Original Article

Hyponatremia as Predictor of Adverse Outcome in Children with acute Lower Respiratory Tract Infections

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Abstract

Background: Lower respiratory tract infection is one of the major causes of mortality in children with estimated one million deaths every year. Hyponatremia is the most common electrolyte abnormality seen in lower respiratory tract infection. **Objectives:** To assess the impact of hyponatremia on morbidity and the course of illness in patients with acute lower respiratory tract infection. **Materials and Methods:** This prospective analytic study was conducted at the Child's Central Teaching Hospital from 1st December 2021 to 1st of October 2022. The study sample included 120 patients between 1- 168 month. Data on demographics, clinical status, biochemical status, and radiological findings were collected on admission. Follow-up serum sodium was carried out at 24 hours and 48 hours after admission. **Result:** The median age was 12 months old. The males were 51%. 5% of patients required respiratory care unit admission and endotracheal tube intubation; however, all patients were fully recovered. Concerning chest X- ray findings, the diagnosis of pneumonia was found in 67%; bronchiolitis in 27%; Empyema in 7% of cases. Hyponatremia in general and severe hyponatremia in particular were associated with higher duration of dyspnea (P-value <0.001), higher duration of oxygen requirement (P-value <0.001), longer time to effervescence (P-value = 0.02). **Conclusion:** In this study revealed that hyponatremia in general and severe hyponatremia in particular could adversely affect the morbidity in children with acute lower respiratory tract infection in terms of duration of hospitalization, duration of dyspnea, duration till effervescence, and duration of oxygen requirement.

Keyword: Hyponatremia, acute Lower Respiratory Tract Infections, chest X- ray

Introduction

Acute respiratory infections (ARIs) are the major cause of mortality among children aged less than 5 years. LRTI along with pneumonia a disease of developing countries, have an incidence of about 20–30% in developing countries as compared to 3–4% in developed countries [1]. Worldwide, 1 million (16%) of mortality among children aged less than 5 years is attributed to respiratory tract infections predominantly pneumonia associated [2]. The most important risk factors for ARIs are bottle feeding , malnutrition, low birth weight, absence of measles vaccination in children under age one year, zinc and vitamin A deficiency, concomitant diseases (e.g. asthma, heart disease and diarrhea), low level of the mother's education, poor socioeconomic status, indoor crowding, air pollution, parental smoking, humidity and cold weather [3,4]. Chest radiography is routinely used to confirm the diagnosis of CAP in the developed world. It may reveal complications requiring intervention or

prolonged antibiotic therapy (eg, effusion, abscess) or findings suggestive of certain etiologies (eg, pneumatoceles in staphylococcal pneumonia) [5]. Culture-based methods from normally sterile sites are insensitive for bacterial pneumonia. Less than 10% of children with blood cultures obtained yield a causative pathogen [6]. Moreover, nonpathogenic contaminants are recovered frequently. Pleural fluid cultures are more commonly positive (10%–25% of cases) despite nearly always being collected after initiation of antimicrobial therapy, presumably due to higher concentrations of organisms as well as prolonged time to sterilization compared with blood [7]. Fluids and electrolytes are the main pillars in the maintenance of body homeostasis. Hyponatremia is the most common electrolyte abnormality seen with an incidence as high as 30% in some reports [8-10]. Hyponatremia associated with pediatric pneumonia is most commonly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [11,12]. Hyponatremia associated with bronchiolitis is due to hyperinflation of the lungs. Hyperinflation reduces blood flow to the right atrium and stimulates the release of vasopressin (AVP) from the posterior pituitary causing accumulation of intravascular fluid leading to dilutional hyponatremia [13]. Several studies showed that inflammatory cytokines particularly interleukin (IL-6) and IL-1β are involved in the development of hyponatremia [14,15]. The aim of this study is to assess the impact of hyponatremia and its severity effect on morbidity and the course of illness in patients with acute lower respiratory tract infection.

Materials and Methods

Study design and settings

This prospective analytic study was conducted at the pediatric emergency room, pediatric ward, and pediatric intensive care unit of Child's Central Teaching Hospital, Baghdad from 1st December 2021 to 1st of October 2022. One hundred and twenty patients with LRTI were included for this study.

