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Hospital-acquired Hyponatremia in Children: Incidence and Association with Fluid and Sodium Supplementation

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Abstract

Hospital-acquired hyponatremia (HAH) is a common and preventable electrolyte disorder in hospitalized children, and its pathogenesis involves a complex interplay among fluid therapy, non-osmotic release of antidiuretic hormone, and underlying clinical conditions. This study aimed to determine the incidence of HAH at a tertiary pediatric center and to evaluate the relationship among intravenous fluid (IVF) composition, total fluid volume, and sodium supplementation. This prospective observational study included all pediatric inpatients admitted during a one-year period. Patients who were normonatremic on admission and received IVFs for at least 24 hours were monitored for the development of hyponatremia. At the time hyponatremia was detected, detailed clinical data, biochemical parameters [including urinary sodium and serum pro-B-type natriuretic peptide (proBNP) levels], total IVF intake, and oral/intravenous sodium supplementation were recorded, covering the previous 24 hours. The cohort was stratified into two age groups: younger than 100 days and older than 100 days. Among 8065 hospitalized children, 373 met the study criteria. The incidence of HAH was 4.6%. Hyponatremia occurred earlier in infants under 100 days of age (median 6 days) than in older patients (median 10.5 days), and moderate-to-severe hyponatremia was more frequent in the younger group. Urinary sodium excretion was elevated in most patients, particularly in those older than 100 days. Nearly half of infants who received only IVF developed moderate-to-severe hyponatremia, and 35.8% of these infants received sodium supplementation below physiological requirements. Serum sodium showed a positive correlation with age and inverse correlations with blood urea nitrogen, creatinine, and proBNP levels; no association was found between serum sodium and total IVF volume. In conclusion, HAH remains an important clinical problem, particularly in neonates, critically ill children, and oncology patients. Inadequate sodium supplementation—especially in young infants—appears to contribute to hyponatremia, even in the absence of fluid overload. These findings underscore the importance of individualized fluid prescriptions, routine electrolyte monitoring, and adherence to isotonic fluid strategies to prevent iatrogenic hyponatremia in hospitalized children.

Keywords: Hospital-acquired hyponatremia, intravenous fluids, sodium, SIADH, pediatrics

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Introduction

Hyponatremia is defined as a serum sodium level below 135 mEq/L and is one of the most common electrolyte abnormalities in children[1]. Sodium differs from other electrolytes because its concentration is adjusted by water balance. Increased sodium concentration raises plasma osmolality and thereby stimulates release of antidiuretic hormone (ADH), which regulates thirst and renal water excretion. Conversely, low serum sodium concentration decreases plasma osmolality and suppresses ADH secretion[1,2].

Highlights

- Hospital-acquired hyponatremia (HAH) is a common and preventable electrolyte disorder.
- Hyponatremia was more frequent and more severe in infants younger than 100 days.
- Inadequate sodium supplementation contributed to hyponatremia, especially in neonates.
- Serum sodium correlated negatively with blood urea nitrogen, creatinine, and pro-B-type natriuretic peptide levels.
- Careful sodium monitoring and isotonic-fluid management strategies are essential to prevent HAH.

The majority of hyponatremia cases are hospital-acquired[3]. Hyponatremia is observed in 15-30% of inpatients. Its daily incidence and prevalence were reported as 0.97% and 2.48%, respectively[4]. Hospital-acquired hyponatremia (HAH) is largely iatrogenic, most commonly due to administration of hypotonic intravenous fluids (IVF), which may increase non-osmotic ADH production in sick children. It remains unclear whether hyponatremia is caused by hypotonic IVF or by excessive fluid administration. Although 0.45% sodium chloride solution with 5% dextrose is hypertonic compared to plasma, it behaves differently in the patient because glucose is rapidly metabolized; therefore, its net effect is “hypotonic”[5]. For this reason, hypotonic IVF have been reported to cause hyponatremia, whereas isotonic solutions reduce the risk[6]. Because hospitalized children are at high risk of developing HAH, the routine use of hypotonic maintenance fluids has been questioned since 2003[7-9]. In response to these concerns, three major guidelines were published: the American Academy of Pediatrics (AAP, 2018), the National Institute for Health and Care Excellence (NICE) guideline (2020), and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) guideline (2022). These guidelines consistently recommend isotonic maintenance fluids for most hospitalized children to prevent iatrogenic hyponatremia[8,10,11].

