Successful Extracorporeal Membrane Oxygenation for Respiratory Failure in an Infant With DiGeorge Anomaly, Following Thymus Transplantation

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We report the first successful use of venovenous extracorporeal membrane oxygenation (ECMO) for refractory respiratory failure in an infant with DiGeorge anomaly, following thymus transplantation. A 23-month-old female with complete immune-incompetent DiGeorge anomaly 65 days after allogenic thymus transplantation was treated in our pediatric intensive care unit for acute respiratory failure secondary to bacterial sepsis. She subsequently developed acute hypercarbic respiratory failure unresponsive to conventional medical therapy. She was successfully managed with venovenous ECMO for 4 days, with complete resolution of her respiratory symptoms. This case demonstrates the complex decision making process regarding initiation of ECMO in patients with severe immunodeficiency. *Key words: respiratory failure; extracorporeal membrane oxygenation; ECMO; immunodeficiency; DiGeorge anomaly; hypercarbia; pediatric; mechanical ventilation; sepsis.*
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Introduction

With the increasing success of extracorporeal membrane oxygenation (ECMO) in a wide range of settings, many patients previously deemed unsuitable ECMO candidates are now considered for this support. Despite the expanding utilization of ECMO, severe immunodeficiency remains an important relative contraindication. Survival in selected immunodeficient hematopoietic stem-cell transplantation patients requiring ECMO is exceedingly low, but in other patients with immunodeficiency the outcomes are more variable.[1-3]

A unique population of immunodeficient patients at our institution are those who have undergone thymus transplantation for complete, immune-incompetent DiGeorge anomaly. This abnormality represents a uniformly fatal subtype seen in approximately 1% of DiGeorge cases.[4] These patients often have a prolonged and complex perioperative course. To date, our institutional experience with thymus transplantation includes 60 patients, with a 73% survival rate 2 years after transplantation.[5] Most of the deaths are secondary to overwhelming infection and sepsis in the immediate peritransplant period and are probably related to underlying immunodeficiency, the occasional need for pre-transplant and post-transplant immunosuppression, and the 4–6-month period necessary to generate competent T lymphocytes.[6] Prevention and early goal-directed treatment of infections are of paramount importance.

We report the case of a young child 65 days after thymus transplantation for complete immune-incompetent DiGeorge anomaly, who initially presented with septic shock, and was successfully treated with venovenous ECMO for refractory hypercarbic respiratory failure.

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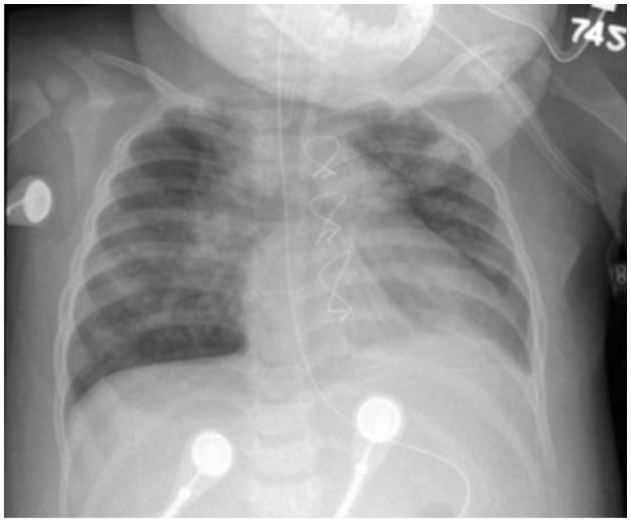

Fig. 1. Chest radiograph on pediatric intensive care unit day 5 shows heterogeneous bilateral opacities.

Case Report

The patient was a 23-month-old, 9.4 kg female with complete, immune-incompetent DiGeorge anomaly and a remote history of repaired congenital heart disease, who underwent thymus transplantation 65 days prior to pediatric intensive care unit (PICU) admission for septic shock. She presented to the pediatric immunology clinic with 2 days of nonspecific symptoms and was immediately admitted to the PICU when found to be in shock.

