The association of fluid accumulation and adverse outcomes: the signal is clear. Time to move the field forward

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Pediatricians have been at the forefront of recognizing the deleterious impact of fluid accumulation (FA) in critical care nephrology.[1,2] Single center work identified the association between the degree of FA at continuous renal replacement therapy (CRRT) initiation and increased mortality. Publications have since identified FA as being associated with adverse outcomes across clinical settings.[3] In 2018 Alobaidi et al. performed a meta-analysis 44 studies (7507 children) demonstrating an association of FA with increased mortality, prolonged mechanical ventilation, and acute kidney injury (AKI).[4]

Victoria Carneiro Lintz and colleagues provide an expansive update of this meta-analysis, including 120 studies and 44,682 patients, highlighting the deleterious impact of FA.[5] This meta-analysis shows a clear association between FA with increased mortality (odds ratio [OR] 4.36; 95% confidence interval [CI] 3.53–5.38), AKI (OR 1.98; 95% CI 1.60–2.44), mechanical ventilation (weighted mean difference [WMD] 38.1 h, 95% CI 19.35–56.84), and intensive care unit length of stay (WMD 2.29 days; 95% CI 1.19–3.38). Based on these findings and the published literature, FA leading to the pathologic state of fluid overload (FO) in a variety of clinical scenarios is independently associated with adverse outcomes.

As with all meta-analyses based on observational studies, the lack of randomisation and associative nature of the findings must be considered when interpreting the data. However, an important strength of the work by Linz and colleagues is the study size, including over three-times more studies than any previous meta-analysis. The generalisability of these findings is also important to consider. As the authors point out, the current literature often treats FA as a static process or threshold that is generalisable. In clinical care, FA is a dynamic process impacted by many factors including but not limited to response to interventions, change over time, pathophysiology, disease severity, and timing. Linz and colleagues[5] accounted for these aspects where feasible, but this remains an important limitation of publications on FA. These factors warrant further investigation and future studies should account for these.

In the early studies on FA, authors utilized the term *fluid overload* to describe the degree of FA at CRRT and its association with increased mortality.[1,3] Although appropriate in this setting as patients were being placed on CRRT, subsequent studies often used the term FO indiscriminately to describe positive fluid balance. As Lintz et al. report, utilizing the terminology in this manner introduces a bias that all states of positive fluid balance are deleterious. In 2021, the 26th Acute Disease Quality Initiative (ADQI) conference proposed unbiased terminology to objectively describe fluid status in sick children: daily fluid balance, cumulative fluid balance, and percent cumulative fluid balance.[6,7] This terminology is similar in nature to the use of "fluid accumulation" by Linz and colleagues. The 26th ADQI defined FO as "a pathologic state of positive fluid balance associated with a clinically observable event(s), which may vary by age, case-mix, acuity, and phase of illness". This terminology is similar to "fluid accumulation syndrome[6]".

In the past FA has classically been thought of in terms of thresholds and associated outcomes. While this work has been important in identifying FA as clinically meaningful and potential target for intervention, it does not account for the dynamic nature of FA. These studies of FA rarely accounted for the timing, trajectory, or response to therapy. Linz and colleagues highlighted the importance of this when they showed the association of "early FA" with increased mortality (OR 7.93 for 5% and 8.77 for 10% within 24 h). This concept was highlighted in a recent secondary analysis of 5079 children across 32 centers which evaluated the impact of varying fluid accumulation thresholds (≥5% or ≥10%) as various timepoints (end of ICU Day 1 and Day 2) and outcomes.[8] These studies highlight future directions in understanding the dynamic nature of FA and the impact of both threshold and timing on outcomes.[5,8]

To continue to move the field forward we must better understand the potentially modifiable iatrogenic contributions to FA.[9] The future of AKI and fluid management will most likely include a dynamic process incorporating risk stratification, biomarkers, functional testing (furosemide stress test), and early intervention. A model for this

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is embodied in the Trial in AKI using NGAL and Fluid Overload to optimize CRRT Use (TAKING FOCUS 2).[10] The current study will provide important data to inform future trials and interventional studies.

For the clinician, Linz and colleagues raise some important points. Importantly, while FA is associated with adverse outcomes the thresholds for FO likely differ pathophysiology, timing, and disease trajectory. Understanding the timing and transitions of the phases of fluid management and the expected responses to interventions aimed at the mitigation of FA is important. Critically, continued FA and the development of FO is associated with adverse outcomes. In treating the patient at the bedside clinicians can use this data to understand thresholds, trends in FA, and expected response to therapy that should trigger escalation or de-escalation of interventions to mitigate FA.

In summary, Linz and colleagues[5] further delineate and strengthen the association between FA and adverse outcomes. As the field continues to move forward, it will remain important to use unbiased terminology and move past thinking of FA simplistically as a threshold. Future areas for study will include better understanding the sources of FA, the dynamic nature of FA (timing and trajectory), sequential risk stratification, and the impact of the response to intervention.

Contributors

Natalie Pudalov performed the literature search, wrote the original draft, subsequent writing and editing of this editorial. David Selewski and Katja Gist contributed project conceptualization, supervision, writing and editing the revision.

Declaration of interests

David Selewski and Natalie Pudalov have no interests to declare. Katja Gist has received grant funding from the Gerber Foundation. Katja Gist is a consultant for Bioporto and Portrero Medical.

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