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LETTER

Hyperchloremia is associated with acute kidney injury in pediatric patients with septic shock

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Dear Editor,

Hyperchloremia is associated with increased mortality and organ failures in pediatric septic shock patients [1] and associated with increased rates of acute kidney injury (AKI) in adults [2]. It is currently unknown whether AKI is associated with hyperchloremia in pediatric patients, and whether AKI contributes to the higher rate of organ failures seen previously [1]. This hyperchloremia is often attributed to the use of unbalanced crystalloids, such as 0.9% sodium chloride, which has been associated with increased rates of AKI [2, 3]. We tested the hypothesis that hyperchloremia is independently associated with AKI in pediatric patients with septic shock.

We performed a retrospective analysis of a pediatric septic shock database that included 619 children from 29 pediatric intensive care units (PICUs) between 2002 and 2015. We considered the minimum, maximum, and mean chloride values within the first 7 days of PICU admission as separate hyperchloremia variables. We considered hyperchloremia as a dichotomized variable defined a priori as a serum concentration $\geq$110 mmol/L. We used multivariable logistic regression to determine the association between hyperchloremia variables and outcomes, after adjusting for illness severity and age. Further details of our methods are provided in Supplement 1 and have been documented previously [1].

Our primary outcome variable was day 3 AKI, defined as KDIGO (Kidney Disease: Improving Global Outcomes) stage 2 or 3. The timing of day 3 AKI was chosen because most PICU patients with AKI will develop AKI by day 3, and this allows enough time for development of severe AKI and for "pre-renal" increased creatinine to improve [4]. Baseline creatinine was estimated in two different ways as subjects did not have baseline data (Supplement).

There were 125 subjects (20%) with AKI. Subjects with AKI were younger and had higher PRISM III scores (Supplemental Table 1). There were 42 subjects (7%) with a minimum chloride $\geq$110 mmol/L, 117 subjects (19%) with a mean chloride $\geq$110 mmol/L, and 359 subjects (58%) with a maximum chloride $\geq$110 mmol/L. Table 1 shows that minimum chloride $\geq$110 mmol/L was associated with increased odds of AKI (OR 2.4; 95% CI 1.2–4.9; $p=0.014$). Sensitivity analysis based on the method for estimating baseline creatinine shows similar findings (Table 1). Further analyses using the first 3 days of chloride values and the resulting minimum, maximum, mean, or change in chloride values are shown in Supplemental Tables 2 and 3.

The development of persistent hyperchloremia during septic shock, as suggested by a minimum chloride $\geq$110 mmol/L, is independently associated with AKI. This further clarifies the association between

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Table 1 Multivariable logistic regression testing for an association between hyperchloremia and KDIGO AKI stage 2–3 on day 3

Patient population	Variable	OR	95% CI	*p* value
All ($n=619$)	Minimum Cl ≥ 110	2.4	1.2–4.9	0.014
	PRISM	1.1	1.0–1.1	< 0.001
	Age	0.9	0.9–1.0	0.009
	Mean Cl ≥ 110	1.8	1.1–2.9	0.014
	PRISM	1.1	1.0–1.1	< 0.001
	Age	0.9	0.9–1.0	0.012
Height-based estimated creatinine ($n=172$)	Minimum Cl ≥ 110	4.0	1.3–12.3	0.016
	PRISM	1.0	1.0–1.1	0.196
	Age	1.0	0.9–1.1	0.630
	Mean Cl ≥ 110	3.0	1.2–7.1	0.015
	PRISM	1.0	1.0–1.1	0.177
	Age	1.0	0.9–1.1	0.594
Age- and gender-based estimated creatinine ($n=447$)	Minimum Cl ≥ 110	2.4	1.1–5.2	0.022
	PRISM	1.0	1.0–1.1	< 0.001
	Age	1.0	0.9–1.0	0.01
	Mean Cl ≥ 110	1.8	1.1–2.9	0.026
	PRISM	1.1	1.0–1.1	< 0.001
	Age	0.9	0.9–0	0.012

Adjusted for PRISM III scores and age

hyperchloremia and organ failures previously documented [1]. With the availability of both resuscitation and "maintenance" fluids with differing chloride concentrations, the amount of chloride given to these patients is a modifiable risk factor. Unfortunately, our database did not contain sufficient details regarding the type or amount of fluid, or the use of nephrotoxic agents, which is a limitation of our study. This data adds to the growing body of literature suggesting a need to further evaluate the optimal fluid to be used to resuscitate pediatric septic shock patients.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5368-5) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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References

1. Stenson EK, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald JC, Checchia PA, Meyer K et al (2018) Hyperchloremia is associated with complicated course and mortality in pediatric patients with septic shock. Pediatr Crit Care Med 19(2):155–160
2. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A et al (2018) Balanced crystalloids versus saline in critically ill adults. N Engl J Med 378(9):829–839
3. 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(7):1177–1183
4. 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(1):11–20