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Prevalence of Inappropriate Antidiuresis Syndrome and its Relationship with Clinical Outcome in Nigerian Children Hospitalised with Pneumonia

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Abstract

Background: Syndrome of Inappropriate Antidiuresis (SIAD) is a recognised complication of various clinical conditions, including pneumonia. However, its prevalence and impact on hospitalised children with pneumonia remain underexplored.

Objectives: To determine the prevalence of SIAD and its association with admission outcomes among children hospitalised for pneumonia.

Methods: A descriptive, cross-sectional study was conducted among 101 children aged 1 month to 14 years hospitalised with pneumonia. Data on socio-demographic, anthropometric, and clinical parameters were recorded using a semi-structured proforma. Blood and urine samples were analysed as required.

Results: The 101 children studied (median age 13.0 months [IQR 5-30]) had a male-to-female ratio of 1.9:1. Seventeen (16.8%), comprising 11 males and 6 females, were diagnosed with syndrome of inappropriate antidiuresis. Two patients, both with SIAD, died. Survivors with SIAD had a significantly longer median hospital stay of 7 days (IQR 3–15) compared to 3 days (IQR 2–6) in those without SIAD ($p = 0.016$).

Conclusion: This study shows that SIAD is a common occurrence among hospitalised children with pneumonia, and it is associated with prolonged hospital stay and increased risk of mortality. Early recognition and management of SIAD in this population may improve clinical outcomes.

Keywords: *Acute Respiratory Infection, Clinical outcome, Hyponatraemia, Osmolality, Syndrome of Inappropriate Antidiuresis.*

Introduction

Globally, pneumonia remains a leading cause of morbidity and mortality among children, making it the most common cause of death beyond the

neonatal period.¹⁻⁴ Each year, an estimated 138 million cases of pneumonia occur worldwide, with over 10% requiring hospitalisation.^{5,6} Children hospitalised with pneumonia are often

critically ill and at risk of complications such as heart failure, hypoxaemia, air leak syndrome, and the Syndrome of Inappropriate Antidiuresis (SIAD).

Syndrome of Inappropriate Antidiuresis is a clinical and biochemical disorder characterised by euvolaemic, hypo-osmolar hyponatraemia.⁷ The diagnosis of SIAD is one of exclusion, based on a set of criteria first proposed by Bartter and Schwartz as the classical criteria.⁸ However, the current, most widely accepted (for its structured exclusion of confounders) and evidence-based diagnostic criteria for SIAD are modifications of the classical criteria endorsed by the 2014 European clinical practice guidelines.⁹ Syndrome of Inappropriate Antidiuresis is a major cause of hyponatraemia, which itself is a frequent complication of pneumonia.¹⁰⁻¹⁵ While other pneumonia-related complications are well-documented, the role of SIAD in morbidity and mortality in pneumonia remains under-reported.

The link between pneumonia and SIAD was first identified by Stormont and Waterhouse in 1962.¹⁶ Since then, pneumonia-related hyponatraemia has outpaced studies of specific SIAD.¹⁷⁻¹⁹ Hospital-based studies from various regions report the prevalence of paediatric pneumonia-associated SIAD to be highly variable, ranging from about 25% to over 60% of patients who developed hyponatraemia.^{11,15,18,20,21} In Africa, and specifically Nigeria, while hyponatraemia is well-documented in up to 72% of children with pneumonia,²² the contribution of SIAD to the picture is likely significant but under-investigated due to diagnostic limitations. Given this knowledge gap, this study aimed to determine the prevalence and admission outcomes of SIAD in children hospitalised with pneumonia.

Methods

Study design

This was a hospital-based, descriptive, cross-sectional study conducted at the Emergency Paediatric Unit (EPU) of a tertiary hospital. The hospital serves as a referral centre for patients from Kwara and neighbouring states, including Oyo, Osun, Niger, Kogi, and Ekiti. The EPU, the primary admission point for paediatric cases, caters for children aged 1 month to 14 years.