Amid ongoing debate, we conducted this study to determine the incidence of HAH in children and to evaluate not only the type of IVF administered but also the effects of total fluid volume and overall sodium intake on the development of hyponatremia.

Materials and Methods

The patients hospitalized at Erciyes University Children’s Health and Diseases Hospital between October 2013 and September 2014 constituted the study population. The primary outcome of this study was to determine the incidence of HAH. Secondary outcomes included the evaluation of potential etiological factors contributing to the development of HAH. Accordingly, the study was conducted in two phases. In the first phase, the incidence of HAH was detected prospectively in an observational study. For this purpose, the daily number of hospitalized patients was recorded to obtain the total annual number of inpatients. Body weight, blood pressure, clinical findings, and serum sodium values at admission were documented. An automated alert system was developed to notify the research team when hyponatremia was detected in any blood samples during hospitalization. Thus, patients who developed hyponatremia after admission were identified, and the incidence of HAH was calculated as the proportion of these patients among all inpatients during the study year. The inclusion criteria were as follows: a) normonatremia at admission (135-145 mEq/L); b) receipt of any type of IVF [isotonic, hypotonic, total parenteral nutrition (TPN), etc.] for at least 24 hours; c) detection hyponatremia (serum Na <135 mEq/L) during follow-up. Patients who were hyponatremic (<135 mEq/L) or hypernatremic (>145 mEqL) at admission were excluded. For patients with recurrent events, only the first hyponatremia episode was included (**Figure 1**).

In the second phase of the study, the etiology of hyponatremia was evaluated cross-sectionally. When hyponatremia was detected during hospitalization, patients were re-assessed. Data recorded included body weight, blood pressure, physical examination findings, 24-hour urine output, the amount and sodium content of the IVF administered during the preceding 24 hours, and the amounts of oral intake and medications received. Some patients received only IVF, whereas others received both oral therapy and IVF. Since infusion rates varied significantly among patients, the analysis focused on total sodium intake [intravenous (IV) and oral]. Additionally, urinary sodium levels, serum uric acid levels, blood urea nitrogen (BUN) levels, serum creatinine levels, and serum pro-B-type natriuretic peptide (proBNP) levels were measured.

Due to the large number and heterogeneity of underlying diseases and acute illnesses in the study population, statistical analyses according to specific diagnoses were not feasible. Many patients presented with concurrent conditions at the time of HAH, such as pneumonia, gastroenteritis, or neurological disorders, precluding disease-based subgrouping. Major underlying diagnoses and acute illnesses present at the time of hyponatremia were therefore recorded descriptively. Surgical patients were excluded from the analysis because the pediatric hospital was separate from the surgical unit. Considering the distinct physiological characteristics of neonates, the initial plan was to evaluate neonatal patients separately. However, the high proportion of preterm infants, particularly early preterm infants would have resulted in very small subgroups with insufficient statistical power. Although neonates are frequently excluded from

similar studies, they were intentionally included in the present study because of their inherently fragile fluid and electrolyte homeostasis. Therefore, patients were grouped into two age categories (≤100 days and >100 days) to allow a physiologically relevant and statistically sound analysis. This age-based stratification, supported by previous studies including Storey et al.[12], was preferred over ward-based grouping because it more closely reflects physiological maturity (**Figure 1**).