Data collection

Detailed medical history and clinical examination were conducted on all patients. Clinical data such as age, sex, duration of symptoms, and duration of hospitalization was collected. Laboratory data acquired at admission, included: complete blood cell counts, erythrocyte sedimentation rate (ESR), C-reactive protein, serum electrolytes (sodium, & potassium), renal function testing (blood urea and creatinine), and pCO2. Follow-up serum sodium was carried out at 24 hours and 48 hours after admission. A chest X-ray was performed on all patients and was interpreted by the hospital's radiologists. Daily follow-up was done to find out the need for respiratory support, duration of hypoxia resolution, duration to fever-free, duration of antibiotic use, type and amount of fluid given, total duration of hospitalization, and outcome of the patients. Hyponatremia was defined as a serum sodium concentration (Na+) <135 mEq/L. furthermore, the severity of hyponatremia was classified into mild hyponatremia (131-135 mEq /L), moderate hyponatremia (126-130 mEq/L), and severe hyponatremia (<125 mEq/L).

Inclusion criteria

The study included children between 1- 168 month who had cough for less than 2 weeks In addition to fast breathing and chest in drawing and fever. Chest X-ray finding of LRTI is crucial to be included. It also included children who had Pediatric respiratory severity score (PRESS) of 2-3 or 4-5.

Exclusion criteria

Children with other co-morbidities that may alter the serum electrolyte level were excluded from this study. For instance, children who were a known case of congenital heart disease, renal disease, endocrine disease. Moreover, children were excluded if they had a history of recent surgery, acute gastroenteritis and meningitis. Other exclusion criteria are cystic fibrosis and chromosomal or genetic disorders (Gitelman's syndrome).

Statistical analysis

Depending on whether the distribution was normal or skewed, continuous variables were expressed as means and standard deviations or medians with interquartile ranges (IQRs). Categorical variables were expressed as percentages. The Welch's t-test & ANOVA (for normally distributed variables) and Wilcoxon rank sum & Kruskal-Wallis (for non-normally distributed variables) were performed. The difference between categorical variables was investigated using either the $\chi 2$ test or Fisher's exact test, depending on the context. Univariate logistic regression analysis was performed to assess the risk of hyponatremia. A P-value less than 0.05 was considered statistically significant. R software was used for data processing, administration, and statistical analysis ("R version 4.1.3, R Foundation for Statistical Computing, Vienna, and Austria").

Ethical statement

Ethical and scientific approval for the research was obtained from the Scientific Committee at the Department of Pediatrics, Iraqi board for medical specialization. Verbal consent was obtained from all patients' parents before starting data collection and after explaining the aims of the study and assuring confidentiality.

Results

One hundred twenty patients with Lower respiratory tract infections were included in this study. The median (IQR) age was 12 (2.9 - 29.7) months old. The male proportion was 51% and a female was 49%. Five percent of patients required RCU admission and endotracheal tube intubation, however all patients fully recovered. Concerning CXR findings, the diagnosis of pneumonia was found in 67%, bronchiolitis in 27%, Empyema in 7% of cases. The amount of fluid used in all patients was 2/3 maintenance glucose saline. An 87.5% received ½ glucose saline.

Table 1: Descriptive statistics of age, sex, Clinical findings and type of fluids.

Characteristics	Total, N = 120[1]
Age, month	12 (2.9 - 29.7)
<12 months	57 (48%)
12-36 months	43 (36%)
>36 months	20 (17%)
Gender	
Male	61 (51%)
Female	59 (49%)
Duration of Dyspnoea (days)	4.9 ± 2.7
Duration of O_2 requirement (days)	5.6 ± 3.3
Time to defervescence (days)	2.7 ± 2.0
Antibiotics duration (days)	10.7 ± 5.6
Duration of hospitalization (days)	9.7 ± 5.2
Blood culture (positive)	10 (8%)
Type of Maintenance fluid used	
1/2 Glucose Saline	105 (87.5%)
1/5 Glucose saline	15 (12.5%)
Outcome, Recovery	120 (100%)
RCU admission and ETTI	6 (5%)
CXR findings	
Pneumonia	80 (66.6%)
Bronchiolitis	32 (26.6%)
Empyema	8 (6.6%)

[1] Median (IQR); n (%); Mean ± SD

When comparing hyponatremia and normonatremia patients, a significant difference was found between the two groups regarding duration of dyspnea (P-value <0.001), duration of oxygen requirement (P-value <0.001), time to efferves-cence (P-value = 0.02), antibiotic duration (P-

value <0.001), duration of hospitalization (P-value <0.001). Eight cases with empyema all found to have hyponatremia.

Table 2: Age, sex, clinical findings, type of fluids used according to serum sodium status.

