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Association between Hyponatremia and Higher Bronchiolitis Severity among Children in the Intensive Care Unit with Bronchiolitis

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Abstract

Background—It remains unclear whether hyponatremia independently predicts a higher severity in children with bronchiolitis.

Objective—To investigate the association between hyponatremia and bronchiolitis severity in children hospitalized to the intensive care unit (ICU) for bronchiolitis.

Methods—We conducted a 16-center, prospective cohort study of hospitalized children age <2 years with bronchiolitis during the winters of 2007 to 2010. We classified patients into two groups: normonatremia (135–145 mEq/L) and hyponatremia (<135 mEq/L) based on the first-measured serum sodium concentration on the day of hospitalization. Outcomes were use of mechanical ventilation and ICU length-of-stay (LOS). To examine the association of sodium status with outcomes, we fit logistic and linear regression models with propensity score adjustment.

Results—Of 231 children hospitalized to the ICU for bronchiolitis, 193 patients (84%) were categorized into the normonatremia group, and 38 children (16%) into hyponatremia group. Compared to children with normonatremia, those with hyponatremia had higher risks of mechanical ventilation use (40% vs. 58%; $P=0.04$) and longer ICU LOS (median, 3 days vs. 6 days; $P=0.007$). Likewise, in the adjusted analyses, children with hyponatremia had significantly higher risks of mechanical ventilation use (OR, 2.14; 95%CI, 1.03–4.48; $P=0.04$) and longer ICU LOS (β -coefficient 2.21 days; 95%CI, 0.68–3.73 days; $P=0.003$).

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Conclusions—In this prospective, multicenter study of children hospitalized for bronchiolitis, hyponatremia on the day of hospitalization was associated with a higher severity. Our data support hyponatremia as a prognostic factor that might improve the ability of clinicians to predict the disease course of children with severe bronchiolitis.

Keywords

bronchiolitis; hyponatremia; intensive care unit; mechanical ventilation; length of stay

INTRODUCTION

Bronchiolitis is the leading cause of hospitalization in infants, accounting for 18% of all infant hospitalizations in the US — 129,000 hospitalizations in 2009.¹ Approximately 10%-15% of these children require intensive care.^{2, 3} Despite the substantial burden of this life-threatening bronchiolitis, clinicians continue to struggle with predictions about the disease course and the appropriate level of care for these children. Prior studies document marked variability in acute management,⁴ highlighting the need for evidence-based assessments. Two single-center retrospective studies of children hospitalized to the intensive care unit (ICU) reported unadjusted associations between hyponatremia — the most common electrolyte abnormality in ICUs — and more severe disease course.^{5, 6} However, these earlier studies were potentially limited by small sample sizes (n=102 and 59, respectively), confounding, and potential problems with generalizability. Additionally, prior studies of children with pneumonia also suggested associations of hyponatremia with higher severity of illness potentially through fluid shift to the lungs and syndrome of inappropriate secretion of antidiuretic hormone (SIADH).^{7, 8} Despite its clinical importance, it remains unclear whether hyponatremia independently predicts a higher severity in children with bronchiolitis.

To address this knowledge gap in the literature, using data from a multicenter prospective cohort study, we investigated the association between hyponatremia and higher bronchiolitis severity, as measured by use of mechanical ventilation and ICU length-of-stay (LOS), among 231 children hospitalized to the ICU for bronchiolitis.

METHODS

Design and Setting

This study was a planned secondary analysis of a prospective cohort study of children hospitalized with bronchiolitis. The study design, setting, participants, and methods of data collection have been reported previously.⁹⁻¹⁴ Briefly, we conducted this prospective cohort study at 16 sites across 12 US states during the 2007–2010 winter seasons, as part of the Multicenter Airway Research Collaboration (MARC). MARC is a program of the Emergency Medicine Network (EMNet) (www.emnet-usa.org), a collaboration with >225 participating hospitals. Site investigators enrolled a target number of consecutive patients from the inpatient wards and the ICU. We aimed to enroll 20% of the total sample from the ICU; to achieve this over sampling from the ICU, the ward and ICU enrollments were

monitored separately. All patients were managed at the discretion of the treating physician. The institutional review board at all participating hospitals approved the study.

