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Hyperchloremia is associated with complicated course and mortality in pediatric patients with septic shock

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Abstract

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Objective—Hyperchloremia is associated with poor outcome among critically ill adults, but it is unknown if a similar association exists among critically ill children. We determined if hyperchloremia is associated with poor outcomes in children with septic shock.

Design—Retrospective analysis of a pediatric septic shock database.

Setting—Twenty-nine pediatric intensive care units in the United States

Patients—Eight hundred and ninety children ≤ 10 years of age with septic shock.

Interventions—None.

Measurements and Main Results—We considered the minimum, maximum, and mean chloride values during the initial seven days of septic shock for each study subject as separate hyperchloremia variables. Within each category, we considered hyperchloremia as a dichotomous variable defined as a serum concentration ≥110 mmol/L. We used multivariable logistic regression to determine the association between the hyperchloremia variables and outcome, adjusted for illness severity. We considered all cause 28-day mortality and complicated course as the primary outcome variables. Complicated course was defined as mortality by 28 days or persistence of ≥2 organ failures at day 7 of septic shock. Secondarily, we conducted a stratified analysis using a biomarker-based mortality risk stratification tool. There were 226 (25%) patients with a complicated course and 93 (10%) mortalities. Seventy patients had a minimum chloride ≥110 mmol/L, 179 had a mean chloride ≥110 mmol/L, and 514 had a maximum chloride ≥110 mmol/L. A minimum chloride ≥110 mmol/L was associated with increased odds of complicated course (O.R. 1.9, 95% C.I. 1.1 – 3.2, p = 0.023) and mortality (O.R. 3.7, 95% C.I. 2.0 – 6.8, p < 0.001). A mean chloride ≥110 mmol/L was also associated with increased odds of mortality (O.R. 2.1, 95% C.I. 1.3 – 3.5, p = 0.002). The secondary analysis yielded similar results.

Conclusion—Hyperchloremia is independently associated with poor outcomes among children with septic shock.

Keywords

Septic Shock; Sepsis; Chloride; Hyperchloremia; Mortality

Introduction

A growing body of evidence shows that hyperchloremia is associated with worse outcomes in the adult critically ill population. [1]. In post-operative patients, hyperchloremia has been associated with increased morbidity and mortality [2, 3]. In addition, hyperchloremia in patients with sepsis is associated with increased acute kidney injury and worsening morbidity and mortality [4–10]. It is currently unknown whether hyperchloremia is also detrimental in critically ill children.

In the pediatric population, septic shock is a major cause of morbidity and mortality [11]. Children with septic shock are at risk for hyperchloremia because standard of care includes aggressive volume resuscitation with crystalloid solutions to expand intravascular volume [12]. The most frequently used crystalloid solution is 0.9% NaCl [13]. Since the amount of chloride in this solution is 154 mEq/L, it is considered supraphysiologic compared to the

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chloride content of plasma, which is around 100 mEq/L [14]. Resuscitation with unbalanced, chloride-rich solutions, such as 0.9% NaCl, was recently found to be associated with worse outcomes in pediatric patients[15].

The purpose of this study was to test the hypothesis that hyperchloremia is associated with poor outcomes in pediatric patients with septic shock, after taking illness severity into consideration. Secondarily, we sought to determine if the association between hyperchloremia and poor outcomes is dependent on baseline risk of mortality, as determined by the Pediatric Sepsis Biomarker Risk Model (PERSEVERE) [16].

Materials and Methods

Study and Data Collection

Subjects were part of an ongoing, 29 center epidemiologic and genomic study of patients admitted with septic shock (n = 890). This was a retrospective analysis; the ongoing study was approved by Institutional Review Boards at each participating institution. The protocol has been previously described [17–28]. After obtaining informed consent, blood samples were obtained within 24 hours of PICU admission and clinical and laboratory data were collected daily based on each institution's standard of care. Mortality within 28 days of admission and organ failure were assessed for each subject.