Characteristics	Hyponatremia N = 93[1]	Normonatremia N = 27[1]	P-value[2]
Age, month	11.4 (2.5 - 34.5)	12 (7.8 - 24)	0.7
<12 months	45 (48%)	12 (44%)	0.5
12-36 months	31 (33%)	12 (44%)	
>36 months	17 (18%)	3 (11%)	
Gender			
Male	50 (54%)	11 (41%)	0.2
Female	43 (46%)	16 (59%)	
Duration of Dyspnoea (days)	5.4 ± 2.9	3.2 ± 1.2	<0.001
Duration of O_2 requirement (days)	6.1 ± 3.5	3.7 ± 1.1	<0.001
Time to defervescence (days)	3.0 ± 2.2	1.8 ± 1.0	0.002
Antibiotics duration (days)	11.8 ± 5.7	6.3 ± 1.4	<0.001
Duration of hospitalization (days)	10.8 ± 5.5	6.1 ± 1.3	<0.001
Blood culture (positive)	10 (11%)	0 (0%)	0.11
Type of Maintenance fluid used			
1/2 Glucose Saline	82 (88.2%)	23 (85.2%)	0.7
1/5 Glucose saline	11 (11.8%)	4 (14.8%)	
RCU admission and ETTI	6 (6%)	0 (0%)	0.3
CXR findings			
Pneumonia	68 (73.1%)	12 (44.4%)	0.004
Bronchiolitis	17 (18.3%)	15 (55.6%)	<0.001
Empyema	8 (8.6%)	0 (0.0%)	<0.001

[1]Median (IQR); n (%); Mean ± SD

[2]Wilcoxon rank sum test; Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test

Regarding vital signs, the temperature was significantly higher (P-value = 0.03) and SpO2 measurement was significantly lower (P-value <0.001) in the hyponatremia group than normonatremia suggesting a more severe form of the disease in those with low Na+.

Table 3: Vital signs of patients according to serum sodium status.

Vital Signs	Total, N = 120[1]	Hyponatremia N = 93[1]	Normonatremia N = 27[1]	P-value[2]
Heart rate (beat/min)				
<12 months	129.9 ± 14.3	129.5 ± 15.1	131.4 ± 11.4	0.6
12-36 months	127.8 ± 16.7	129.7 ± 18.6	122.8 ± 8.9	0.11
>36 months	119.4 ± 21.0	123.1 ± 20.0	98.3 ± 14.4	0.07
Respiratory rate (breath/min)				
<12 months	65.2 ± 11.8	66.9 ± 11.1	58.8 ± 12.6	0.05
12-36 months	63.8 ± 13.5	65.5 ± 14.3	59.6 ± 10.6	0.2
>36 months	49.6 ± 17.2	52.1 ± 17.6	36.0 ± 0.0	0.002
Temperature (°C)	38.4 ± 1.1	38.5 ± 1.2	38.1 ± 0.5	0.033
SpO_2, %	90.5 ± 9.0	89.1 ± 9.7	95.6 ± 2.9	<0.001

[1] Mean ± SD

[2] Welch Two Sample t-test

The mean serum sodium was 126.9 ± 5.3 in hyponatremia group and 136.2 ± 1.5 mg/dL in normonatremia group. Blood urea, WBC count, CRP, and ESR values were significantly higher in the hyponatremia group when compared with the normonatremia group (P-value <0.05). pCO2 values were much lower in the hyponatremia group 28.4 ± 10 versus 34.0 ± 2.2 with a P-value of 0.001.

Table 4: serum electrolytes and blood biomarkers on admission in the total cohort and different sodium statuses.

Parameters at admission	Total, N = 120[1]	Hyponatremia N = 93[1]	Normonatremia N = 27[1]	P-value[2]
Serum Na^+ mg/dL	128.9 ± 6.1	126.9 ± 5.3	136.2 ± 1.5	<0.001
Serum K^+ mEq/L	4.2 ± 4.4	3.8 ± 2.3	4.0 ± 3.2	0.009
Blood urea mmol/L	5.6 ± 2.7	5.9 ± 2.8	4.4 ± 1.4	0.004
Serum creatinine mg/dL	1.3 (0.9 - 24)	1.4 (1 - 26.5)	1.1 (0.9 - 2)	0.13
WBC count	19.5 (15 - 25.8)	20.8 (16 - 26.8)	18 (14.9 - 19.2)	0.033
Neutrophil count (< 4 yr. old)	75 (66 - 90)	80 (70 - 90)	68.0 (60.0 - 80.0)	0.012
Neutrophil count (> 4 yr. old)	80 (63.5 - 80)	79 (57 - 80)	80 (80 - 83)	0.15
C-reactive protein mg/dL	41 (22 - 99)	54.5 (22 - 116)	28.0 (22.8 - 36)	0.014
ESR, mm/hr	15 (6.2 - 34.2)	24 (8 - 36)	8.0 (5.8 - 12.8)	0.009
Random blood sugar, mg/dL	64 (6 - 81)	60.5 (6 - 78)	80.5 (40.2 - 83.8)	0.13

Urine specific gravity	1.017 ± 0.012	1.016 ± 0.009	1.019 ± 0.021	0.6
pCO_2, mmHg	29.6 ± 9.2	28.4 ± 10	34.0 ± 2.2	0.001

[1]Median (IQR); Mean ± SD
[2]Wilcoxon rank sum test; Welch Two Sample t-test.