On PICU arrival her vital signs were heart rate 140 beats/min, blood pressure 73/46 mm Hg, respiratory rate 44 breaths/min, and arterial oxygen saturation (S_{aO_2}) 100%, with a mixed metabolic and respiratory acidosis. Broad-spectrum antibiotics were initiated, and blood cultures from her Broviac catheter grew *Enterobacter aerogenes*. The Broviac catheter was removed within 24 hours of PICU admission.

Her hemodynamic status rapidly improved with volume resuscitation and initiation of an epinephrine infusion, but her respiratory status progressively deteriorated. Within 12 hours of admission she was endotracheally intubated and quickly transitioned to high-frequency oscillatory ventilation (HFOV) due to progressive deterioration in gas exchange.

Her respiratory status and gas exchange initially stabilized, but then worsened on PICU day 5, with worsening bilateral infiltrates on chest radiograph (Fig. 1). On the seventh day of mechanical ventilation she developed severe respiratory acidosis of unclear etiology (Table 1). Her HFOV settings at that time were mean airway pressure 24 mm Hg, amplitude 64 cm H_2O, F_{IO_2} 0.45, and respiratory frequency 8 Hz. Chest radiograph did not reveal a process that would explain her acute decompensation (Fig. 2).

Noninvasive monitoring and clinical examination at that time were most consistent with severe bronchospasm. To our knowledge, episodic bronchospasm is not associated with thymus transplantation, and the etiology of this acute change in our patient's pathophysiology was not completely clear. We theorized that the inflammatory response related to her severe septic shock led to bronchospasm and severe obstructive pathology. Evaluation for an infectious etiology, including a respiratory viral screen and culture, was negative.

We attempted multiple interventions, including high-frequency jet ventilation and a return to conventional mechanical ventilation, without improvement in her respiratory acidosis. In addition, we initiated adjunctive therapies, including aminophylline infusion, heliox, intravenous methylprednisolone, inhaled bronchodilators, and inhaled nitric oxide, without improvement. Given her progressive tachycardia, and concern about inducing an arrhythmia, we opted not to use intravenous β agonists, although this decision could be debated. In addition, we were not able to attempt isoflurane (an inhaled anesthetic that some centers use for refractory bronchospasm) due to the inability to scavenge aerosolized anesthetic in our PICU.

Given this child's refractory respiratory failure, we decided to offer ECMO as a rescue therapy, despite concerns about her underlying immunodeficient state. On PICU day 7, she was cannulated for venovenous ECMO via the right internal jugular vein, with an 18 French double-lumen cannula (OriGen Dual Lumen Catheter, OriGen Biomedical, Austin, Texas). Immediately prior to cannulation she was ventilated with pressure-limited, synchronized intermittent mandatory ventilation, at 40 breaths per min, peak inspiratory pressure 45 cm H_2O, PEEP 10 cm H_2O, and F_{IO_2} 0.80. These ventilation settings were necessary as a brief, temporizing measure while awaiting ECMO cannulation, due to her worsening gas exchange, air trapping, and inability to adequately ventilate with HFOV or high-frequency jet ventilation. Despite these ventilation settings, the delivered tidal volume was only 3 mL/kg, and, at the time of cannulation, arterial blood gas analysis revealed pH 6.96, P_{CO_2} 210 mm Hg, P_{aO_2} 103 mm Hg, HCO_3 44 mmol/L, and oxygenation index 29.

Upon cannulation she was placed on an ECMO circuit, which included a Stockert 3 rollerhead pump (Sorin Group, Arvada, Colorado) with a flow of 75–100 mL/kg/min, and a Jostra Quadrox D oxygenator (Maquet Cardiopulmonary, Hirrlingen, Germany). We used our standard ECMO setup, without additional shunt tubing, to increase flow to the oxygenator. Despite the relatively low ECMO flow rate we used in this 9.4-kg patient, gas exchange markedly improved, and mechanical ventilation was rapidly weaned to allow lung rest and recovery.

