Pediatric Nephrology (2023) 38:1999–2001
https://doi.org/10.1007/s00467-023-05895-0

EDITORIAL COMMENTARY

Hyperchloremia and acute kidney injury: chicken or the egg?

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Received: 19 January 2023 / Revised: 19 January 2023 / Accepted: 23 January 2023 / Published online: 8 February 2023

Over the last decade, our understanding of the impact of acute kidney injury and disorders of fluid balance on outcomes in children across disease processes and age spectrum has become clear. Seminal multicenter longitudinal studies in critically ill children, congenital heart disease, and neonatal populations have solidified the association of AKI and disorders of fluid balance with adverse outcomes [1–5]. Unfortunately, there remains no definitive treatment for AKI. In the absence of established AKI therapeutics, the care of these patients has shifted toward strategies aimed at the prevention and/or mitigation of AKI.

In this context there has been a renewed interest in understanding the impact of the most commonly prescribed medication in medicine, intravenous fluids, on outcomes and as a potentially modifiable risk factor to improve outcomes in critically ill patients. Intravenous fluid management is a cornerstone of the management of critically ill patients. Virtually every critically ill child receives intravenous fluids and frequently receives very large volumes. Despite these drugs being used nearly ubiquitously, there remains a lack of clear understanding of the optimal fluid management strategy. There is an ongoing evolution in our understanding and practices regarding intravenous fluids in critically ill patients. This includes understanding the importance of early fluid resuscitation in critical illness [6] and the phases of fluid management in critical illness [7]. More recently, isotonic fluids have been favored as "maintenance" fluids in efforts to prevent hospital-acquired hyponatremia. Over time, the paradigm of how we manage intravenous fluids has evolved to better understand the impact of volume, timing, and tonicity of intravenous fluid choices [8]. In recent years there has been increasing interest in understanding the impact of intravenous fluid composition (balanced electrolyte solutions vs. 0.9% saline) and associated electrolyte abnormalities (acidosis, dyschloremias) with adverse outcomes.

In the article "Hyperchloremia and association with acute kidney injury in critically ill children," Ginter et al. report on the impact of hyperchloremia on outcomes in a single-center retrospective study of critically ill children [9]. The authors demonstrate that hyperchloremia is independently associated with AKI in critically ill children after adjusting for severity of illness, renal angina index, change in the serum chloride, and fluid balance. Their single-center study importantly evaluated the chloride load as well as the change in the serum chloride. The patients with hyperchloremia received a larger volume of fluid, a higher chloride load, and had a greater increase in chloride. Furthermore, the utilization of balanced electrolyte solutions was relatively uncommon (5% plasmalyte and 12% Ringer's lactate). This study adds to the existing literature (Table 1) by further understanding the potentially deleterious impact of utilizing solutions with supraphysiologic chloride content on outcomes in critically ill children.

In interpreting the current study and the existing literature on the topic, it is important to highlight the difficulty of fully understanding the impact of serum chloride levels and chloride loads in critically ill patients. Is the serum chloride the chicken or the egg? Is hyperchloremia merely a reflection of the tubular injury that has occurred because of the etiology of the AKI? Does hyperchloremia represent an exposure to a detrimental internal milieu that in turn causes AKI? Serum chloride likely reflects both the chloride load administered as well as the body's ability to manage that load and maintain a normal chloride level. Patients with AKI frequently receive more resuscitation fluids and thus chloride load when the overwhelming amount

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Table 1 Studies evaluating the impact of intravenous fluid composition and hyperchloremia in critically ill children

