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ECMO, Dialysis, and Mortality: Let's Agree to Agree

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Advances in technology and procedures related to pediatric ECMO have not been met with a commensurate improvement in survival or reduction of complications (1). Similarly, improved survival of patients with sepsis and acute respiratory distress syndrome (ARDS) were also stymied until the adoption of consensus definitions and guidelines (2, 3). In this issue of *Pediatric Critical Care Medicine* Lou *et al.* investigates the complex interactions between fluid overload (FO), acute kidney injury (AKI), extracorporeal membrane oxygenation (ECMO), and continuous renal replacement therapy (CRRT). He reports that CRRT used primarily to treat FO was not significantly associated with in hospital death (44%) compared to those not treated with CRRT (35%) during ECMO (4). Subjects were children treated with ECMO for all major indications (eg. sepsis, 'E-CPR', cardiac and respiratory failure) using primarily venoarterial support (>80%). Propensity matching was used to select a similarly ill comparison group not treated with CRRT. Although mortality was similar, those treated with CRRT had longer length of stay and were treated with more blood products. The authors concluded that CRRT could be safely used to treat FO and inferred this intervention caused greater survival than historically predicted. Contradictory to Lou's finding, the Extracorporeal Life Support Organization (ELSO) and others consistently report that patients with elevated creatinine (Cr) and those treated with renal support have greater mortality across all pediatric ECMO indications (1, 5–7)

Lou reported AKI in only 33% of subjects, while other single centers report that AKI occurs in over 50% of all ECMO patients (6). Relevant to pediatrics, serum Cr based scoring

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systems fail to account for differences in muscle mass, and distribution of Cr into both the intracellular and extracellular fluid compartments. The ELSO registry includes two measures of elevated Cr (1.5–3.0 mg/dL, and > 3 mg/dL) regardless of patient age or size (1). Furthermore, patients with FO; the leading cause for initiation of CRRT during ECMO (8), may have a ‘diluted Cr’ leading to delayed diagnosis of AKI (9, 10).

The ELSO registry cords renal support therapies as dialysis, hemofiltration (HF), and continuous arterial venous hemofiltration with a countercurrent dialysis [(CAVHD); which is rarely deployed in the current era]. Unfortunately, missing from the registry are indications for initiation of renal support, accurate classification of the renal replacement therapy and type of equipment and methods for integration with the ECMO circuit. Broad application of research results is hindered by the clinical environments that are not controlled for nuances such as thresholds and timing for initiating and stopping renal replacement therapies and diuretics, rate and volume of fluid removal, and choice of ECMO and dialysis equipment.

AKI in patients on ECMO is heterogenous and multifactorial which limits extrapolation of data even when patients are matched for severity of illness. AKI is highly contextual and effected not only by the pre-ECMO status, but also by the sequela of diminished pulsatility (11), hemolysis from centrifugal pumps (12), and rapid volume shifts during fluid removal. Thus comparing renal support therapies in critical care exclusive of ECMO remains complex with key questions unanswered (13). It is unlikely that investigations using only the present ELSO registry data will provide sufficiently accurate information to assess optimal definitions and ideal adjunctive therapies.

Furthermore, while CRRT may hasten removal of lung water, it is not expected to restore Na/K ATPase activity or lower inflammatory mediators that also favor alveolar fluid accumulation (14). Caution regarding complications or rapid fluid removal is prudent. Multi-disciplinary physician leadership and study collaboration are needed to define objective clinical and biochemical markers for pediatric AKI and FO during ECMO and then to systematically compare therapies with consistent assessment measures.

Lou reports data from a single center using propensity matching to adjust for severity of illness. Of note, data regarding severity of FO during ECMO was not included as a matching variable but has been shown to be associated with mortality (5). Some of the statistical analysis also warrants exploration. The authors report mortality rates of 44% compared to 35%, an increase of almost 10% with exposure to CRRT. Using a power calculation based on this mortality difference; if $\alpha = 0.05$ and power = 0.8, the sample size needed to demonstrate this difference is 432 per treatment group which is about 10 fold larger than available for analysis. The 43 subjects per group, was sufficiently large to provide 95% confidence to find a significant difference if mortality in the CRRT group increased to 66% compared to 35% (15). Like many pediatric ECMO studies, the current study is hampered by insufficient power to draw firm conclusions.

The report by Lou *et al.* is provocative and attempts to addresses a common problem among a high risk, high cost patient population in an era of limited resources. Ultimately, the

question as to how, when, and who (if anyone) will benefit from CRRT during ECMO, appears to require the adoption of similar consensus definitions, standards, technologies, and systems based practices that effectively changed the course of ARDS (3) and sepsis (2) nearly 20 years ago.

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Abbreviations

CRRT	continuous renal replacement therapy
FO	fluid overload
ELSO	Extracorporeal Life Support Organization
Cr	creatinine
AKI	Acute kidney injury
CAVHD	continuous arterial venous hemofiltration with a countercurrent dialysis
ECMO	extracorporeal membrane oxygenation

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