Hyponatremia was defined as a serum sodium level below 135 mEq/L[1,3,4]. Serum sodium concentrations of 130–134 mEq/L, 125-130 mEq/L, and <125 mEq/L were defined as mild, moderate, and severe hyponatremia, respectively. Hypertension was defined as blood pressure above the 95th percentile for age, sex, and height, or for gestational age in newborns[13]. Urine output categories were defined as follows: polyuria (>4 mL/kg/h), oliguria (<1 mL/kg/h), and anuria (<0.5 mL/kg/h)[14]. Daily sodium requirements were defined based on established pediatric fluid and electrolyte recommendations. In accordance with the classical Holliday and Segar approach, a sodium intake of 3 mEq/kg/day was accepted as the standard requirement[15]. Given that a substantial proportion of the study population consisted of neonatal patients, age-related physiological differences in sodium and electrolyte requirements were taken into consideration. Yapıcıoğlu Yıldızdaş et al.[16] reported that sodium requirements in neonates are approximately 1-2 mEq/kg/day during the first postnatal week, increasing to 3-4 mEq/kg/day thereafter, with greater variability observed in very preterm infants due to renal immaturity. Accordingly, in the present study, a sodium intake of ≥3 mEq/kg/day was categorized as adequate, whereas a sodium intake of ≤2 mEq/kg/day was categorized as insufficient.

We retrospectively reviewed all sources of sodium intake within the last 24 hours for each patient. Dietary intake was assessed by recording whether the patient consumed formula, breast milk, or hospital meals. For formula-fed infants, both the type and the exact volume of formula were recorded. For breastfed infants, breast milk volume was estimated from feeding frequency and duration, or recorded directly in milliliters when expressed breast milk was administered in the neonatal unit. For older children receiving hospital meals, we confirmed whether the entire meal was consumed. Subsequently, a single dietitian calculated the nutrient content, including sodium, of the consumed foods using the BEBIS (Nutrition Information Program-full 7 version) nutrition analysis software based on the daily hospital menu. Parenteral sodium intake was evaluated by reviewing hourly IVF administration records, including fluid type, volume, and sodium concentration. For patients receiving TPN, both the sodium content of the solution and the infusion rate (mL/min) were recorded. Through this systematic approach, total daily fluid and sodium intake were calculated accurately for each patient.

Blood samples (2 mL) were collected into a biochemistry tube for measurement of serum sodium, BUN, creatinine, and uric acid using the Architect C-16000 analyzer. Reference values were as follows: BUN 20 mg/dL; serum creatinine 0.8 mg/dL; and uric acid 1.7-7.0 mg/dL. Urine sodium was measured in 1 mL urine samples using the same analyzer. Urinary sodium excretion was considered high when >20 mEq/L in children and >30 mEq/L in neonates. Serum proBNP was measured using the Immulite 2000 system with a 2 mL blood sample collected in a heparinized tube. A serum proBNP measurement is considered elevated if it is above the age-specific reference range[17].