Ethical considerations

Ethical clearance was obtained from the institution's Health Research Ethical Committee (approval number NHREC/02/05/2010 dated 30th August 2020). In addition, written informed consent and assent were obtained from the caregivers and the subjects.

Study population

The study population comprised children aged 1 month to 14 years who presented at the EPU with clinical features of pneumonia. A hundred and one subjects were recruited consecutively for the study.

Exclusion criteria

Excluded from the study were children who had clinical evidence of shock or dehydration requiring fluid boluses; a history of diuretic and/or corticosteroid use within the preceding 24 hours; known renal, liver, cardiac, thyroid, or adrenal diseases; subcutaneous oedema, ascites, or raised jugular venous pressure (JVP); severe acute malnutrition or meningitis; pneumonia with concurrent diarrhoea, and intravenous fluid administration within the last 48 hours.

Subject recruitment

Children aged one month to 14 years who presented at the EPU with clinical features of pneumonia, including cough lasting less than 28 days, difficult breathing, fever, tachypnoea (age-related increased respiratory rate), chest wall indrawing, and abnormal auscultatory findings (such as crepitation, reduced breath sound intensity, or bronchial breath sounds), were

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consecutively recruited.²³ The study spanned one year, from 31st August 2020 to 30th August 2021.

A semi-structured pro forma was used to collect socio-demographic and clinical information from subjects and caregivers. Clinical examinations were performed and verified by the EPU senior registrar and consultant, respectively, and findings were documented. Chest radiographs were taken within 24 hours of admission, interpreted by a consultant radiologist, and the findings were recorded.

At presentation, blood samples were drawn for serum sodium, serum osmolality, and random serum cortisol measurements. Urine samples were also obtained for analysis of urine sodium and urine osmolality. Serum and urine sodium levels were measured using direct Ion Selective Electrodes (ISE) (Genrui® GE300 semi-automated analyser). In contrast, serum and urine osmolality were determined using the OSMETTE™ Model 5005 automatic Osmometer (Precision Systems Inc., Natick, Massachusetts, USA). Random serum cortisol levels were measured using a cortisol ELISA kit (Calbiotech Inc., El Cajon, California, USA).

Syndrome of Inappropriate Antidiuresis was diagnosed based on fulfilment of all the following criteria:^{9,24}

Hyponatraemia: Serum sodium <135 mmol/L.

Hypo-osmolar state: Serum osmolality <275 mOsm/kg.

Inappropriate urinary concentration: Urine osmolality >100 mOsm/kg.

Increased urine sodium: Urine sodium >30 mmol/L with normal salt intake.

Clinical euvoaemia, defined by the absence of: Hypovolaemic signs (orthostatic hypotension, tachycardia, decreased skin turgor, dry mucous membranes and delayed capillary refill).

Hypervolaemic signs (subcutaneous oedema, ascites and raised Jugular Venous Pressure).

Exclusion of other conditions: No clinical features of hypothyroidism, secondary adrenal failure, or renal insufficiency.

Adrenal sufficiency confirmed: Random serum cortisol >552 nmol/L (>20 µg/dL).

Socioeconomic classification was computed based on Oyedeji's model.²⁵ All subjects received treatment in accordance with institutional guidelines.

Data analysis

Data were entered into SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) for analysis. Categorical variables were summarised using median and inter-quartile range, while mean and standard deviation were used to summarise continuous variables. A comparative analysis was conducted using Chi-square tests to examine the associations between categorical variables. Odds ratios (OR) and confidence intervals (CI) were calculated for statistically significant Chi-square outputs. Mann-Whitney U tests compared the median duration of hospitalisation and oxygen therapy among survivors with and without SIAD. A 95% confidence interval (CI) was applied, and statistical significance was set at $p < 0.05$.

