REVIEW ARTICLE

Use of Extracorporeal Membrane Oxygenation for the Treatment of Influenza-Induced Acute Respiratory Distress Syndrome in Immunocompromised Adults

M. Veronica Dioverti, MD, Kelly A. Cawcutt, MD, Gregory J. Schears, MD and Larry M. Baddour, MD

ABSTRACT

Influenza infection in the adult immunocompromised hosts can have severe presentations and rapid progression to lower respiratory tract infection requiring mechanical ventilation, and it even can progress to acute respiratory distress syndrome. Little is known about the role of extracorporeal membrane oxygenation for management in this setting. We present a review of the current literature on the subject.

Key Indexing Terms: Acute respiratory distress syndrome; Extracorporeal membrane oxygenation; Influenza; Immunocompromised. **[Am J Med Sci 2016;352(1):81–85.]**

INTRODUCTION

Influenza infection in immunocompromised hosts (ICH) can rapidly progress to lower respiratory tract infections, which can be complicated with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, and in severe cases, extracorporeal membrane oxygenation (ECMO). Earlier reports showing no survival benefit for adults managed with ECMO hampered the use of this modality. During the influenza A (H1N1) epidemic, ECMO was increasingly used for the management of ARDS resulting in more studies looking at outcomes, which showed improved survival rates of up to 67%; with higher survival rates noted in those with viral pneumonia.[1] The improvements in technology and positive results from the Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial resulted in renewed interest in this treatment modality, however, most studies focus on immunocompetent hosts.

Little is known about the potential role of ECMO in ICH. Therefore, we performed a literature search on this topic and provide a narrative review for further guidance for clinicians.

BACKGROUND OF ECMO

Before the introduction of ECMO, conventional positive-pressure ventilation resulted in high airway pressures and oxygen concentrations, leading to exacerbation of lung injury due to barotrauma, volutrauma, biotrauma and toxicity from high oxygen concentrations. Improvement in such trauma and toxicity occurred after the initiation of lung-protective ventilation, however, all these can be minimized by using ECMO.[2]

The use of ECMO as a management strategy for ARDS has gone through different phases since early trials failed to show survival benefits, whereas more recent ones showed more encouraging results. A randomized prospective multicenter study performed in 1979 by Zapol et al looked at 90 adult patients with acute hypoxemic respiratory failure of diverse etiologies, mostly secondary to bacterial and viral pneumonia; 48 patients received conventional mechanical ventilation and the rest were initiated on ECMO. Only 4 patients survived in each group, with no survival benefit for those on ECMO.[3] Another study by Morris et al[4] in 1994 randomized 40 patients to pressure-controlled mechanical ventilation and ECMO, and found again no survival benefit for those managed with ECMO.

Advances in medicine led to improvements in case selection, ventilation strategies, extracorporeal circuits and disease management.[5] The CESAR trial studied patients randomized to ECMO versus conventional management, and found that 63% of those managed with ECMO had survived without severe disability at 6 months of follow-up compared with only 47% of those managed with a conventional strategy.[2] However, results of this study need to be carefully interpreted as those patients managed with ECMO were treated at specialized centers, whereas the control group was managed in nonspecialized hospitals without standardized ventilator management protocol raising the question as to whether ECMO per se or the best standards of care in specialized

hospitals contributed to better outcomes. A clinical trial to address some of these limitations is currently going on (www.clinicaltrials.gov [NCT01470703]).

BACKGROUND OF INFLUENZA-RELATED RESPIRATORY FAILURE AND USE OF ECMO

There was a large increase in ECMO use during the 2009 influenza pandemic, resulting in multiple studies to evaluate outcomes. Data from the 2012 Extracorporeal Life Support Organization (ELSO) registry report showed overall survival rates of up to 67% in 2009.[6] The increase in ECMO use followed more recent data that showed an overall improvement in survival with ECMO use at large specialized ECMO centers, particularly for those patients diagnosed with viral pneumonias.[1,2,7-9]