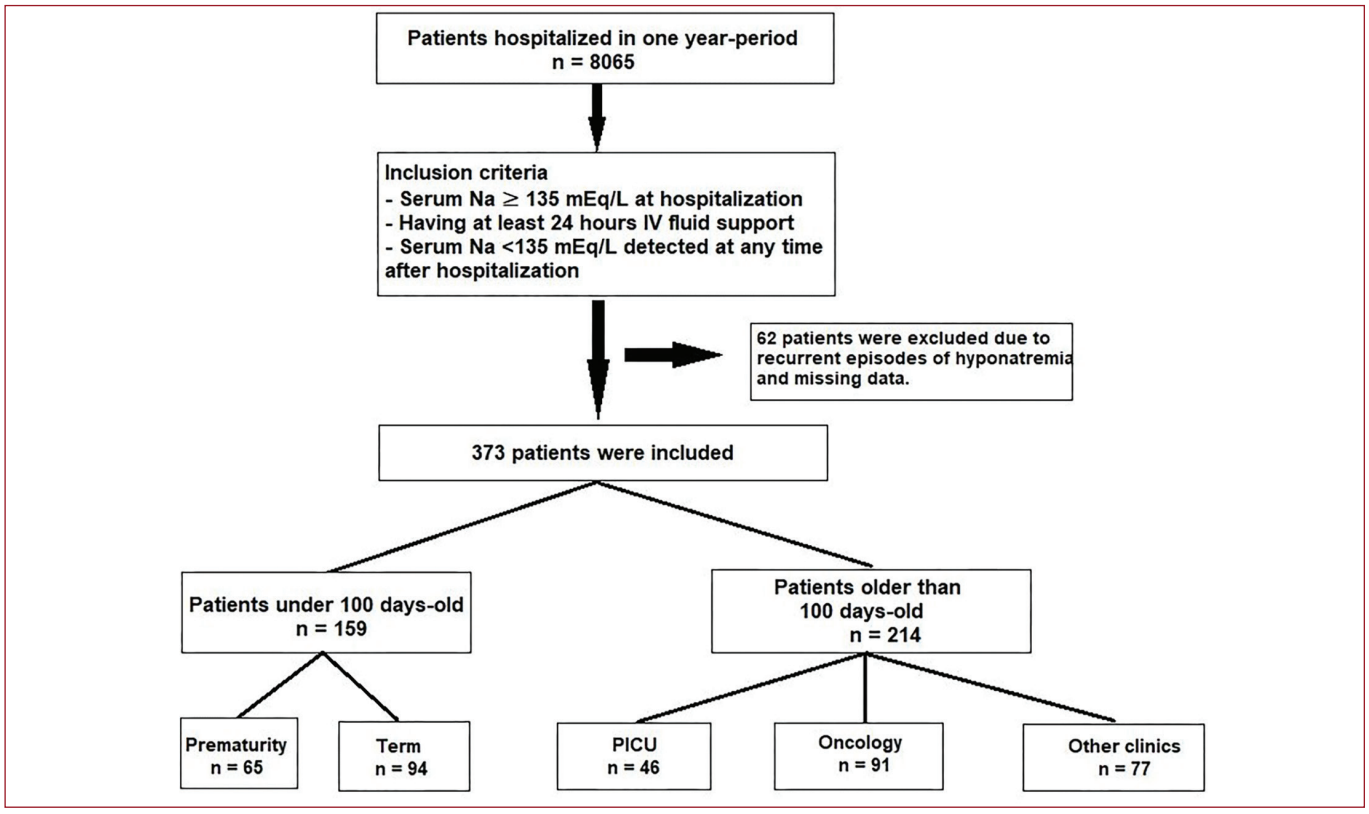

Figure 1. The inclusion criteria and the study design
PICU: Pediatric intensive care unit

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 17.0. Normality was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Normally distributed variables were expressed as mean ± standard deviation, and non-normally distributed variables were expressed as median (minimum-maximum). The chi-square test was used to compare categorical variables; the McNemar test for dependent categorical variables; the independent t-test for normally distributed continuous variables; and the Kruskal-Wallis and Mann-Whitney U tests for non-parametric comparisons. A p-value <0.05 was considered statistically significant.

Ethics committee approval of the study was obtained from the Erciyes University Non-Interventional Clinical Research Ethics Committee (decision no: 2013/514, date: 30.07.2013) the study was conducted according to the principles of the Declaration of Helsinki. .Consent was obtained from the parents of the patients included in the study. ChatGPT was used to assist with language editing and grammatical corrections; all scientific content and interpretations were produced and verified by the authors.

Results

During one year of follow-up, 8,065 patients were hospitalized. Of these, 435 patients met the study criteria. After excluding patients with recurrent episodes of hyponatremia and those with missing data, 373 patients were included in the final analysis. The incidence of HAH during the one-year period was 4.6%. Patients were evaluated in two age groups: those younger than 100 days and those older than 100 days (**Figure 1**). Because classification based on underlying or concurrent illnesses was difficult, statistical analyses were primarily conducted between these two age groups. HAH was most frequently detected in the Neonatal Unit (38.9%), followed by the Pediatric Hematology-Oncology clinic (24.9%) and the Pediatric Intensive Care Unit (13.7%).