Table 1. Ventilation and Blood Gas Variables on Hospital Days 2, 4, and 6

Hospital Day	Mean Airway Pressure (cm H_2O)	Amplitude (cm H_2O)	F_{IO_2}	pH	P_{aCO_2} (mm Hg)	P_{aO_2} (mm Hg)	HCO_3 (mmol/L)	Base Excess (mmol/L)	Oxygenation Index
2	22	50	1.00	7.12	80	80	25	–5	27
2.5	30	63	0.65	7.29	50	52	24	–3	37
4	27	56	0.40	7.41	47	61	29	+5	17
6	26	65	0.55	7.32	89	52	44	+16	27

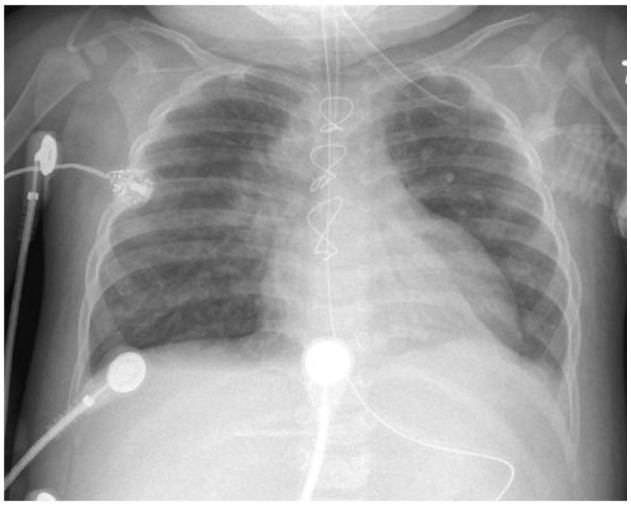

Fig. 2. Chest radiograph on pediatric intensive care unit day 7, prior to cannulation for venovenous extracorporeal membrane oxygenation, shows stable lower-lobe and perihilar atelectasis, but no other important changes.

While on ECMO the patient's immunocompromised state was an important ongoing consideration. Unique aspects of her management included reverse isolation, consisting of an isolation room and mandatory gowns, masks, and gloves for all visitors, along with the use of blood products that were leuko-reduced, irradiated, and cytomegalovirus-negative. Tacrolimus was continued, as were broad-spectrum antibiotics and antifungals. She was not receiving corticosteroids as part of her immunosuppressive therapy.

During the 4 days on ECMO, her cardiac, renal, and liver functions all remained stable, and she had no important bleeding complications. However, she did have one isolated seizure of unclear etiology. She was started on fosphenytion at that time and a brain computed tomogram was normal. She was eventually transitioned to levetiracetam and had no further seizures. Prior to hospital discharge, she returned to her neurologic baseline. She had no further complications during her ECMO course.

For the 24 hours preceding ECMO decannulation, the ECMO sweep gas was turned off, with continued adequate gas exchange on pressure-limited, synchronized intermittent mandatory ventilation at 20 breaths/min, peak inspiratory pressure 26 cm H_2O, PEEP 8 cm H_2O, and F_{IO_2} 0.40. She also received heliox, intravenous methylprednisolone, inhaled budesonide, and inhaled levalbuterol. She was successfully decannulated on hospital day 13, after 131 hours on venovenous ECMO, and was successfully extubated to nasal cannula on hospital day 20.

She was transferred to the pediatric ward on hospital day 28, with continued inhaled steroids and bronchodilators and a slow taper of systemic steroids. She was ultimately discharged after a hospital stay of 78 days, in good condition and without the need for respiratory support, and is currently stable at home on her baseline immunosuppressive therapy.