Manuscript	Exposure	Population	Outcomes
Pediatric studies			
Emrath et al. [10]	Children who received balanced fluids for resuscitation in the first 24 and 72 h of treatment were compared to those receiving unbalanced fluids	Pediatric intensive care unit patients diagnosed with severe sepsis (43 children's hospitals)	Those treated with balanced electrolyte solutions had: - Lower mortality - Lower prevalence of AKI - Fewer vasoactive infusion days
Barhight et al. [11]	Chloride > 110 mmol/L	Critically ill children receiving CKRT	Higher mortality risk
Barhight et al. [12]	Increase of chloride of 5 mmol/L in first 24 h	Critically ill children	Higher mortality risk Increased MV duration
Stenson et al. [13]	Chloride > 110 mmol/L	Critically ill children with septic shock	Higher mortality risk Higher risk for complicated course
Stenson et al. [14]	Chloride > 110 mmol/L	Critically ill children with septic shock	Higher AKI risk
Barhight et al. [15]	Chloride > 110 mmol/L	Critically ill children with AKI	Lower renal recovery
Stanski et al. [16]	> 75% of IVF from 0.9% saline, > 75% of fluids from lactated ringers, and a mixed group	Critically ill children who received ≥ 20 mL/kg of fluid resuscitation and were admitted to two pediatric intensive care units	Electrolyte derangements more common in 0.9% saline group: - Extreme hyperchloremia - Extreme acidosis

AKI acute kidney injury, *CKRT* chronic kidney replacement therapy, *IVF* intravenous fluids, *MV* mechanical ventilation

of intravenous fluids (> 80–90%) administered is 0.9% saline as is the case in this study. In future studies urinary biomarkers, fluid management algorithms, and ultimately trials will help us to further tease out whether hyperchloremia is the chicken or egg as it is related to AKI.

As we move forward in research, we will also need to further refine our understanding of the timing and dose of chloride administration on outcomes. As an example, resuscitation fluids that are rapidly administered likely have a very different impact than slow continuous fluids. Logically, the clinical impact of a rapid infusion of 60 mL/kg of 0.9% saline with a pH of 5 is a very different type of chloride load than that same 60 mL/kg delivered over 18 h while being mixed with D5W medication carriers regardless of the chloride content of the fluid. This is highlighted by the recent study evaluating the detrimental impact 0.9% saline has on the endothelial health of patients [17]. Separately, the optimal way to manage these patients may depend upon the patient's serum chloride. Patients initially with hypochloremia may need hyperchloremic fluids, and patients with hyperchloremia may need hypochloremic fluids. As with any drug prescribed in critically ill children, the provision of intravenous fluids likely needs to be individualized and evaluated on a daily basis.

In summary, there is a complex interplay between the tubular function of the kidneys, the chloride load given to critically children, and the resultant serum chloride. Serum chloride may be a biomarker for AKI or a reflection of the chloride load which in turn may be a risk factor for the development of AKI. Future studies should help to discern these important differences and help answer the question of chicken (modifiable risk factor) or the egg (biomarker for AKI). In the meantime, clinically, patients should be given fluids thoughtfully with an individualized approach and with consideration of their kidney function.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Alten JA, Cooper DS, Blinder JJ, Selewski DT, Tabbutt S, Sasaki J, Gaies MG, Bertrandt RA, Smith AH, Reichle G, Gist KM, Banerjee M, Zhang W, Hock KM, Borasino S, Neonatal and Pediatric Heart and Renal Outcomes Network (NEPHRON) Investigators (2021) Epidemiology of acute kidney injury after neonatal cardiac surgery: a report from the multicenter neonatal and pediatric heart and renal outcomes network. Crit Care Med 49:e941–e951
2. Fleming GM, Sahay R, Zappitelli M, King E, Askenazi DJ, Bridges BC, Paden ML, Selewski DT, Cooper DS (2016) The incidence of acute kidney injury and its effect on neonatal and pediatric extracorporeal membrane oxygenation outcomes: a multicenter report from the kidney intervention during extracorporeal membrane oxygenation study group. Pediatr Crit Care Med 17:1157–1169
3. Goldstein SL, Akcan-Arikan A, Alobaidi R, Askenazi DJ, Bagshaw SM, Barhight M, Barreto E, Bayrakci B, Bignall ONR, Bjornstad E, Brophy PD, Chanchlani R, Charlton JR, Conroy AL, Deep A, Devarajan P, Dolan K, Fuhrman DY, Gist KM, Gorga SM, Greenberg JH, Hasson D, Ulrich EH, Iyengar A, Jetton JG, Krawczeski C, Meigs L, Menon S, Morgan J, Morgan CJ, Mottes