Male patients constituted 56% of the study group; the median age was 266 days (range: 1-8,342 days). While most of the patients were normovolemic and normotensive on admission, 17% of infants ≤100 days and 19% of older patients were hypervolemic when hyponatremia was detected (**Table 1**). The mean time to onset of hyponatremia after hospitalization was 6 days in infants aged under 100 days and 10.5 days in older children. Moderate hyponatremia occurred more frequently in younger infants; 14.5% had moderate and 6.3% had severe hyponatremia (**Table 1**).

Urinary sodium excretion was elevated in most patients, particularly among those older than 100 days (p<0.001). On the day hyponatremia occurred, 10% of patients were polyuric and nearly 4% were oligoanuric (**Table 2**). Biochemical abnormalities detected at the time of hyponatremia are summarized in **Table 2**.

Serum proBNP levels demonstrated a wide distribution, and almost half of the patients had elevated proBNP levels above age-specific reference ranges (**Table 2**). Among patients with elevated proBNP, the rate of hypervolemia was significantly higher (24.3%) compared those with normal proBNP levels (15.2%, p<0.05) No significant associations were found between serum proBNP and the degree of hyponatremia, urine output, or the amount of IVF administered (p>0.05) (**Table 3**).

In the last 24 hours prior to hyponatremia, the average sodium intake in infants younger than 100 days was 1.35 mEq/kg/day IV and 1.0 mEq/kg/day orally, and in older children was 1.08 mEq/kg/day IV and 2.61 mEq/kg/day orally. Sodium intake was below physiological requirements in 35.8% of patients aged under 100 days (**Table 2**). Serum sodium correlated positively with age and negatively with serum proBNP, BUN, and creatinine. No significant relationship was found between serum sodium and total IVF volume (**Table 4**).

When patients were reclassified by hyponatremia severity, those with moderate-to-severe hyponatremia experienced longer hospital stays before the onset of hyponatremia in both age groups. Urine output was within the normal range for most patients, although urinary sodium excretion was markedly higher in older children than in infants. In both groups, moderate-to-severe hyponatremia developed in nearly half of the patients who received only IVF . Older children with moderate-to-severe hyponatraemia received larger volumes of IVF, although this difference was not statistically significant. Among infants and older children with moderate-to-severe hyponatremia, sodium supplementation was below daily physiological requirements in 27.3% and 14.3%, respectively (**Table 5**).

Among patients who received only IVF, urinary sodium excretion was higher in older children compared with infants. Severe hyponatremia occurred significantly more frequently in infants under 100 days who received lower parenteral sodium supplementation despite having lower daily IVF intake compared with older patients (**Table 6**).

Table 1.
Evaluation of patients during hospital admission and in the period when hyponatremia develops

	≤100 day old (n=159)		>100 day old (n=214)	
	At admission	**At hyponatremia**	**At admission**	**At hyponatremia**
Age (day) (min-max)		15 (1-100)		349 (104-4679)
Blood pressure				
High	-	0.6%	1.9%	1.4%
Normal	-	62.3%	87.9%	96.3%
Low	-	9.4%	0.5%	1.9%
Volume status				
Hypovolemia	0.6%	-	0.5%	-
Euvolemia	97.5%	83%	98.1%	80.4%
Hypervolemia	1.9%	17%	1.4%	19.6%
Serum sodium (mEq/L) (min-max)	138 (135-144)	132 (109-134)	137 (135-143)	133 (123-134)
Hyponatremia detection time (day) (min-max)		6 (1-71)		10.5 (1-106)
Severity of hyponatremia				
Mild		79.2%		93.5%
Moderate		14.5%		5.1%
Severe		6.3%		1.4%

Min-max: Minimum-maximum

Table 2.
Laboratory parameters and the content of intravenous fluids when hyponatremia was detected