Results

General characteristics of the subjects

A total of 101 eligible subjects completed the study. The median (IQR) age was 13.0 (5-30) months, with an age range of 1-168 months. Eighty-eight subjects (87.1%) were under 60 months of age. Males were predominant (66 subjects), resulting in a male-to-female ratio of 1.9:1. The mothers of 74 subjects (73.3%) had at least a secondary school education. Socioeconomic classification showed that 75.2% ($n = 76$) belonged to the upper and middle socioeconomic classes.²⁵ Using the WHO pneumonia severity classification, 59 subjects (58.4%) had severe pneumonia (Table I).

Table I: General characteristics of subjects

Variable	Frequency (n = 101)	Percentage (%)
Age group (months)		
1 - < 12	47	46.5
12 - < 60	41	40.6
≥ 60	13	12.9
Gender		
Male	66	65.3
Female	35	34.7
Socioeconomic class		
Upper	38	37.6
Middle	38	37.6
Lower	25	24.8
Pneumonia severity		
Severe	59	58.4
Very severe	42	41.6

Frequency distribution of SIAD diagnostic criteria

Among the 101 subjects evaluated, 17 had SIAD, with a prevalence rate of 16.8%. The frequency distribution of key diagnostic criteria of SIAD is presented in Table II. All the subjects were clinically euvolaemic and had normal renal function. The mean (SD, range) serum osmolality was 280.44 mOsm/kg (10.58, 259 – 306). Twenty-eight subjects (27.7%) had low serum osmolality (< 275 mOsm/kg), meeting the threshold for hypo-osmolality. The mean (SD, range) random serum cortisol level was 546.00 nmol/L (272.45, 19 – 1095). Fifty-three subjects (52.5%) had random serum cortisol levels exceeding 552 nmol/L, the defined cut-off for excluding adrenal insufficiency.

Immediate outcome of subjects with and without SIAD

Ninety-nine subjects (98.0%) recovered from the primary illness (pneumonia). Two subjects (2.0%) died, both within 12 hours of admission. The two subjects who died had oxygen therapy

and also had SIAD. No deaths occurred in subjects without SIAD.

The overall median (IQR) hospital stay was 3 (2 – 6) days. Survivors with SIAD had a significantly longer hospital stay (7 [3 – 15] days) compared to those without SIAD (3 [2 – 6] days) ($U = 388.000, p = 0.016$). Sixty per cent of SIAD survivors stayed beyond six days ($p = 0.002$) (Table III).

Thirteen (86.7%) of 15 SIAD survivors (86.7%) required supplemental oxygen, compared to 65 of 84 subjects without SIAD (77.4%). The median (IQR) oxygen therapy duration was 28.0 (0.0–524.3) hours. Although the median oxygen therapy duration was higher in SIAD survivors (52.5 [15.0 – 83.0] hours) than in those without SIAD (27.8 [5.1 – 45.1] hours), the difference was not statistically significant ($p = 0.192$) (Table III).

Discussion

The findings in this study suggest that the Syndrome of Inappropriate Antidiuresis (SIAD) in children hospitalised with pneumonia is common. The prevalence rate of 16.8% for SIAD in this study is comparable to 18.6% reported by Das & Narain in India.²⁶ However, it is significantly higher than the 3.3% reported in a study from Madrid, Spain.²⁰ This disparity may be due to differences in diagnostic criteria. This study used a urinary sodium threshold of >30 mmol/L, while the Spanish study used a higher cut-off of >40 mmol/L. Additionally, missing data in the Spanish study, where some subjects lacked serum osmolality or urine sodium values, may have contributed to the lower reported prevalence.

Conversely, the SIAD prevalence in this study is lower than the 30.0% reported by Guruswamy *et al.*^[27] in India. This may be due to differences in subject inclusion criteria: the present study excluded individuals with adrenal insufficiency, whereas the Indian study did not.