Discussion

ECMO in Immunodeficiency

Immunodeficiency is a strong relative contraindication to ECMO. Few data are available on ECMO in immunodeficiency, and data from a review of the Extracorporeal Life Support Organization registry from its inception through 2004 identified 183 patients with various forms of immunodeficiency treated with ECMO. Immunodeficiency was an independent risk factor for mortality: overall survival to hospital discharge was 20% in the immunodeficient patients.[3] Similarly, mortality following bone-marrow transplantation (a particularly immunodeficient population) was extremely high: only 1 of 19 patients treated with ECMO survived to hospital discharge in a review of the Extracorporeal Life Support Organization database from 1991 to 2004.[7]

However, another well recognized cause of immunodeficiency is malignancy, and ECMO use is becoming more prevalent in that patient population. Gow et al[8] found, in a series of 86 patients with various malignancies and treated with ECMO, that survival to hospital discharge was better (35%) than in other immunodeficient patients. As part of that investigation, 95% of physicians interviewed indicated that they would consider ECMO in patients with malignancies.[8]

Infants with DiGeorge anomaly following thymus transplantation remain substantially immunocompromised for at least 4–6 months, given the time necessary for immune

reconstitution. These infants have a primary T cell immunodeficiency and require ongoing supplementation with intravenous immunoglobulin, especially during periods of critical illness. Our patient was substantially immunocompromised and at an extremely high risk for infectious complications, being only 65 days removed from thymus transplantation.

There is substantial heterogeneity among this patient population, which clearly influences discussions on ECMO in these patients. In our patient the overall degree of immunodeficiency was an important concern, but consideration of other factors known to impact both duration and survival with ECMO support was also important. Factors that should be considered in these exceptional circumstances include pre-ECMO underlying organ dysfunction, comorbid conditions, duration and complexity of pre-ECMO therapies, and likelihood of reversibility of the acute disease process, along with any other issues that may impact the patient's ECMO course. Overall, in the absence of data to predict its success, initiation of ECMO in immunocompromised patients remains a difficult clinical and administrative dilemma, involving medical, financial, and ethical considerations.[9]

Ethics of ECMO Expansion: The New Frontier?

While ECMO can be life-saving in many circumstances, the risks, morbidity, and mortality of ECMO are considerable.[10] Furthermore, due to the technical and personnel requirements, ECMO remains a limited resource, even in the largest medical centers. One cost analysis of ECMO in neonatal respiratory failure found that, despite the initial expense, cost-effectiveness is reached at a survival of only 7 years.[11] There are no cost-effectiveness data for ECMO in patients such as the one reported here, but appropriate resource utilization is an important consideration as the potential pool of ECMO candidates with unclear outcomes expands, especially given the excellent survival rates for ECMO in certain situations, such as meconium aspiration syndrome, neonatal respiratory failure, and viral-induced respiratory failure.[10-15]

As discussions regarding the utilization of ECMO arise, it is crucial to remember that ECMO represents a bridge to recovery rather than a treatment for an underlying process, and, in unique or unusual clinical circumstances, providers will generally need to tailor the approach based on the patient's specific underlying condition. In our patient, despite her high mortality risk with ECMO, due to her immunodeficient state, several factors improved her prognosis including: presumably reversible single-organ (pulmonary) dysfunction, obstructive rather than parenchymal respiratory pathology, and only 6 days of lung-protective ventilation prior to initiation of ECMO. At the time of her decompensation, each of these factors was considered in the decision to proceed with ECMO.

Had she needed ECMO at the time of her initial presentation, in the setting of overwhelming septic shock, the decision would have been even more difficult. There are few absolute contraindications to ECMO, and the decision of whether to use ECMO continues to become more difficult as therapeutic options for various diseases expand and improve.

To our knowledge this is the first successful use of ECMO for refractory respiratory failure following thymus transplantation for complete immune-incompetent DiGeorge anomaly. ECMO was life-saving in this circumstance, and our experience highlights a novel application of ECMO in a patient who previously may have not been considered for it. We encourage early discussion and evaluation of ECMO candidacy in critically ill PICU patients, even in the setting of substantial comorbidities and complex underlying illnesses, including some forms of immunodeficiency. We do not believe this single case is sufficient to establish an algorithm or guideline for ECMO eligibility, but it does serve as a reminder that as providers "push the envelope" and demonstrate ECMO success in increasingly extraordinary circumstances, the decision making process regarding ECMO will continue to become more difficult.

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