Association Between Hyponatremia and Higher Bronchiolitis Severity Among Children in the ICU With Bronchiolitis

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ABSTRACT

BACKGROUND AND OBJECTIVES: It remains unclear whether hyponatremia independently predicts a higher severity of bronchiolitis in children. The objective of this study was to investigate the association between hyponatremia and bronchiolitis severity in children hospitalized in the ICU for bronchiolitis.

METHODS: We conducted a 16-center, prospective cohort study of hospitalized children aged <2 years with bronchiolitis during the winters of 2007 through 2010. Patients were classified into 2 groups (normonatremic [135–145 mEq/L] and hyponatremic [<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 in the ICU for bronchiolitis, 193 (84%) were categorized into the normonatremic group and 38 (16%) into the hyponatremic group. Compared with children with normonatremia, those with hyponatremia had higher risks of mechanical ventilation use (40% vs 58%; P = .04) and longer ICU LOS (median, 3 vs 6 days; P = .007). Likewise, in the adjusted analyses, children with hyponatremia had significantly higher risks of mechanical ventilation use (odds ratio, 2.14 [95% confidence interval, 1.03–4.48; P = .04]) and longer ICU LOS (bet-coefficient, 2.21 days [95% confidence interval, 0.68–3.73; P = .005]).

CONCLUSIONS: In this prospective, multicenter study of children hospitalized for bronchiolitis, hyponatremia on the day of hospitalization was associated with a higher severity of disease. 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.
Bronchiolitis is the leading cause of hospitalization in infants, accounting for 18% of all infant hospitalizations in the United States (ie, 129,000 hospitalizations) in 2009.1 Approximately 10% to 15% of these children require intensive care.2,3 Despite the substantial burden of this life-threatening disease, clinicians continue to struggle with predictions about the disease course and the appropriate level of care for these children. Previous studies have documented marked variability in acute course and the appropriate level of care for hospitalized in the ICU for bronchiolitis.

In a prospective cohort study and investigated the association between hyponatremia and length of stay (LOS), among 231 children hospitalized to the 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 (102 and 59 children, respectively), confounding, and potential problems with generalizability. In addition, earlier 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.7,8 Despite the clinical importance of hyponatremia, it remains unclear whether this condition independently predicts a higher severity in children with bronchiolitis. To address this knowledge gap in the literature, we used data from a multicenter prospective cohort study and 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 in 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.3–14 Briefly, this prospective cohort study was conducted at 16 sites across 12 US states during the 2007–2010 winter seasons, as part of MARC (Multicenter Airway Research Collaboration). MARC is a program of the Emergency Medicine Network (www.emnetusa.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 oversampling 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
Children aged <2 years were enrolled 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 within 18 hours of hospitalization. The purpose of the present 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 preadmission evaluation (clinic or emergency department) and the child’s inpatient course, including vital signs, medical management, and disposition. Data were manually reviewed at the Emergency Medicine Network Coordinating Center; site investigators were queried about missing data, and discrepancies were 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 patients were classified into 2 sodium groups (normonatremic [135–145 mEq/L] and hyponatremic [<135 mEq/L]) based on the first-measured serum sodium concentration on the day of hospitalization (80% during the emergency department visit). Patient demographic characteristics, medical history, and clinical course, according to serum sodium status, were compared by using χ² 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 cases of hyponatremia, propensity score adjustment was used.15 The propensity score was created by using a logistic regression model with sodium concentration status as the dependent variable, and it included 12 potential confounding factors: age, gender, 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 before the hospitalization, and viral pathogens. In a sensitivity analysis, the multivariable analysis was repeated by using a more restrictive definition of bronchiolitis (ie, those aged <12 months and with no history of wheezing). All P values were 2-tailed, with P < .05 considered statistically significant. All analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS
Of 2207 enrolled children, 331 (15%) were hospitalized in the ICU on the day of hospitalization. Among these, 98 children with no sodium concentration measurement and 2 with hypernatremia (>145 mEq/L) were excluded, leaving 231 (70%) children eligible for the present analysis. The analytic (n = 231) and nonanalytic (n = 100) cohorts were similar in age, gender, medical history, disease presentation, and virology test results (all P > .05) (Supplemental Table 3), but the analytic cohort was more likely to undergo
mechanical ventilation and had a longer ICU LOS (both, \( P < .001 \)).

**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 normonatremic group (range, 135–145 mEq/L) and 38 children (16%) into the hyponatremic group (range, 118–134 mEq/L), based on the first-measured serum sodium concentration on the day of hospitalization. Compared with children with normonatremia, those with hyponatremia were more likely to be aged <2 months and female (both, \( P = .06 \)) (Table 1), although neither factor was statistically significant. There was no significant difference in demographic characteristics, medical history, or disease presentations between the 2 groups (all, \( P > .05 \)).

