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EDITORIAL

Is chloride worth its salt?

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Intravenous infusion of salt water to restore circulating blood volume traces its origins to the 1830s cholera pandemic. In a letter to the *Lancet* dated June 2, 1832, Thomas Latta noted with intravenous saline (of unknown composition) "improvement in the pulse and countenance is almost simultaneous, the cadaverous expression gradually gives place to appearances of returning animation, the livid hue disappears, the warmth of the body returns" [1]. In 1896, Hartog Jakob Hamburger recognized erythrocytes did not lyse in a saline solution and concluded that "the blood of man was isotonic with a NaCl solution of 0.9%". Although human plasma is closer to 0.6% NaCl, the use of 0.9% "normal" saline became widespread. Other crystalloid solutions with a more buffered electrolyte composition, including lactated Ringer's, Hartmann's, and PlasmaLyte, were also introduced into clinical practice. Despite a burgeoning literature about the risks of saline-induced hyperchloremia and acidemia compared to buffered crystalloids, 0.9% saline remains the overwhelming preference for fluid resuscitation, particularly in children [2].

In this issue of *Intensive Care Medicine*, Barhight and colleagues report an association of hyperchloremia (serum chloride $\geq$ 110 mEq/L) at admission to the pediatric intensive care unit (PICU) and an increase in chloride of $\geq$ 5 mEq/L ($\uparrow$ Cl $\geq$ 5 mEq/L) on the first calendar day of PICU admission with in-hospital mortality, length of stay, and days on mechanical ventilation among a retrospective cohort of 1,935 general PICU admissions to a single center [3]. Unadjusted mortality was highest (40%) in those with both hyperchloremia and $\uparrow$ Cl $\geq$ 5 mEq/L, although this group was small. The authors used logistic regression to further test the association of hyperchloremia with mortality after adjusting for 19 covariates selected a priori. Although there are some methodologic concerns about the construction of the final multivariable model (e.g., overfitting, collinearity, selection and testing of potential interaction effects), $\uparrow$ Cl $\geq$ 5 mEq/L conferred a 2.3 (95% CI 1.03, 5.21) increased adjusted odds of death. Notably, $\uparrow$ NA $\geq$ 5 mEq/L was also associated with death (adjusted OR 3.53, 95% CI 1.55, 8.05), and rise in sodium appeared more closely associated with mortality than rise in chloride in an analysis stratified by volume of PICU fluid administered on the first day. Interpretation of these findings requires caution in light of potential for measurement bias, with sicker patients most likely to have serial electrolyte assessments and the possibility of unmeasured confounding. However, this study offers another piece of evidence that hyperchloremia can have real consequences for patients, including children.

Most pediatric hyperchloremia is iatrogenic, secondary to the large chloride burden—154 mEq/L—present in 0.9% saline. In addition, an increase in blood chloride has been shown to reduce renal blood flow and glomerular filtration, thereby exacerbating reabsorption of sodium and chloride by the kidney. Saline-induced hyperchloremia is also generally accompanied by a metabolic acidosis due to the dilution of plasma bicarbonate in the absence of an alternative buffer. Hyperchloremic metabolic acidosis is pro-inflammatory in cell culture experiments [4] and, although its clinical relevance is debated, has been associated with mortality. In healthy volunteers, infusion of 0.9% saline caused more abdominal discomfort, drowsiness, and impaired cognition than buffered fluids [5]. Moreover, as in the study by Barhight and colleagues, chloride load has been associated with acute kidney injury (AKI), need for renal replacement therapy, and mortality in adult and pediatric patients [6, 7].

While not yet a settled issue, there are now ample data to support the hypothesis that resuscitation with buffered

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Table 1 Studies comparing 0.9% saline to balanced fluid resuscitation

Study	Population	Design	Sample size	Outcome	0.9% saline (%)	Balanced (%)	*P* Value
Yunos et al. 2012 [15]	Adult ICU	Pre/post	1533	Mortality	15	13	0.44
Raghunathan et al. 2014 [10]	Adult sepsis	Matched cohort	6730	Mortality	23	20	0.001
Yunos et al. 2012 [15]	Adult ICU	Pre/post	1533	AKI	14	8.4	< 0.001
SPLIT Trial 2015 [14]	Adult ICU	Cross-over	2092	AKI	9.2	9.6	0.77
Self et al. 2018 [11]	Adults	RCT	13,347	MAKE30	5.6	4.7	0.01
Semler et al. 2018 [12]	Adult ICU	RCT	15,802	MAKE30	15.4	14.3	0.04
Weiss et al. 2017 [13]	Pediatric sepsis	Matched cohort	4234	Mortality	7.9	7.2	0.20
Emrath et al. 2017 [8]	Pediatric sepsis/ICU	Matched cohort	10,318	Mortality	15	13	0.051
Ngo et al. 2001 [9]	Pediatric dengue fever	RCT	222	Shock recovery	93	80	0.022

ICU intensive care unit, *RCT* randomized controlled trial, *NA* not applicable, *RR* relative risk, *CI* confidence interval, *AKI* acute kidney injury, *MAKE30* major adverse kidney events by 30 days

fluids may improve outcomes compared to 0.9% saline (Table 1) [8–15]. Although absolute benefit is likely to be small, given that millions require fluid resuscitation worldwide each year, even a high "number needed to treat" could translate to a substantial public health benefit. Recently, two large pragmatic trials totaling 29,149 adults demonstrated a small but significant reduction in adverse kidney events and death with use of buffered fluids, although these results were generally confined to patients with predicted mortality of ~ 20–50% [11, 12]. It is uncertain how generalizable these results may be, especially to the pediatric population with a lower ICU mortality. The two largest studies comparing buffered fluids and 0.9% saline in children are contradictory. We conducted a matched analysis of 4234 children with septic shock from 382 US hospitals and did not find superiority for either fluid for death, AKI, or dialysis [13]. In contrast, a propensity-matched analysis of 10,318 septic PICU patients from 43 US hospitals reported 2.1% lower mortality and 0.9% less frequent dialysis with buffered fluids [8]. Reflecting this uncertainty, pediatric sepsis guidelines have not yet prioritized any particular type of crystalloid fluid.

Should we adjust current clinical practice to minimize hyperchloremia? Unfortunately, the answer remains unclear, especially for children. Despite suggestions of benefit, there are some practical challenges to consider. Lactated Ringer's and Hartmann's solution are both hypotonic and have been shown to lower blood osmolality, increase brain water content, and transiently raise intracranial pressure [16]. Infants with a disproportionally large brain and patients with an injured blood–brain barrier may be at particularly high risk of cerebral edema with hypotonic buffered solutions. The presence of calcium may also lead to microvascular thromboses, and some patients with liver failure or very young age (< 6 months) may have a reduced ability to metabolize exogenous lactate. Moreover, patients randomized to receive lactated Ringer's for dengue fever were slower to recover from shock compared to saline [9]. More recent buffered formulations of Plasma-Lyte are limited by a cost that is several times that of other crystalloids and lack data about compatibility with other intravenous medications.

We agree with Barhight and colleagues that the time has come for a comparative effectiveness trial to "address the risks [and benefits] of 0.9% sodium chloride solution versus buffered fluid resuscitation in high-risk critically ill children." One hundred and eighty-six years since Dr. Latta's extraordinary observation, one such trial, the Pragmatic Pediatric Trial of Balanced vs Normal Saline Fluid in Sepsis (PRoMPT BOLUS) study, is underway (Clinicaltrials.gov NCT03340805) with plans for a larger multicenter trial to follow.

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Compliance with ethical standards

Conflicts of interest
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