Abstract: Cytokine Profile in a Pediatric Patient on Extracorporeal Membrane Oxygenation

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Background:

Pediatric extracorporeal membrane oxygenation (ECMO) systemic inflammatory response syndrome (SIRS) is a clinical syndrome noted shortly after initiation of ECMO. ECMO SIRS is characterized by systemic hypotension, fluid overload, pulmonary edema, and renal insufficiency. These adverse events are thought to be secondary to an overwhelming initial inflammatory response to the non-endothelialized ECMO circuit. Host factors, such as age and immaturity of the immune system, may be responsible for the altered inflammatory response seen in the pediatric population. A better understanding of pediatric ECMO SIRS is key in developing targeted therapies aimed at attenuating morbidities.

Objective: To describe the inflammatory milieu of a pediatric patient placed on ECMO.

Methods: This case report is part of an ongoing prospective study evaluating changes in the inflammatory milieu of critically ill pediatric patients who receive maximum medical therapy compared to their counterparts who progress to requiring ECMO support (IRB # 2108008743). Following consultation for ECMO, patients are divided into two groups, patients who remain ECMO consults and patients who require cannulation to ECMO. Blood samples are obtained at initiation of the consult or ECMO, 2 hours, 4 hours, 8 hours and 24 hours. Our index patient was initially in the consult group, but transitioned into the ECMO group after being cannulated onto ECMO approximately twelve hours into her admission. Quantification of chemokine and cytokine was performed using a Luminex 200 x Ponent 3.1 system (Millipore, MA).

Case Summary: A 10-year-old female with nephrotic syndrome presented after being found collapsed on the bedroom floor. History was significant for progressive generalized weakness, decreased appetite and inability to bear weight on the right lower extremity three days prior to arrival. Her clinical status and symptomatology were suggestive of septic shock secondary to a right hip septic arthritis (Table 1). Shortly after admission, she continued to deteriorate and required extensive volume resuscitation in the form of both crystalloid and colloid products in addition to epinephrine, norepinephrine, and milrinone for refractory hypotension. She progressively developed ventricular arrhythmias followed by pulseless ventricular tachycardia. Cardiopulmonary resuscitation ensued and after return of spontaneous circulation, she was started on an amiodarone infusion and cannulated onto veno-arterial ECMO. She developed ECMO SIRS within 24 hours of cannulation (Figure 1, 2) and after 6 days of ECMO support, was successfully de-cannulated. She was subsequently discharged after 59 days of hospitalization with Nephrology and Orthopedic follow up appointments.

Results: Of the 65 analytes evaluated at different time points, specific cytokines were implicated as key players in the evolution of ECMO SIRS. The initiation of ECMO mirrored significant changes in IL-6, IL-8,

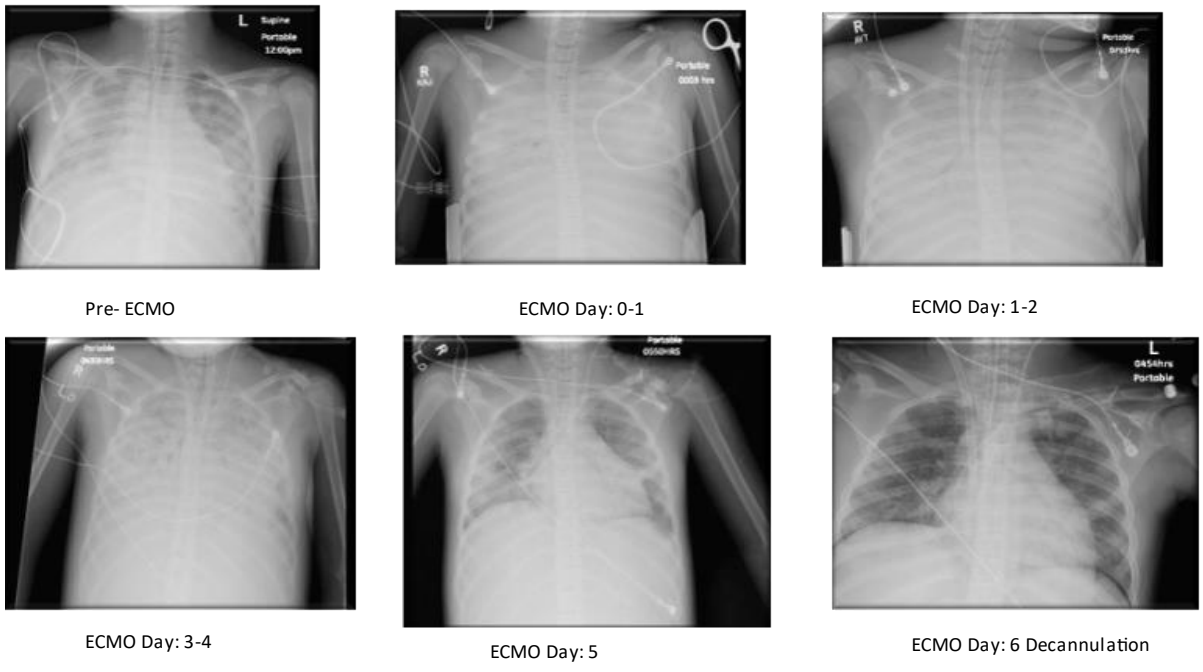
TNF-alpha, IL-10 and interferon gamma. Additional inflammatory markers, such as MCP-1, BLC (CXCL13), MIP 1 beta, and MIP 3 alpha, also demonstrated similar trends.