Participants

We enrolled children aged <2 years who were hospitalized for an attending physician's diagnosis of bronchiolitis, and for whom the parent/guardian gave informed consent. Patients were enrolled within 18 hours of hospitalization. The exclusion criteria were previous enrollment or transfer to a participating hospital >48 hours after the original hospitalization time. For the purpose of this analysis, we identified all children hospitalized to the ICU on the first day of hospitalization.

Data Collection

Investigators conducted a structured interview that assessed patients' demographic characteristics, medical and environmental history, duration of symptoms, and details of the acute illness. Relevant comorbid medical disorders included respiratory, cardiac, neurologic, gastrointestinal, and immunologic diseases. Medical records were reviewed to obtain clinical data from the pre-admission evaluation (clinic or emergency department) and the child's inpatient course, including vital signs, medical management, and disposition. Data were manually reviewed at the EMNet Coordinating Center, and site investigators were queried about missing data and discrepancies identified.

Outcome Measure

The primary outcomes were use of mechanical ventilation (continuous positive airway pressure and/or intubation) and ICU LOS.

Statistical Analyses

Using the approach of Luu et al.,⁵ we classified patients into two sodium groups: normonatremia (135–145 mEq/L) and hyponatremia (<135 mEq/L) based on the first-measured serum sodium concentration on the day of hospitalization (80% during the ED visit). We compared patient demographic characteristics, medical history, and clinical course, by serum sodium status, using χ^2 or Wilcoxon-Mann-Whitney tests as appropriate.

To examine the association of serum sodium status with the outcomes, we fit multivariable logistic and linear regression models. Because of the relatively small number of hyponatremia cases, we used propensity score adjustment.¹⁵ The propensity score was created using a logistic regression model with sodium concentration status as the dependent variable, and included 12 potential confounding factors: age, sex, race/ethnicity, maternal smoking during pregnancy, gestational age, admission to ICU at birth, breast-fed, history of intubation, or wheezing, comorbid medical disorder, duration of difficulty breathing prior to the hospitalization, and viral pathogens. In a sensitivity analysis, we repeated the multivariable analysis using a more restrictive definition of bronchiolitis (i.e., those younger than 12 months and without history of wheezing). All P-values were two-tailed, with $P < 0.05$ considered statistically significant. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 2,207 enrolled children, 331 (15%) were hospitalized to the ICU on the day of hospitalization. Among these, 98 without sodium concentration measurement and 2 with hyponatremia (>145 mEq/L) were excluded, leaving 231 (70%) eligible for the current analysis. The analytic ($n=231$) and non-analytic ($n=100$) cohorts were similar in age, sex, medical history, disease presentation, and virology results (all $P>0.05$; Supplemental Table 1), but the analytic cohort was more likely to undergo mechanical ventilation and had a longer ICU LOS (both $P<0.001$).

Patient Characteristics and Disease Presentations

Of the 231 children in the analytic cohort, the median age was 3 months (interquartile range, 1–7 months), 58% were male, and 45% were non-Hispanic white. Among the analytic cohort, 193 patients (84%) were categorized into the normonatremia group (range, 135–145 mEq/L) and 38 children (16%) into the hyponatremia group (range, 118–134 mEq/L), based on the first-measured serum sodium concentration on the day of hospitalization. Compared to children with normonatremia, those with hyponatremia were more likely to be aged <2 months and female (both $P=0.06$; Table 1), although neither factor was statistically significant. There was no significant difference in demographic characteristics, medical history, or disease presentations between the two groups (all $P>0.05$).

Association of Sodium Status with Bronchiolitis Severity

In contrast, compared to children with normonatremia, those with hyponatremia had a higher risk of mechanical ventilation use (40% vs. 58%; $P=0.04$ by χ^2 test) and longer ICU LOS (median, 3 days vs. 6 days; $P=0.007$ by Wilcoxon-Mann-Whitney test; Table 1). Likewise, in multivariable analyses using propensity score (Table 2), children with hyponatremia continued to exhibit higher risks of mechanical ventilation use (OR, 2.14; 95% CI, 1.03–4.48; $P=0.04$) and longer ICU LOS (β -coefficient 2.21 days; 95% CI, 0.68–3.73 days; $P=0.005$). Moreover, the sensitivity analyses demonstrated that these significant associations persisted with the use of the stricter definition of bronchiolitis (both $P<0.05$; Table 2).