Hyperchloremia variables

Subjects with at least three chloride values during the initial 7 days of PICU admission were included in the analysis. If a subject had more than one value per day, the highest of these values was used in calculations. From these daily values, we extracted the minimum, mean, and maximum chloride values for the initial 7 days of PICU admission. We considered these values for each study subject as separate hyperchloremia variables. Within each category, we considered hyperchloremia as a dichotomous variable defined as a serum concentration ≥110 mmol/L. This cut-off was chosen *a priori* based on our laboratory's upper limit of normal. Adult data used this same cut-off when evaluating the effect of hyperchloremia on critically ill septic patients [7]. We also performed a secondary analysis treating chloride as a continuous variable.

Stratification

Subjects were stratified using PERSEVERE, which assesses the baseline risk of 28-day mortality among children with sepsis [16]. The PERSEVERE biomarkers and the method for calculating baseline risk of mortality were previously published. Of the 890 initial subjects, 687 (77%) had PERSEVERE data available. The remaining 203 subjects had no PERSEVERE data available as there was no remaining serum to allow for biomarker testing.

Data Analysis

Statistical analyses were performed using SigmaPlot Software (Systat Software, Inc., San Jose, CA). The clinical characteristics between the study groups are presented as median, frequencies, and percent[29].

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We used logistic regression to estimate the odds of poor outcome associated with hyperchloremia. We adjusted for illness severity using the Pediatric Risk of Mortality (PRISM)-III score. In a secondary analysis, we used PERSEVERE to adjust for baseline risk of mortality.

There were two outcomes of interest: 28-day mortality and complicated course. The term “complicated course” has been previously described, and is defined as either death by 28 days or ≥ 2 organ failures at 7 days after meeting criteria for septic shock [30]. A p-value of <0.05 was considered to be statistically significant for all analyses.

Results

Demographics and Clinical Characteristics

There were 890 children included, of which 514 subjects had a maximum chloride ≥ 110 mmol/L, 179 had a mean chloride ≥ 110 mmol/L, and 70 had a minimum chloride ≥ 110 mmol/L. Table 1 compares the subjects with a complicated course (n=226) and subjects without a complicated course (n=664). Patients with a complicated course had a significantly higher PRISM-III score, a higher PERSEVERE-based mortality probability, and a smaller proportion had culture-negative sepsis. No other differences were noted.

Supplemental table 1 shows the difference between minimum chloride values, PRISM-III scores, and PERSEVERE risk of mortality scores based on center.

Table 2 compares the 93 subjects who were non-survivors with the 797 patients who were survivors. Similar to the subjects with complicated course, non-survivors had a significantly higher PRISM-III score, a higher PERSEVERE-based mortality probability, and a smaller proportion had culture-negative sepsis.

Patients with PERSEVERE data were compared to patients without PERSEVERE data. Patients with PERSEVERE data had a significantly higher rate of viral infections (Supplemental Table 2). No other differences were noted.

Association between Hyperchloremia and Outcomes

The three hyperchloremia variables were moderately correlated with each other: maximum versus minimum chloride ($r = 0.250$, $p < 0.001$); maximum versus mean chloride ($r = 0.429$, $p < 0.001$); and minimum versus mean chloride ($R = 0.582$, $p < 0.001$). Because of this co-linearity, we considered the three hyperchloremia variables separately in the logistic regression procedures.

Table 3 shows the results of logistic regression testing for an association between hyperchloremia and complicated course. A minimum chloride ≥ 110 mmol/L was independently associated with increased odds of complicated course (OR 1.9, 95% CI 1.1–3.2). A maximum or mean chloride ≥ 110 mmol/L was not associated with complicated course.

Table 4 shows the results of logistic regression testing for an association between hyperchloremia and mortality. A minimum chloride ≥ 110 mmol/L (OR 3.7, 95% CI 2.0–

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6.8) and a mean chloride ≥110 mmol/L (OR 2.1, 95% CI 1.3–3.5) were independently associated with increased risk of mortality. A maximum chloride ≥ 110 mmol/L was not associated with increased odds of mortality.

Association between Hyperchloremia and Outcomes in PERSEVERE Stratified Patients

There were 687 subjects (77%) with available PERSEVERE data. Table 5 shows the results of logistic regression testing for an association between hyperchloremia and complicated course, and hyperchloremia and mortality, after adjustment for baseline mortality probability, as estimated by PERSEVERE. A minimum chloride ≥110 mmol/L was associated with increased odds of complicated course (OR 1.9, 95% CI 1.0–3.4). A minimum chloride ≥ 110 mmol/L (OR 4.1, 95% CI 2.1–8.1) and mean chloride ≥ 110 mmol/L (OR 2.3, 95% CI 1.3–3.9) were associated with increased risk of mortality.