Discussion: This case of septic shock compounded by ECMO SIRS showed significant increases in inflammatory proteins occurring within two to four hours after ECMO initiation. Risnes et al suggested that a rapid rise in IL-6 is associated with initiation of ECMO and survivors had a 95% decrease in IL-6 levels by hour 24 to 48 compared to survivors. On the other hand, Liu et al suggests that sustained IL-10 levels better predicted death. Our patient had a significant increase in both IL-6 and IL-10 levels with a rapid decline of both within 24 hours of cannulation, potentially supporting the role of these proteins in prognostication. Rapid elevations in protein levels of MCP-1, MIP 1 Beta, and MIP 3 Alpha, BLC(CXCL13) and IL-2R were observed. Such findings implicate significant roles of monocytes, macrophages, and lymphocytes in pediatric ECMO SIRS as compared to purported neutrophils alone.

Conclusion: Key inflammatory proteins implicated in the known cytokine storm were observed in this case of pediatric ECMO SIRS. Such observation, though not surprising, needs to be studied further. Additionally, early involvement of monocytes, macrophages, and lymphocytes in this syndrome warrants further investigation.

Table 1: Laboratory Findings

	At admission	At Cannulation	After Cannulation
WBC	10.4	12.7	10.2
ESR	120	X	X
CRP	12.16	18.94	12.72
Gas: Acidosis	7.455	7.275	7.451
Gas: Lactate	1.9	2.7	6.2



Pre- ECMO

ECMO Day: 0-1

ECMO Day: 1-2

ECMO Day: 3-4

ECMO Day: 5

ECMO Day: 6 Decannulation

Figure 1. Radiographic progression of ECMO SIRS to decannulation

Table 2: ECMO parameters and Oxygen Consumption

ECMO parameters and Oxygen Consumption

	D0	D1	D2	D3	D4*	D5	D6
Max Pump flow(ml/kg/min)	91	73	77	74	71	71	63
Circuit fiO_2	100	100	100	100	90	40	23
SVO_2 (%)	75-85	78-82	78-84	79-85	65-82	65-82	74-81
Max sweep gas flow (L/min)	2.5	2.5	4	3.5	2	2	0.3
Lactate (mmol/L)	18.4	3.8	1.5	1.5	1.8	1.3	1.2
O_2 consumption (ml/min)	297	268	161	127	214	120	140
O_2 consumption (ml/kg/min)	8	7.2	4.3	3.4	5.8	3.2	3.8

*Circuit change
O_2 consumption estimated by cardiac output (pump flow) x 1.34 x hemoglobin × (outlet-inlet saturation).
D, day; FiO_2, fraction inspired oxygen; SVO_2, mixed venous O_2 saturation.