Many studies were done at ECMO centers throughout the world. The Australia and New Zealand ECMO Influenza Investigators (ANZ ECMO) group looked at 68 patients with influenza-ARDS managed with ECMO, and showed a mortality rate of 21%. Comorbidities in this group of patients included obesity (body mass index [BMI] $>$ 30 kg/m^2), asthma and diabetes mellitus; in addition, 10 patients were either pregnant or were in postpartum period.[8] Most patients were on veno-venous ECMO (VV-ECMO) via peripheral cannulation, with a median duration of ECMO support of 10 days and a median of 2 days of mechanical ventilation before cannulation. The experience of the German ARDS Network reported need for ECMO in 53% of patients despite conventional management. The mortality rate in the ECMO group without pre-existing conditions was 41.9% in contrast to a mortality of 72.2% in those with concomitant malignancy or immunologic diseases.[10] The higher overall mortality in the German experience may be explained by the larger number of patients with severe pre-existing comorbidities compared to the ANZ ECMO experience.

A study in France looked at 123 patients with pandemic H1N1 managed with ECMO, of which 76% had one or more risk factors for influenza-related complications, mostly obesity (40%, BMI $>$ 30 kg/m^2) followed by immunosuppression (19%) and pregnancy or postpartum (15%).[11] ECMO was instituted less than 8 days after initiation of mechanical ventilation in 84%; VV-ECMO predominated. Mortality rate in the intensive care unit was 36%. Interestingly, after matching for similar medical history and initial severity only 52 unique pairs were found, and there was no mortality rate difference among patients on ECMO and those with non-ECMO. There was a higher proportion of younger age, obesity and pregnant women with more severe disease that were not matched, and this group had lower mortality rates (22%; $P < 0.01$).[11] This finding may support the need for further evaluation of these subgroups of patients that may benefit from ECMO.

Certainly, studies have been conducted to try to identify a risk-assessment tool to aid in early identification of mortality risk;[12] older age, immunocompromised status, higher simplified acute physiology scores II, higher pre-ECMO plateau pressures, lower pre-ECMO positive end-expiratory pressure, absence of pre-ECMO prone positioning and longer duration of mechanical ventilation before ECMO were all associated with worse outcomes, whereas higher BMI was found to be protective. It is noteworthy that a fourth of the patients in this study (a total of 36) had H1N1-ARDS, and had the lowest mortality rate reported (17%).[12] Another study identified pre-ECMO variables independently associated with hospital mortality to develop the "RESP score": older age, cardiac arrest before ECMO, central nervous system dysfunction, renal dysfunction, immunocompromised status (defined as hematological malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus (HIV) and cirrhosis), associated nonpulmonary infection, the use of inhaled nitric oxide and bicarbonate infusion, longer mechanical ventilation, higher $PaCO_2$ and higher peak inspiratory pressure.[7]

USE OF ECMO FOR INFLUENZA AMONG ICH—HOPE FOR THE FUTURE?

Although ECMO has been used in the management of influenza-induced ARDS in immunocompetent hosts, there is very limited experience in adult ICH. Per the ELSO guidelines, the presence of leukopenia or other immunocompromising conditions may be a contraindication for the use of ECMO, and a cutoff neutrophil count of 500 cells/mm^3 has been used in some centers; however, this has not been clearly defined and is not an absolute contraindication.[6,13] Studies conducted to develop a pre-ECMO risk score to better define a population that would benefit from ECMO have consistently identified immunocompromised states as a marker of worse outcomes.[7,12,14] However, there have been successful reports in using ECMO for *Pneumocystis jiroveci* pneumonia and Legionella pneumonia in HIV and AIDS,[15,16] as well as one case report of a 36-year-old male patient with systemic lupus erythematosus, on maintenance therapy with prednisone and cyclosporine, who met criteria for influenza A–induced ARDS, and who survived to hospital discharge after 3 days of VV-ECMO.[17] Another report presented a 31-year-old male patient with influenza-ARDS on ECMO, with a new diagnosis of hairy cell leukemia, who initiated and completed chemotherapy while on ECMO; he was weaned off ECMO after 20 days and survived to hospital discharge.[18] Other studies have included ICH as detailed below and summarized in Table.

The benefits of ECMO in adult ICH as part of management of influenza-induced ARDS remain to be established. Several studies evaluating pandemic influenza have included immunocompromised patients; however, most have not been powered to analyze this subset of patients. During the 2009 pandemic H1N1, 30-53% of patients managed initially with mechanical ventilation required ECMO, with mortality rates ranging