DISCUSSION

This multicenter prospective cohort study demonstrated that 16% of children hospitalized to the ICU for bronchiolitis had hyponatremia on the day of hospitalization. Consistent with two single-center retrospective studies,^{5, 6} our multicenter study with more than twice the sample size of the prior studies, demonstrated that children with hyponatremia had significantly higher risks of mechanical ventilation use and longer ICU LOS. Our data corroborate and build on the earlier reports of an association between hyponatremia and higher bronchiolitis severity, a finding of clinical and research importance.

While hyponatremia has long been recognized as a predictor of worse severity in critically ill adults,¹⁶ less is known about critically ill children.⁵ Underlying mechanisms are also not well understood. Hyponatremia may be causal in the development of severe illness through inappropriate fluid shift to lung parenchyma. Alternatively, hyponatremia may be simply a

marker of higher severity (e.g., hyponatremia secondary to increased antidiuretic hormone secretion, deficient sodium intake, or iatrogenic hypotonic fluid resuscitation associated with severe illnesses).¹⁷

Potential Limitations

We acknowledge several potential limitations. First, 30% of ICU patients did not have sodium data, and this is a potential source of bias. The higher proportion of children undergoing mechanical ventilation in the analytic cohort suggests that our study population was sicker than overall children hospitalized to the ICU for bronchiolitis. Second, despite an adjustment for important confounding factors with the propensity score analysis the observed association might be explained by unmeasured confounders, such as hypotonic fluid administration before serum sodium measurement. However, 80% of the first sodium measurement was performed during the ED visit, arguing against this confounding. Third, bronchiolitis is a clinical diagnosis without a common international definition. Therefore, it is possible that we included other respiratory illnesses, such as asthma, in this population. However, the significant association of hyponatremia with a higher risk of mechanical ventilation use and prolonged ICU LOS persisted even when the data were restricted to children with "classic" bronchiolitis (i.e., those younger than 12 months and without history of wheezing). Finally, our sample consisted of children hospitalized to the ICU in academic medical centers; therefore, our inferences may not be generalizable to the non-ICU setting or community hospitals. Nevertheless, our inferences are of direct relevance to thousands of U.S. children with bronchiolitis who require intensive care every year.¹⁻³

Conclusions

In sum, this large multicenter study of children with severe bronchiolitis demonstrated that those with hyponatremia had higher severity in the ICU – i.e., an increased risk of mechanical ventilation use and a longer ICU LOS. As research in bronchiolitis advances, critically ill children will be of particular interest. Our findings suggest that hyponatremia might be a readily-available clinical variable that improves the ability of clinicians to predict the disease course of children with severe bronchiolitis. These data should facilitate further prospective investigation of all children hospitalized to the ICU to validate our inference about hyponatremia as a prognostic factor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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We thank the MARC-30 investigators (Supplemental Table 2) for their ongoing dedication to bronchiolitis research.

Abbreviations

CI	confidence interval
ICU	intensive care unit

EMNet	Emergency Medicine Network
LOS	length-of-stay
MARC	Multicenter Airway Research Collaboration
OR	odds ratio

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Demographic Characteristics, Medical History, and Clinical Course of Children Admitted to the Intensive Care Unit with Bronchiolitis, by Serum Sodium Status

TABLE 1

Characteristics	Normonatremia, Na 135–145 mEq/L n=193	Hyponatremia, Na < 135 mEq/L n=38	P value*
Serum sodium concentration (mEq/L), mean ($\pm$ SD)	138 ($\pm$ 2)	131 ($\pm$ 3)	—
Demographics			
Age			0.06
<2 month	75 (39)	23 (61)	
2–5.9 months	54 (28)	9 (24)	
6–11.9 months	36 (19)	2 (5)	
12–23.9 months	28 (15)	4 (11)	
Female sex	75 (39)	21 (56)	0.06
Race/ethnicity			0.70
Non-Hispanic white	85 (44)	19 (50)	
Non-Hispanic black	30 (16)	5 (13)	
Hispanic	69 (36)	11 (29)	
Other	9 (5)	3 (8)	
Insurance			0.38
Non-private	131 (68)	23 (61)	
Private	62 (32)	15 (39)	
Medical history			
Maternal smoking during pregnancy			0.75
Gestational age			0.17
<32 weeks	10 (5)	2 (5)	
32–36 weeks	38 (20)	13 (34)	
37 weeks or “full term”	139 (72)	23 (61)	
Admission to ICU at birth	52 (27)	13 (34)	0.36
Breast-fed	105 (54)	19 (50)	0.62
History of intubation	22 (11)	6 (16)	0.42
History of wheezing	45 (23)	5 (13)	0.16
Major, relevant, comorbid medical disorder [†]	40 (21)	9 (24)	0.70