Figure 2: Cytokine profile of index case

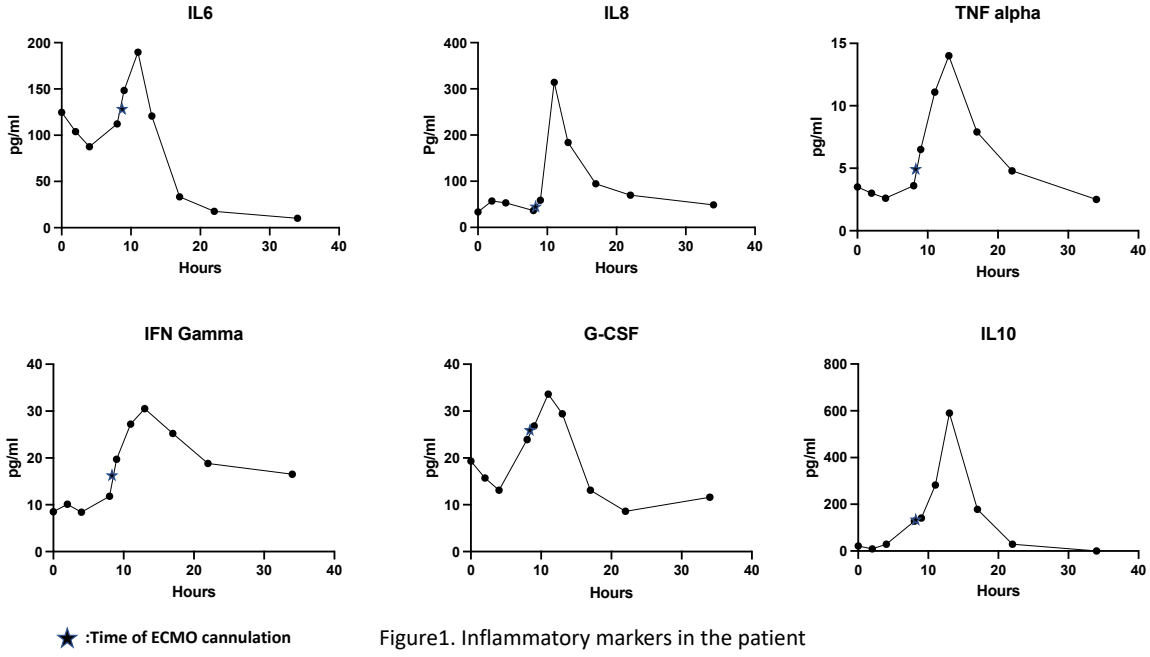


Figure1. Inflammatory markers in the patient

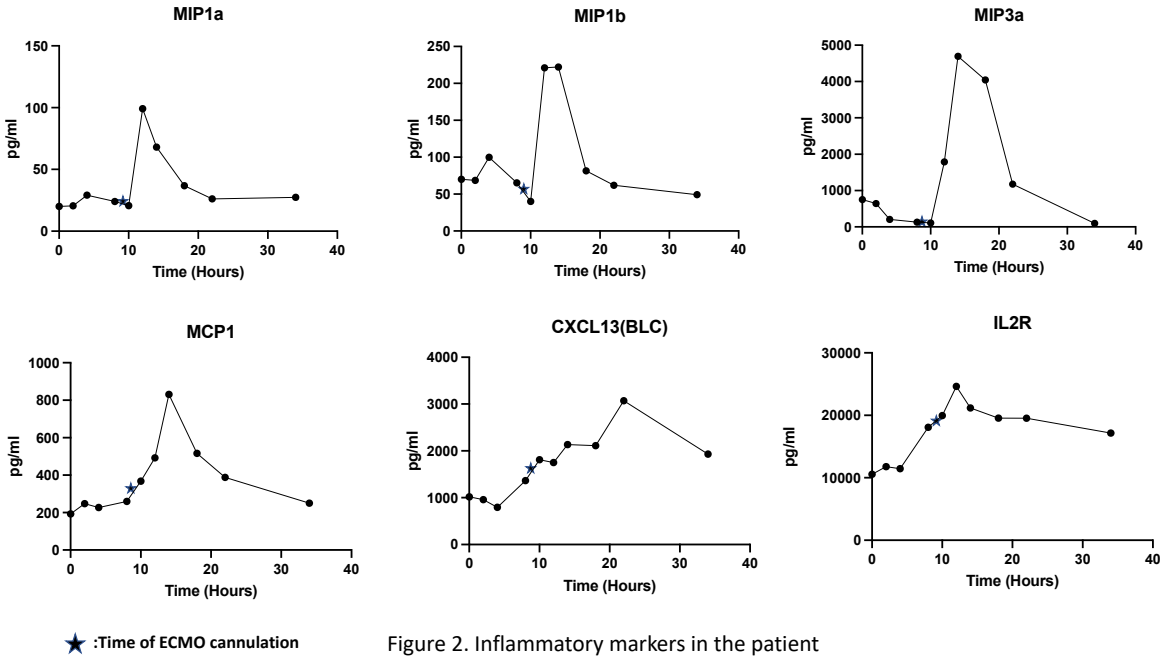


Figure 2. Inflammatory markers in the patient

References:

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Liu, CH., Kuo, SW., Ko, WJ. Early measurement of IL-10 predicts the outcomes of patients with acute respiratory distress syndrome receiving extracorporeal membrane oxygenation. *Sci Rep* **7**, 1021 (2017).