	≤100 day	**>100 day**	**p**
Blood urea nitrogen			
Median (min-max)	9.0 (1-70)	7.0 (2-19)	
≤20 mg/dL	89 (71.2%)	166 (93.3%)	<0.001
>20 mg/dL	36 (28.8%)	12 (6.7%)	
Creatinine			
Median (min-max)	0.5 (0.01-6.77)	0.35 (0.05-0.5)	
≤0.8 mg/dL	130 (81.8%)	196 (91.6%)	0.001
>0.8 mg/dL	29 (18.2%)	18 (8.4%)	
Uric acid			
Median (min-max)	2.35 (0.4-12)	2.45 (0.9-5.6)	
≤1.7 mg/dL	34 (21.7%)	34 (16.5%)	0.779
1.8-7 mg/dL	104 (66.2%)	164 (79.6%)	
≥7.1 mg/dL	19 (12.1%)	8 (3.9%)	
Serum sodium			
Median (min-max)	132 (109-134)	133 (123-134)	<0.001
Serum proBNP			
Median (min-max)	2279 (65-261817)	983 (46-94560)	
Normal	79 (58.1%)	79 (47.6%)	<0.001
High	57 (41.9%)	87 (52.4%)	
Urine sodium [n (%)]			
Normal	79 (57.7)	24 (12.2)	<0.001
High	58 (42.3)	173 (87.8)	
Excretion of urine [n (%)]			
Normal	131 (82.3)	171 (85.9)	
Polyuria	16 (10)	20 (10)	0.224
Oligo-anuria	6 (3.7)	8 (4)	
Therapy route of fluid [n (%)]			
Only with parenteral route	50 (31.4)	44 (20.6)	0.022
Peroral and parenteral route	109 (68.6)	170 (79.4)	
Intravenous fluids' amount [median (min-max)]			
Patients receiving parenteral fluid only (mL/m^2)	1240 (379-2647)	1820 (166-4190)	0.001
Patients receiving parenteral and peroral fluid (mL/m^2)	670 (96-4141)	1709 (95-4190)	<0.001
Daily sodium consumption	**Median (min-max)**	**Median (min-max)**	
Peroral (mEq/kg/day)	1.0 (0.08-5.83)	1.08 (0-1.91)	<0.001
Parenteral (mEq/kg/day)	1.35 (0-12.23)	2.61 (0.42-8.57)	<0.001
Total (mEq/kg/day)	2.86 (0.08-14.91)	3.75 (1.82-8.63)	<0.001
	n (%)	**n (%)**	
<2 mEq/kg/day	57 (35.8%)	13 (6.1%)	
2-3 mEq/kg/day	30 (18.9%)	15 (7.0%)	<0.001
>3 mEq/kg/day	72 (45.3%)	186 (86.9%)	

Min-max: Minimum-maximum, proBNP: Pro-B-type natriuretic peptide

Table 3.
Comparison of patients in terms of volume status, severity of hyponatremia and urinary excretion by level of serum proBNP

Variables	Serum proBNP level		p-value
	Normal n=158	High n=144	
Volume status			
Normovolemia	134 (84.8%)	109 (75.7%)*	0.042
Hypervolemia	24 (15.2%)	35 (24.3%)	
Severity of hyponatremia			
130-134 mEq/L	136 (86.1%)	128 (88.9%)	0.492
<130 mEq/L	22 (13.9%)	16 (11.1%)	
Excretion of urine			
Normal	128 (88.2%)	116 (87.9%)*	0.852
Polyuria	16 (11.1%)	16 (12.1%)	
Intravenous fluid amount (mL/m^2)	1378 ± 852	1433 ± 843	0.660

*: p<0.05, compared to the patients with normal serum proBNP levels
Min-max: Minimum-maximum, proBNP: Pro-B-type natriuretic peptide

Table 4.
Correlation between serum sodium level at hyponatremia day and some variables

Variables	Serum sodium	
	r	p
Age	0.186	<0.001
Serum proBNP level	-0.166	0.004
Blood urea nitrogen	-0.154	0.007
Serum creatinine	-0.116	0.026
Urine sodium	0.111	0.042
Total content of sodium (PO+IV) (mEq/kg)	0.093	0.072
Amount of IV fluids (mL/m^2/day)	-0.065	0.453
Serum sodium at hospitalization	-0.031	0.550