**Association of Sodium Status With Bronchiolitis Severity**

Children with hyponatremia (compared with those with normonatremia) had a higher risk of mechanical ventilation use (40% vs 58%; \( P = .04 \) by \( \chi^2 \) test) and longer ICU LOS (median, 3 vs 6 days; \( P = .007 \) according to the Wilcoxon-Mann-Whitney test) (Table 1). Likewise, in multivariable analyses using propensity scores (Table 2), children with hyponatremia continued to exhibit higher risks of mechanical ventilation use (odds ratio, 2.14 [95% confidence interval, 1.03–4.48]; \( P = .04 \)) and longer ICU LOS (beta-coefficient, 2.21 days [95% confidence interval, 0.68–3.73; \( P = .005 \)). Moreover, the sensitivity analyses showed that these significant associations persisted with the use of the stricter definition of bronchiolitis (both, \( P < .05 \)).

**DISCUSSION**

This multicenter prospective cohort study found that 16% of children hospitalized to the ICU for bronchiolitis had hyponatremia on the day of hospitalization. Consistent with 2 single-center retrospective studies, the multicenter study (with more than twice the sample size of the previous studies) showed...
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. Although hyponatremia has long been recognized as a predictor of worse severity,16 less is known about this condition in 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, it may simply be a marker of higher severity, such as hyponatremia secondary to increased antidiuretic hormone secretion, deficient sodium intake, or iatrogenic hypotonic fluid resuscitation associated with severe illnesses.17 We acknowledge several potential limitations of this study. First, 30% of ICU patients did not have sodium data, and this absence 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 children hospitalized to the ICU for bronchiolitis overall. 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 emergency department visit, arguing against this confounding. Third, bronchiolitis is a clinical diagnosis with no common international definition. Therefore, it is possible that other respiratory illnesses, such as asthma, were included 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 (ie, those aged <12 months and with no 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 to community hospitals. Nevertheless, our inferences are of direct relevance to the thousands of US children with bronchiolitis who require intensive care every year.1–5

**CONCLUSIONS**

This large, multicenter study of children with severe bronchiolitis found that those with hyponatremia had higher severity of illness in the ICU (ie, an increased risk of mechanical ventilation use, 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

**TABLE 1 Continued**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normonatremia: Serum Sodium 135–145 mEq/L (n = 193)</th>
<th>Hyponatremia: Serum Sodium &lt;135 mEq/L (n = 38)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital LOS, median (IQR), d</td>
<td>5 (3–8)</td>
<td>7 (5–14)</td>
<td>.002</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation (intubation and/or CPAP)</td>
<td>77 (40)</td>
<td>22 (58)</td>
<td>.04</td>
</tr>
<tr>
<td>ICU LOS, median (IQR), d</td>
<td>3 (2–6)</td>
<td>6 (3–9)</td>
<td>.007</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are presented as n (%). CPAP, continuous positive airway pressure; IQR, interquartile range; RSV, respiratory syncytial virus.

* The χ² test or Fisher’s exact test was used for categorical variables, and the Wilcoxon-Mann-Whitney U test was used for continuous variables.

† Defined according to 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; Mycoplasma pneumoniae, Bordetella pertussis, and no pathogens identified from the testing panel.

**TABLE 2 Unadjusted and Multivariable Associations Between Serum Sodium Status and Clinical Outcomes Among Children Admitted to the ICU With Bronchiolitis**

<table>
<thead>
<tr>
<th>Models</th>
<th>Unadjusted</th>
<th>Adjusted With Propensity Score*</th>
<th>Sensitivity Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Ref</td>
<td>—</td>
<td>Ref</td>
</tr>
<tr>
<td>Normonatremia</td>
<td>2.07 (1.02–4.19)</td>
<td>.04</td>
<td>2.14 (1.03–4.48)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU LOS, d</td>
<td>β-coefficient (95% CI)</td>
<td>P</td>
<td>β-coefficient (95% CI)</td>
</tr>
<tr>
<td>Normonatremia</td>
<td>Ref</td>
<td>—</td>
<td>Ref</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2.20 (0.75–3.66)</td>
<td>.003</td>
<td>2.21 (0.68–3.73)</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

* Propensity score adjustment for 12 potential confounding factors (age, gender, 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 before the hospitalization, and viral coinfection status [respiratory syncytial virus plus rhinovirus pathogens and respiratory syncytial virus plus non-rhinovirus pathogens]).

† Logistic regression models.

‡ Linear regression models.
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.

Acknowledgment
We thank the MARC-30 investigators (Supplemental Table 4) for their ongoing dedication to bronchiolitis research.

REFERENCES
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