T, Neumayr TM, Ricci Z, Selewski D, Soranno DE, Starr M, Stanski NL, Sutherland SM, Symons J, Tavares MS, Vega MW, Zappitelli M, Ronco C, Mehta RL, Kellum J, Ostermann M, Basu RK, Pediatric ADQI Collaborative (2022) Consensus-based recommendations on priority activities to address acute kidney injury in children: a modified Delphi consensus statement. JAMA Netw Open 5(9):e2229442. https://pubmed.ncbi.nlm.nih.gov/36178697/

4. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, Chishti AS, Woroniecki R, Mammen C, Swanson JR, Sridhar S, Wong CS, Kupferman JC, Griffin RL, Askenazi DJ, Neonatal Kidney Collaborative (NKC) (2017) Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health 1:184–194
5. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, AWARE Investigators (2017) Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 376:11–20
6. Han YY, Carcillo JA, Dragotta MA, Bills DM, Watson RS, Westerman ME, Orr RA (2003) Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics 112:793–799
7. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, Kellum JA, Mythen MG, Shaw AD, ADQI XII Investigators Group (2014) Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth 113:747
8. Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD, Austin K, Basu RK, Conway EE Jr, Fehr JJ, Hawkins C, Kaplan RL, Rowe EV, Waseem M, Moritz ML, Subcommittee on fluid and electrolyte therapy (2018) Clinical practice guideline: maintenance intravenous fluids in children. Pediatrics 142:e20183083
9. Ginter D, Gilfoyle E, Wade A, Lethebe BC, Gilad E (2022) Hyperchloremia and association with acute kidney injury in critically ill children. Pediatr Nephrol. https://doi.org/10.1007/s00467-022-05823-8
10. Emrath ET, Fortenberry JD, Travers C, McCracken CE, Hebbar KB (2017) Resuscitation with balanced fluids is associated with improved survival in pediatric severe sepsis. Crit Care Med 45:1177–1183
11. Barhight MF, Lusk J, Brinton J, Stidham T, Soranno DE, Faubel S, Goebel J, Mourani PM, Gist KM (2018) Hyperchloremia is independently associated with mortality in critically ill children who ultimately require continuous renal replacement therapy. Pediatr Nephrol 33:1079–1085
12. Barhight MF, Brinton J, Stidham T, Soranno DE, Faubel S, Griffin BR, Goebel J, Mourani PM, Gist KM (2018) Increase in chloride from baseline is independently associated with mortality in critically ill children. Intensive Care Med 44:2183–2191
13. Stenson EK, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald JC, Checchia PA, Meyer K, Quasney M, Hall M, Gedeit R, Freishtat RJ, Nowak J, Raj SS, Gertz S, Grunwell JR, Wong HR (2018) Hyperchloremia is associated with complicated course and mortality in pediatric patients with septic shock. Pediatr Crit Care Med 19:155–160
14. Stenson EK, Cvijanovich NZ, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald JC, Jain PN, Meyer K, Quasney M, Hall M, Gedeit R, Freishtat RJ, Nowak J, Lutfi R, Gertz S, Grunwell JR, Wong HR, Anas N (2018) Hyperchloremia is associated with acute kidney injury in pediatric patients with septic shock. Intensive Care Med 44:2004–2005
15. Barhight MF, Brinton JT, Soranno DE, Faubel S, Mourani PM, Gist KM (2020) Effects of hyperchloremia on renal recovery in critically ill children with acute kidney injury. Pediatr Nephrol 35:1331–1339
16. Stanski NL, Gist KM, Pickett K, Brinton JT, Sadlowski J, Wong HR, Mourani P, Soranno DE, Kendrick J, Stenson EK (2022) Electrolyte derangements in critically ill children receiving balanced versus unbalanced crystalloid fluid resuscitation. BMC Nephrol 23:388
17. Fernandez-Sarmiento J, Salazar-Pelaez LM, Acevedo L, Nino-Serna LF, Florez S, Alarcon-Forero L, Mulett H, Gomez L, Villar JC (2023) Endothelial and glycocalyx biomarkers in children with sepsis after one bolus of unbalanced or balanced crystalloids. Pediatr Crit Care Med. https://doi.org/10.1097/PCC.0000000000003123