Published in final edited form as:

Pediatr Crit Care Med. 2016 December ; 17(12): 1186–1187. doi:10.1097/PCC.0000000000000990.

ECMO: Insult to Acute Kidney Injury

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Keywords

ECMO; extracorporeal; acute kidney injury; AKI; renal support therapy; renal replacement therapy; hemofiltration; children

Acute kidney injury (AKI) is encountered frequently in children supported on extracorporeal membrane oxygenation (ECMO) and has been shown to be an independent risk factor for mortality in these critically ill patients (1–5). Reports vary widely with respect to the prevalence of AKI in neonatal and pediatric ECMO patients, mostly due to the variation in the definitions used. The 2016 Extracorporeal Life Support Organization (ELSO) Registry Report describes a prevalence of up to 18% based on a serum creatinine cutoff of 1.5 mg/dL, and up to 35% when the need for renal support therapy is included (3). Previous single-center pediatric studies have found the prevalence of AKI to range between 18% to as high as 71% in specific populations such as neonates with congenital diaphragmatic hernia or children who underwent congenital heart disease repair (5–7). Using a single creatinine cutoff of 1.5 mg/dL surely underestimates the prevalence of AKI, especially in newborns and infants. And existing AKI definitions such as Pediatric RIFLE, AKI Network (AKIN) or Kidney Disease Improving Global Outcomes (KDIGO), can vary in their estimation of the true AKI incidence in the pediatric population (8), and have not been tested in large, multicenter, studies of pediatric ECMO.

In this issue of *Pediatric Critical Care Medicine*, Flemming et al present a retrospective analysis of neonatal and pediatric AKI during ECMO, using data collected from six ECMO centers in the U.S. (9). The authors' goals were to determine the prevalence of AKI in ECMO patients using the KDIGO criteria with or without the initiation of renal support therapy, and explore the association of AKI with mortality and ECMO duration (9). Patients were grouped by primary indication for ECMO (pulmonary, cardiac, or extracorporeal cardiopulmonary resuscitation) and ECMO mode (venoarterial, venovenous, and other). Presence and staging of AKI were determined during three pre-determined time periods:

prior to ECMO initiation, 48 hours on ECMO, and >48 hours on ECMO. The proportion of study participants who met KDIGO criteria for AKI was 60% based on serum creatinine, and 74% when renal support therapy was included. Of those who developed AKI, 52% and 86% met KDIGO criteria for AKI based on serum creatinine prior to ECMO initiation and by 48 hours on ECMO, respectively, and 65% and 93% met the same criteria with inclusion of renal support therapy, in the same time periods. After adjusting for potential confounders such as age or presence of other complications during ECMO, AKI by KDIGO criteria with and without renal support therapy initiation was significantly associated with decreased survival to hospital discharge and longer ECMO duration (9).

The timing of onset of AKI by any definition is difficult to establish, which is why the study explores the prevalence, rather than a true incidence (classically defined as number of events per person-time), of AKI. The authors made a strong effort to determine time of onset within the three periods of time established *a priori*, using the more “dynamic” KDIGO definition that takes into account the percent change in serum creatinine, rather than just a preset cutoff (2). For this reason and the fact that the KDIGO criteria incorporate elements of prior AKI scores (e.g., RIFLE, AKIN), the choice of the definition itself seems appropriate, even if the KDIGO definition for AKI was not previously validated in the ECMO population and has been criticized for the relative lack of high-grade evidence supporting it (10, 11).

The Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) study group is to be commended for taking this first step towards describing the epidemiology of AKI in the neonatal and pediatric ECMO population. As stated in the manuscript, the challenges related to the study of AKI in ECMO patients are many, but the investigators led a truly major effort to attempt to overcome them by creating a multicenter network with contributing members from multiple disciplines, and by collecting longitudinal data that will allow for future time-to-event and longitudinal data analysis. Of remaining challenges, two stand out. First, establishing whether AKI was present pre-ECMO is difficult, especially in newborns, as nicely discussed by the authors, and in patients who may have not had baseline serum creatinine measurements prior to an emergent ECMO cannulation. This problem is similar to the study of other acute complications noted during ECMO that may reflect morbidity that pre-dated cannulation (e.g., coagulopathy, neurologic injury, etc). Second, in the absence of prospectively designed studies, it remains extremely difficult to determine how clinicians decide to initiate renal supporting therapies and how a specific therapy is chosen (e.g., continuous renal replacement therapy, inline hemodiafilter, etc). These decisions could be dictated by physician preference, institutional protocols, or hospital resources at a specific point in time, and less so by the rather scarce existing evidence. The authors comment on the fact that the question of when renal supporting therapies were initiated in study participants remains unclear in view of the retrospective design, leading to potential indication bias. The inclusion of renal supporting therapies as an additional diagnostic criterion to the KDIGO definition of AKI did not seem to significantly impact the results of the study, perhaps partially neutralizing these concerns.

The authors suggest that the multicenter dataset they compiled will be used for further data analysis that will delve deeper into how, when, in whom, and why AKI occurs in neonatal and pediatric ECMO patients. Similar to work conducted in the general pediatric critical

care population (12, 13), these studies will start to answer important questions for critical care practitioners related to susceptibility and risk factors for AKI, as well as potential mitigating strategies. They will also help build the required background data that could serve as foundation to future prospective trials for therapeutic strategies for AKI in the ECMO population.

References

1. Askenazi D, Ambalavanan N, Hamilton K, Cutter G, Laney D, Kasklow R, Georgeson K, Barnhart DC, Dimmitt RA. Acute kidney injury and renal replacement independently predict mortality in neonatal and pediatric noncardiac patients on extracorporeal membrane oxygenation. *Pediatr Crit Care Med*. 2011 Jan; 12(1):e1–e6. [PubMed: 20351617]
2. KDIGO AKI Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012; 2:1–138.
3. ELSO. ECLS Registry Report: International Summary. Extracorporeal Life Support Organization. Ann Arbor MI. 2016:24–72.
4. Lou S, MacLaren G, Paul E, Best D, Delzoppo C, Butt W. Hemofiltration is not associated with increased in mortality in children receiving extracorporeal membrane oxygenation. *Pediatr Crit Care Med*. 2015 Feb; 16(2):161–6. [PubMed: 25560421]
5. Smith AH, Hardison DC, Worden CR, Fleming GM, Taylor MB. Acute renal failure during extracorporeal support in the pediatric cardiac patient. *ASAIO J*. 55:412–416.
6. Fortenberry JD, Paden ML, Goldstein SL. Acute kidney injury in children: an update on diagnosis and treatment. *Pediatric clinics of North America*. 2013; 60:669–688. [PubMed: 23639662]
7. Alkandari O, Eddington KA, Hyder A, Gauvin F, Ducruet T, Gottesman R, Phan V, Zappitelli M. Acute Kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study. *Critical Care*. 2011 Jun 10.15(3):R146. [PubMed: 21663616]
8. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol*. 2015 Apr 7; 10(4):554–61. [PubMed: 25649155]
9. Fleming G, Sahay R, Zappitelli M, et al. The incidence of Acute Kidney Injury and its Effect on Neonatal and Pediatric ECMO Outcomes: A multicenter report from the KIDMO Study Group. *Pediatr Crit Care Med*. In Press.
10. Alseieri, M.; Meyer, KB.; Wong, JB. Evidence Underlying KDIGO (Kidney Disease: Improving Global Outcomes) Guideline Recommendations: A Systematic Review.
11. Selewski DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, Lombel RM, Blatt NB, Luckritz K, Hieber S, Gajarski R, Kershaw DB, Shanley TP, Gipson DS. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. *Intensive Care Med*. 2014 Oct; 40(10): 1481–8. [PubMed: 25079008]
12. Arian AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med*. 2012 May; 13(3):253–8. [PubMed: 21760565]
13. Modem V, Thompson M, Gollhofer D, Dhar AV, Quigley R. Timing of continuous renal replacement therapy and mortality in critically ill children. *Crit Care Med*. 2014 Apr; 42(4):943–53. [PubMed: 24231758]