BUN: Blood urea nitrogen, PO: Peroral, IV: Intravenous, proBNP: Pro-B-type natriuretic peptide

Table 5.
Comparison of the patients according to the severity of hyponatremia

Variables	Severity of hyponatremia				
	≤ 100 day old (n=159)		> 100 day old (n=214)		p-value**
	Mild hyponatremia (Serum Sodium =130-134 mEq/L) n=126	Moderate-severe hyponatremia (Serum sodium <130 mEq/L) n=33	Mild hyponatremia (Serum sodium =130-134 mEq/L) n=200	Moderate-severe hyponatremia (Serum sodium <130 mEq/L) n=14	
Age (day)	18 (1-100)	10 (4-28)	561 (104-5326)	156 (123-190)	-
Duration of hospitalisation at hyponatremia (day)	6 (1-71)	10 (3-27))	7 (1-106)	27.5 (22-33)	0.025
Serum sodium (at hospitalization)	137 (135-144)	139 (136-142)	137 (135-143)	136.5 (136-137)	-
Serum sodium (at hyponatremia)	133 (130-134)	127 (109-129)	133 (130-134)	125 (123-127)	0.540
Excretion of urine (mL/kg/h)	3.0 (0.36-14)	2.0 (0.32-3.8)	3.1 (1.57-6.25)	3.15 (1.3-5.0)	0,770
Excretion of urine					
Oligo-anuria	1 (0.7%)	5 (15.1%)	8 (4%)	0 (0%)	
Normal	107 (84.9%)	24 (72.7%)	159 (79.5%)	12 (85.7%)	
Polyuria	12 (9.5%)	4 (12.1%)	19 (9.5%)	1 (7.1%)	
Urine sodium (mEq/L)					
Median (min-max)	20 (4-84)	30 (20-59)	77 (20-188)	62.5 (39-86)	
Low*	66 (%52.4)	13 (39.4%)	24 (12%)	0 (0%)	<0.001
High	47 (37.3%)	11 (33.3%)	160 (80%)	13 (92.9%)	
BUN	9 (1-61)	17 (7-70)	7 (4-33)	5.0 (2.0-8.0)	0.013
Serum creatinine	0.4 (0.01-3.5)	0.7 (0.3-6.77)	0.4 (0.05-0.8)	0.28 (0.17-0.4)	0.017
Serum uric acid					
Median (min-max)	2.2 (0.4-12)	3.0 (1.5-8.2)	2 (0.9-5.6)	2.5 (2.0-3.0)	
≤1.7 mg/dL	30 (23.8%)	4 (12.1%)	30 (15%)	4 (28.6%)	0.015
1.8-7 mg/dL	82 (65.1%)	22 (66.7%)	154 (77%)	10 (71.4%)	
>7 mg/dL	13 (10.3%)	6 (18.2%)	8 (4%)	0 (0%)	

