. A change in survival of a few patients would influence the results of the EOLIA trial. This experimental design flaw reduces the credibility of the survival result in patients treated with mechanical ventilation only. "Crossover" indicates the treating physicians' bias toward ECMO as a beneficial therapy at the time of crossover, although the evidence for ECMO benefit in ARDS is tenuous. This design flaw thus reduces the credibility of favorable interpretations of EOLIA study results.

I believe that once physicians have carried out all treatments known to be beneficial (the most important of which is the lung-protective mechanical-ventilation strategy that targets tidal volumes of 6 ml per kilogram of predicted body weight), they have discharged their ethical and professional obligations to patients. The use of treatments, like ECMO, that have considerable dangers and that might harm more than help should be restricted to scientifically rigorous clinical investigations that are designed to produce maximally credible results. They should not be used widely in clinical care, and I would not introduce ECMO support for Mr. Jackson.

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1. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 2002;346:1281-6.
2. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017;318:1335-45.
3. Sahetya SK, Brower RG. Lung recruitment and titrated PEEP in moderate to severe ARDS: is the door closing on the open lung? JAMA 2017;318:1327-9.
4. Han F, Sun R, Ni Y, et al. Early initiation of continuous renal replacement therapy improves clinical outcomes in patients with acute respiratory distress syndrome. Am J Med Sci 2015;349:199-205.
5. Brun-Buisson C, Richard JC, Mercat A, Thiébaut AC, Brochard L. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med 2011;183:1200-6.
6. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965-75.
7. Ioannidis JPA. Why most published research findings are false. PLoS Med 2005;2(8):e124.

8. Wennberg JE. Time to tackle unwarranted variations in practice. BMJ 2011;342:d1513.
9. Miller RR III, Markewitz BA, Rolfs RT, et al. Clinical findings and demographic factors associated with ICU admission in Utah due to novel 2009 influenza A(H1N1) infection. Chest 2010;137:752-8.
10. Fan E, Pham T. Extracorporeal membrane oxygenation for severe acute respiratory failure: yes we can! (But should we?) Am J Respir Crit Care Med 2014;189:1293-5.
11. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253-63.
12. Meadow W, Pohlman A, Frain L, et al. Power and limitations of daily prognostications of death in the medical intensive care unit. Crit Care Med 2011;39:474-9.

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