Chloride as a Continuous Variable

There was no association with between chloride values and complicated course when treating chloride as a continuous variable. However, there was an association between continuous chloride values and mortality. When adjusting for PRISM-III scores, the minimum chloride had an OR of 1.04 (95% CI 1.01–1.07, p-value 0.022). There was a similar association when using PERSEVERE to stratify baseline mortality risk (OR 1.04, 95% CI 1.01–1.08, p-value 0.026).

Discussion

This analysis explored the association between hyperchloremia and outcomes in a large, heterogeneous cohort of children with septic shock. Hyperchloremia was independently associated with increased risk for mortality and complicated course after adjusting for illness severity (PRISM-III). We saw similar results when adjusting for baseline mortality risk, as estimated by PERSEVERE.

Although mean chloride levels were not significantly different between patients with and without complicated course and between survivors and non-survivors, it appears that persistently elevated chloride levels, reflected by a minimum chloride concentration ≥110 mmol/L during the first 7 days of septic shock, are detrimental. Hyperchloremia may be injurious to a number of organ systems [7, 31–36], and these combined insults are potential contributors to the increased morbidity and mortality seen in these patients.

Adult septic patients with hyperchloremia were more likely to be anemic and require blood transfusions [7], and post-operative patients who received chloride-rich solutions had coagulation abnormalities and were more likely to bleed [34, 37]. Chloride may also affect the kidney by reducing velocity of renal blood flow and reducing renal cortical tissue perfusion [31]. Hyperchloremic acidosis is also associated with impaired cardiac contractility and hypotension[32], as well as reduced gastric blood flow [33].

Of particular interest in the sepsis population may be the effects of chloride on the immune system. Hyperchloremic metabolic acidosis induced an augmented pro-inflammatory response via increased interleukin (IL)-6 to IL-10 ratios in an *in vitro* cell model [36], as

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well as in animal models [35]. It is currently unknown whether these inflammatory responses are present in humans with hyperchloremia.

This growing evidence of the detrimental effects of hyperchloremia has led to discussions around the use of 0.9% NaCl for resuscitation, which is the current standard of care. 0.9% NaCl is neither normal nor physiologic and is associated with worse outcomes [38]. In adult trauma patients, the use of sodium acetate instead of 0.9% NaCl led to improvement of hyperchloremia with no ill effect on hemodynamics [39], and clinicians have argued that balanced crystalloid solutions may be superior to 0.9% NaCl for pediatric and adult septic patients [15, 40].

Although the association between outcomes and type of fluid has been examined, our study is the first to examine hyperchloremia itself in the pediatric septic population. It adds to the growing evidence from adult literature that hyperchloremia may be harmful in certain patient populations. The strengths of our study include its large sample size and the ability to control for illness severity in two independent ways: controlling for PRISM-III scores as well as controlling for baseline mortality risk using the PERSEVERE biomarkers.

Our study has limitations. First, our database did not reliably capture the type and amount of fluid used in resuscitation. Second, as an observational study the amount of fluid and the type of fluid used for resuscitation were not standardized. There are therefore multiple confounders that could affect our results. However, given that initial resuscitation with unbalanced crystalloid solution is standard of care, it is likely that this fluid was commonly used for these patients. In addition, we accounted for several confounders by considering illness severity and baseline mortality risk. Finally, this study only included patients ≤10 years of age with septic shock. It is unknown whether these findings will be true for older children and in other forms of critical illness.

Conclusions

In conclusion, hyperchloremia is common in children with septic shock and is independently associated with increased odds of poor outcome. Since the chloride composition in fluid differs, the degree of chloride load is a modifiable factor that may influence patient outcomes. Although we cannot conclude that this association reflects the type of fluid used for resuscitation, the data nonetheless suggest a continuing need for further evaluation of the optimal fluid to use in resuscitation of pediatric patients with septic shock.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical characteristics of patients with and without a complicated course.