The type of fluid used (1/2, 1/5 glucose saline) was compared with serial sodium measurements at admission, after 24 hours, and after 48 hours from admission. All three measurements show significant improvement in serum sodium levels over time.

Table 5: Serum sodium values at admission, 24 hours, and 48 hours after admission in patients who received different types of glucose saline.

Type of fluid used	Serum Na^+, Admission	Serum Na^+, After 24h	Serum Na^+, After 48h	P-value[1]
1/2 Glucose Saline	129.7 ± 4.4	134.7 ± 3.4	139.8 ± 2.8	<0.001
1/5 Glucose Saline	126.2 ± 6.3	133.0 ± 3.5	139.5 ± 2.6	<0.001

[1]Repeated Measure ANOVA test

A repeated measure ANOVA test with sphericity correction and Bonferroni adjustment was used to check the mean difference between serial sodium measurements. Serum sodium levels were significantly improved from admission, to 24 hours to 48 hours after admission (P-value <0.001).

Table 6: Comparison between the severity of hyponatremia and different patients' characteristics.

Characteristics	Mild N = 29[1]	Moderate N = 31[1]	Severe N = 33[1]	P-value[2]
Age, month	10.8 (2.4 - 30)	12 (3.7 - 27)	12 (2.6 - 36)	>0.9
Gender				
Male	10 (34%)	19 (61%)	21 (64%)	0.042
Female	19 (66%)	12 (39%)	12 (36%)	
Vital Signs				
Heart rate (beat/min)	121.4 ± 17.6	126.3 ± 11.8	138.2 ± 19.7	0.008
Respiratory rate (breath/min)	60.5 ± 13.6	59.6 ± 15.7	68.7 ± 15.8	0.12
Temperature (°C)	37.9 ± 1.2	38.5 ± 1.1	39.0 ± 1.1	0.008
SpO_2, %	94.2 ± 3.5	87.8 ± 14.5	86.3 ± 4.9	0.030
Duration of Dyspnoea (days)	3.9 ± 2.1	4.6 ± 2.0	7.3 ± 3.1	<0.001
Duration of O_2 requirement (days)	3.6 ± 1.7	5.3 ± 2.4	8.8 ± 3.7	<0.001
Time to defervescence (days)	1.9 ± 1.0	2.5 ± 1.4	4.3 ± 2.7	<0.001
Antibiotics duration (days)	7.5 ± 2.9	11.6 ± 4.7	15.5 ± 5.8	<0.001
Duration of hospitalization (days)	7.1 ± 2.7	9.7 ± 3.6	14.6 ± 6.2	<0.001
Blood culture (positive)	0 (0%)	5 (16%)	5 (15%)	0.060
Type of Maintenance fluid used				
1/2 Glucose Saline	29 (100.0%)	29 (93.5%)	24 (72.7%)	0.001
1/5 Glucose saline	0 (0.0%)	2 (6.5%)	9 (27.3%)	
RCU admission and ETTI	0 (0%)	0 (0%)	6 (18%)	0.003

[1]Median (IQR); n (%); Mean ± SD
[2]One-way ANOVA; Kruskal-Wallis test; Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test

Concerning the severity of hyponatremia. Heart rate, respiratory rate and temperature show a significant positive association with severity status. Also, the duration of dyspnoea, duration of O2 requirement, time of defervescence, antibiotics duration, and duration of hospitalization show a similar trend to vital signs P-value <0.01. Univariate logistic regression analysis was conducted in this research to assess the risk of hyponatremia and severe hyponatremia in patients with LRTI. CRP, WBC count, and duration of hospitalization increases the risk of hyponatremia and severe hyponatremia with a significant odds ratio.

Table 7: Univariate logistic regression analysis for the assessment of the risk of hyponatremia in children with respiratory infections.