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Table II: Frequency distribution of SIAD diagnostic criteria

Laboratory values	SIAD present (n = 17)	SIAD absent (n = 84)
	Mean ± SD (range)	Mean ± SD (range)
Serum sodium (mmol/L)	< 135 (n=34) 130.24±2.71 (123-134)	≥ 135 (n=67) 138.95±3.54 (135-150)
Urine sodium (mmol/L)	> 30 (n=101) 70.26±7.53 (49-93)	≤ 30 (n=0) 0
Serum osmolality (mOsm/kg)	< 275 (n=28) 267.29±4.50 (259-274)	≥ 275 (n=73) 285.48±7.41 (275-306)
Random serum cortisol (nmol/L)	> 552 (n=53) 755.55±153.06 (553-1095)	≤ 552 (n=48) 314.63±166.80 (19-540)
Urine osmolality (mOsm/kg)	> 100 (n=101) 957.0 (795.5-990.5) [†] (150-1151)	≤ 100 (n=0) 0

[†]Median (IQR); IQR - Interquartile range

Table III: Bivariate analysis of length of hospitalisation and oxygen therapy among survivors with and without SIAD.

Variable	Total (%)	Survivors (n = 99)		OR (95%CI)	p-value
		SIAD present n (%)	SIAD absent n (%)		
Duration of hospital stay (days)					
>6	23(23.2%)	9 (60.0)	14 (16.7)	7.5 (2.30-24.45)	0.002
≤6	76(76.8%)	6 (40.0)	70 (83.3)		
Total	99(100.0%)	15 (100.0)	84 (100.0)		
Duration of oxygen therapy (hours)					
>48	28(35.9%)	8 (61.5)	20 (30.8)	3.6 (0.89-15.58)	0.077
≤48	50(64.1%)	5 (38.5)	45 (69.2)		
Total	78(100.0%)	13(100.0)	65(100.0)		

OR - Odds ratio; CI - Confidence Interval

Since secondary adrenal insufficiency can mimic SIAD due to preserved mineralocorticoid activity, its inclusion in the latter study likely confounded the results. Additionally, this study reported a lower prevalence (16.8%) than the 29.9% reported by Kumar *et al.*¹⁵ This could be due to differences in the age groups of the subjects studied. Whereas subjects aged one month to 14 years were studied in the current work, the Indian study was conducted among under-fives, the age group with the highest burden of pneumonia with its attendant complications.

This study also found that children with SIAD had significantly longer hospital stays than those without SIAD. This is consistent with the findings of Das & Narain,²⁶ who reported that SIAD was associated with prolonged hospitalisation, increased complications, and higher mortality. Although both mortalities in this study were among children with SIAD, there was no death among children without SIAD to enable comparison. However, this finding raises a critical concern and warrants further investigation. Furthermore, although the median

duration of oxygen therapy was not statistically significant, SIAD survivors showed a notable trend towards a longer duration. This suggests a clinically significant association that may have lacked statistical power due to the small size of the SIAD subgroup.

Strengths and limitations

A major strength of this study was strict adherence to the 2014 Joint European Clinical Practice Guidelines for diagnosing SIAD, which, because of its structured exclusion of confounders, represents the most accurate and widely used standard. However, the study was single-centred, and the relatively small number of SIAD cases may limit the generalisability of the findings. A multi-centre study with a larger sample size would provide a broader perspective on the burden and outcomes of SIAD in children with pneumonia.

Conclusion

This study highlights that SIAD is relatively common in children hospitalised with pneumonia

and significantly prolongs hospital stays. Given these findings, it is crucial for healthcare facilities, especially in resource-limited settings, to develop the capacity for early diagnosis and appropriate management of SIAD to improve patient outcomes.

Acknowledgement: The authors acknowledge the contributions of all consultants, residents, and the entire nursing staff of the EPU, and they remain grateful to the parents who consented to partake in this study.

Authors' Contributions: HAO and IRM conceived and designed the study. HAO conducted the literature review, data analysis, and interpretation, along with IRM, KOS, ITL, and AR. HAO drafted the manuscript, and IRM, KOS, ITL, SI, and AR revised it for sound intellectual content. All the authors approved the final version of the manuscript.

Conflicts of Interest: None declared.

Funding supports: The researchers did not receive any financial support for this research or for the preparation of the manuscript.

Accepted for publication: 21st November 2025.

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