Variable	Complicated Course (n=226)	Non-Complicated Course (n=664)	p-value
Median Age (IQR)	3.2 (0.8 – 7.6)	3.9 (1.4 – 8.1)	0.130
Male, n (%)	134 (59%)	360 (54%)	0.236
PRISM Score (IQR)	16 (10 – 23)	11 (6 – 15)	<0.001
Pediatric Sepsis Biomarker Risk Model Probability of Mortality (95% CI)	0.2 (0.2 – 0.2)	0.06 (0.05 – 0.07)	<0.0001
Mean Chloride ± S.D.	105.8 ± 6.4	105.7 ± 5.6	0.876
No. of patients with Gram-positive infection (%)	61 (27%)	143 (21%)	0.062
No. of patients with gram-negative infection (%)	57 (25%	141 (21%)	0.210
No. of patients with viral infection (%)	13 (6%)	31 (5%)	0.560
No. of patients with fungal infection (%)	7 (3%)	13 (2%)	0.382
No. of patients with mixed infection (%)	1 (1%)	4 (1%)	1
No. of patients with no organism identified (%)	86 (38%)	328 (49%)	0.004

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Table 2

Clinical Characteristics of survivors and non-survivors.

Variable	Non-Survivors (n=93)	Survivors (n=797)	p-value
Median Age (IQR)	4.2 (0.8 – 8.7)	3.7 (1.2 – 8.0)	0.906
Male n (%)	58 (62%)	438 (55%)	0.160
PRISM Score (IQR)	19 (11 – 28)	11 (7 – 16)	<0.001
Pediatric Sepsis Biomarker Risk Model Probability of Mortality (95% CI)	0.3 (0.2 – 0.3)	0.08 (0.07 – 0.09)	<0.0001
Mean Chloride ± S.D.	106.8 ± 7.4	105.6 ± 5.6	0.063
No. of patients with Gram-positive infection (%)	25 (27%)	179 (22%)	0.275
No. of patients with gram-negative infection (%)	26 (28%)	172 (22%)	0.191
No. of patients with viral infection (%)	5 (5%)	39 (5%)	1
No. of patients with fungal infection (%)	2 (2%)	18 (2%)	1
No. of patients with mixed infection (%)	0 (0%)	5 (1%)	0.333
No. of patients with no organism identified (%)	34 (37%)	380 (48%)	0.044

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Table 3

Multivariable logistic regression testing for an association between hyperchloremia and complicated course.

Variable		O.R.	95% CI	p-value
Minimum Chloride ≥110 mmol/L		1.9	1.1–3.2	0.023
	PRISM	1.1	1.1–1.1	<0.001
Maximum Chloride ≥110 mmol/L		0.9	0.7–1.3	0.603
	PRISM	1.1	1.1–1.1	<0.001
Mean Chloride ≥110 mmol/L		1.3	0.9–1.8	0.221
	PRISM	1.1	1.1–1.1	<0.001

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Table 4

Multivariable logistic regression testing for an association between hyperchloremia and mortality.

Variable		O.R.	95% CI	p-value
Minimum Chloride ≥110 mmol/L		3.7	2.0–6.8	<0.001
	PRISM	1.1	1.1–1.1	<0.001
Maximum Chloride ≥110 mmol/L		1.2	0.7–1.9	0.483
	PRISM	1.1	1.1–1.1	<0.001
Mean Chloride ≥110 mmol/L		2.1	1.3–3.5	0.002
	PRISM	1.1	1.1–1.1	<0.001

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Table 5

Multivariable logistic regression testing for an association between hyperchloremia and complicated course (CC) or mortality, after adjusting for PERSEVERE-based risk of mortality.

Outcome	Variable	OR (95% CI)	P value
Complicated Course	Minimum Chloride ≥110 mmol/L	1.9 (1.0–3.4)	0.047
	Maximum Chloride ≥110 mmol/L	0.9 (0.6–1.3)	0.572
	Mean Chloride ≥110 mmol/L	1.3 (0.8–2.0)	0.223
Mortality	Minimum Chloride ≥110 mmol/L	4.1 (2.1–8.1)	<0.001
	Maximum Chloride ≥110 mmol/L	1.3 (0.7–2.1)	0.384
	Mean Chloride ≥110 mmol/L	2.3 (1.3–3.9)	0.003