Characteristics	Normonatremia, Na 135–145 mEq/L n=193	Hyponatremia, Na < 135 mEq/L n=38	P value [*]
Clinical course			
When difficulty breathing began (pre-hospitalization)			0.34
1 day	58 (30)	15 (40)	
>1 day	132 (68)	21 (55)	
None	3 (2)	0 (0)	
Inadequate oral intake	131 (68)	27 (71)	0.80
Weight (kg), median (IQR)	5 (3–7)	4 (3–6)	0.15
Pulse (bpm), median (IQR)	174 (157–184)	171 (150–186)	0.66
Respiratory rate per minute, median (IQR)	52 (40–65)	50 (41–60)	0.58
Oxygen saturation on room air, median (IQR)	95 (89–98)	93 (83–98)	0.35
Virology			0.48
Sole RSV infection	95 (49)	20 (53)	
Sole rhinovirus infection	12 (6)	1 (3)	
RSV + rhinovirus	21 (11)	8 (21)	
RSV + any other non-rhinovirus pathogens	19 (10)	3 (8)	
Rhinovirus + any other non-RSV pathogens	10 (5)	1 (3)	
Neither RSV nor rhinovirus [‡]	36 (19)	5 (13)	
Hospital length of stay (days), median (IQR)	5 (3–8)	7 (5–14)	0.002
Outcomes			
Mechanical ventilation (intubation and/or CPAP)	77 (40)	22 (58)	0.04
ICU length-of-stay (days), median (IQR)	3 (2–6)	6 (3–9)	0.007

Abbreviations: bpm, beats per minute; CPAP, continuous positive airway pressure; ICU, intensive care unit; IQR, interquartile range; RSV, respiratory syncytial virus; SD, standard deviation.

Data were expressed as n (%) unless otherwise indicated.

^{*} Chi-square test or Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables.

[‡] Defined by respiratory, cardiac, neurologic, gastrointestinal, and immunologic diseases.

[‡] Included parainfluenza virus types 1, 2, and 3; influenza A, B, and the 2009 novel H1N1; human metapneumovirus; coronaviruses NL-65, HKU1, OC43, and 229E; enterovirus; adenovirus; M pneumoniae; B pertussis; and no pathogens identified from the testing panel

Unadjusted and Multivariable Associations between Serum Sodium Status and Clinical Outcomes among Children Admitted to the Intensive Care Unit with Bronchiolitis

Table 2

Models	Unadjusted			Adjusted with propensity score [*]			Sensitivity analysis [‡]		
Mechanical ventilation [‡]	OR (95% CI)	P value		OR (95% CI)	P value		OR (95% CI)	P value	
Normonatremia	Reference	-		Reference	-		Reference	-	
Hyponatremia	2.07 (1.02–4.19)	0.04		2.14 (1.03–4.48)	0.04		2.43 (1.04–5.67)	0.04	
ICU length-of-stay (days) [§]	β -coefficient (95% CI)	P value		β -coefficient (95% CI)	P value		β -coefficient (95% CI)	P value	
Normonatremia	Reference	-		Reference	-		Reference	-	
Hyponatremia	2.20 (0.75–3.66)	0.003		2.21 (0.68–3.73)	0.005		2.36 (0.63–4.10)	0.008	

CI, confidence interval; ICU, intensive care unit; OR, odds ratio

^{*} Propensity score adjustment for 12 potential confounding factors (age, sex, race/ethnicity, maternal smoking during pregnancy, gestational age, admission to ICU at birth, breast-fed, history of intubation, or wheezing, comorbid medical disorder, duration of difficulty breathing prior to the hospitalization, and viral co-infection status [RSV plus rhinovirus and RSV plus non-rhinovirus pathogens]).

[‡] Using the restrictive definition of children with bronchiolitis (i.e., those younger than 12 months and without history of wheezing) (n=162), with propensity score adjustment.

[§] Logistic regression models

[§] Linear regression models