Parameters at admission	Risk of Hyponatremia		Risk of severe hyponatremia	
	Odds ratio	P-value	Odds ratio	P-value
Age, months	1.00	0.7	1.00	0.6
Gender (Male)	0.89	0.8	2.08	0.2
CRP	1.03	0.014	1.02	<0.001
WBC	1.11	0.028	1.29	<0.001
Duration of hospitalization Days	1.46	0.004	1.41	<0.001

OR = Odds Ratio, CI = Confidence Interval

Discussion

Acute Lower respiratory tract infection is associated with electrolyte abnormalities like

hyponatremia, hypernatremia, hypokalemia, and hyperkalemia. Among them, hyponatremia is the most common electrolyte imbalance [16]. In the current study, the frequency of mild hyponatremia was reported to be 31%, moderate hyponatremia (33%), and severe hyponatremia (35%). Chaitra et al. [12] found that the prevalence of mild, moderate, and severe hyponatremia in India was (71%, 21%, and 7%, respectively); quite different from our results. This may be because most of the children presented late at our Child's Central Teaching Hospital. However, a cross-sectional study conducted by Nyambura et al. [13] at Kenyatta national hospital found that 40% of children had severe, 28% had moderate and 31% had mild hyponatremia similar to the result findings. In this study, the diagnosis of LRTI according to the CXR findings was pneumonia (67%), bronchiolitis (27%), and empyema (7%). Park et al. [14] cross -sectional study in Korea also found that pneumonia was the most common findings (50.5%) followed by bronchiolitis (18.4%). In the prospective cohort study by Chaitra et al. [12], they found that 66% of cases with LRTI had broncho-pneumonia, 7% had bronchiolitis, and 6% had empyema. No significant difference in the distribution of age was noticed between the hyponatremia and normonatremia group (P-value = 0.7). On the other hand, Park et al. [14] found that older children are more susceptible to the development of hyponatremia (OR = 1.007, P-value = 0.006). Similar to our study Sakellaropoulou et al. [15] found no gender difference in serum sodium status at admission. Six children (6.4%) in our study needed RCU admission and ETTI and all had severe hyponatremia (Na+ <125 mEq/L). In that study, children with hyponatremia had more risk of mechanical ventilation compared to children with normal sodium (58% vs 40%, p=0.04). Further consolidating our results Lamichhane et al. [17] in his study also found that 6 (7.5%) of cases needed mechanical ventilation and all were having hyponatremia. We found that out of 93 cases with hyponatremia, 29 (31%) of cases had mild hyponatremia on admission; 21 (33.3%) had moderate hyponatremia, and 33 (35.4%) had severe hyponatremia. Contrary to our results, Joshi et al. [18] found that most of the hyponatremia cases in their study were in mild hyponatremia 21 (77.78%) followed by moderate hyponatremia 5 (18.51%) and only one case (3.71%) was in severe hyponatremia. Also, in Chaitra et al. [12] study, a similar trend to Joshi et al. [18] study was found. A 29 (70.7) of the cases had mild hyponatremia, 9 (21.9%) had moderate hyponatremia, and 3 (7.3%) had severe hyponatremia. In this study, it was found that children with hyponatremia had prolonged hospital stay, and the time for resolution of hypoxia was longer compared to those with normal sodium levels (P-value <0.05). A similar result was reached by Lamichhane et al. [17] and Park et al. [14] studies. Both found a significantly high duration in the hyponatremia group. Hyponatremia was statistically associated with low oxygen saturation at presentation; however, Lamichhane et al. [17] study in Nepal didn’t find such a correlation, one possible reason is that they included 80 children with PRESS 4-5 score only in their study. pCO2 was found to be low in hyponatremia (mean = 34 mmHg, P-value = 0.001) and severe hyponatremia (mean = 24.9 mmHg, P-value = 0.056) suggesting a higher respiratory rate and thus more severe condition. Unadjusted logistic regression analysis in this study found that high CRP, high WBC count, and prolonged duration of hospitalization increase the risk for the development of hyponatremia and severe

hyponatremia. Park et al. [14] in a cross-sectional analysis of a cohort of 3938 patients reached a similar finding regarding CRP (odds ratio = 1.09, P-value <0.001) but not for WBC count (odds ratio = 1.003, P-value = 0.8) and hospital stay (odds ratio = 1.014, P-value = 0.07). The main limitation of this prospective study is that it included one non-homogeneous cohort of patients. Also, the single-center design and small sample size may limit the generalizability of the study results.

Conclusion

In this study, hyponatremia in general, and severe hyponatremia in particular, had a negative impact on morbidity in children with LRTI in terms of hospitalization time, dyspnea time, time till effervescence, and time required for oxygen. Increased WBC count, CRP, and ESR, as well as considerably low pCO2, indicate a more severe form of the disease and a degree of hyponatremia. Regular serum electrolyte checkup (especially serum sodium) in children with LRTI is important since its value can provide insight into the severity status of the illness. Moreover, longitudinal studies with a larger sample size and more than one center are recommended to study the impact of low sodium on mortality.

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