Table 5.
Continued

Variables	Severity of hyponatremia				
	≤100 day old (n=159)		>100 day old (n=214)		p-value**
	Mild hyponatremia (Serum Sodium =130-134 mEq/L) n=126	Moderate-severe hyponatremia (Serum sodium <130 mEq/L) n=33	Mild hyponatremia (Serum sodium =130-134 mEq/L) n=200	Moderate-severe hyponatremia (Serum sodium <130 mEq/L) n=14	
Serum proBNP Normal for age High for age	2259 (65-70080) 63 (50%) 46 (36.5%)	4943 (498-261817) 16 (48.5%) 11 (33.3%)	732 (46-17676) 73 (36.5%) 82 (41%)	47773(986-94560) 6 (42.9%) 5 (35.7%)	0.064
Therapy route of fluid Peroral + intravenous Only intravenous	 91 (72.2%) 35 (27.8%)	 18 (54.5%) 15 (45.5%)	 163 (81.5%) 37 (18.5%)	 7 (50%) 7 (50%)	0.775
Amount of intravenous fluids (mL/m²/day)	938 (96-4141)	1064 (204-3387)	1772 (95-4190)	1564 (166-2835)	0.034
Intravenous sodium support (mEq/kg/day)	2.88 (0-7.58)	1.76 (0-14.84)	3.47 (0-19.98)	3.44 (0.48-6.41)	0.121
Peroral sodium consumption (mEq/kg/day)	0.91 (0.08-5.83)	1.91 (0.54-4.23)	1.15 (0.05-2.71)	0.56 (0.35-0.77)	0.672
Total sodium support (mEq/kg/day) <2 mEq/kg/day 2-3 mEq/kg/day >3 mEq/kg/day	2.66 (0.08-7.56) 48 (38.1%) 24 (19%) 54 (42.9%)	5.31 (0.54-14.91) 9 (27.3%) 6 (18.2%) 18 (54.5%)	3.7 (1.82-8.63) 11 (5.5%) 14 (7%) 175 (87.5%)	3.05 (1.85-4.26) 2 (14.3%) 1 (7.1%) 11 (%78.6)	0.218

*: The urine sodium cutoff value for newborn is <30 meq/L and for older children <20 mEq/L
**: Statistical analysis was made among patients with severe hyponatraemia by age groups
proBNP: Pro-B-type natriuretic peptide, BUN: Blood urea nitrogen

Table 6.
Characteristics of patients receiving only IV fluid

	≤ 100 day (n=50) Median (min-max)	>100 day (n=44) Median (min-max)	p-value
Hospitalization day	5 (1-100)	6 (1-206)	0.903
Serum sodium when hyponatremia detected Degree of hyponatremia Mild hyponatremia Moderate hyponatremia Severe hyponatremia	132 (109-134) 35 (70%) 8 (16%) 7 (14%)	133 (119-134) 37 (84.1%) 6 (13.6%) 1 (2.3%)	0.021 0.046
Excretion of urine	2.6 (0.1-13.3)	2.4 (0.36-6.5)	0.313
Urine sodium	33.5 (7-152)	61 (13-140)	0.004
Intravenous fluids' amount (mL/m²/day)	1230 (379-2647)	1821 (554-4190)	0.001
Daily sodium consumption Parenteral (mEq/kg/day) <2 mEq/kg/day 2-3 mEq/kg/day >3 mEq/kg/day	 2.29 (0-6.48) **n (%)** 19 (38%) 12 (24%) 19 (38%)	 3.2 (0-9.48) **n (%)** 6 (13.6%) 7 (15.6%) 31 (70.6%)	 0.001 0.002

Min-max: Minimum-maximum

Discussion

Hospital-acquired hyponatremia has long been recognized as a common yet preventable electrolyte disturbance in hospitalized children. Over the past two decades, it has gained increasing attention due to its association with significant morbidity and its largely avoidable nature. This study aimed to determine the frequency of HAH and evaluate the influence of IVF composition and sodium supplementation on its development. Our study, conducted over one year and including all hospitalized pediatric patients, demonstrated that HAH may develop not only within the first 24-48 hours, as reported previously[18-20], but also during prolonged hospitalizations. Patients admitted to intensive care, neonatal, or oncology units exhibited a markedly higher risk; nearly half of those receiving only maintenance IVF developed moderate-to-severe hyponatremia. These findings underscore the importance of careful monitoring of both fluid composition and total administered volume-particularly in critically ill patients or those unable to receive enteral sodium.

Clinical recognition of the dangers of hypotonic maintenance fluids dates to the early 2000s, when Moritz and Ayus[21] reported cases of hyponatremic

encephalopathy, including fatalities, in otherwise healthy children receiving hypotonic solutions[19,20]. Their observations prompted a major shift away from the traditional Holliday-Segar-based hypotonic regimens. Subsequently, multiple randomized controlled trials and meta-analyses have consistently demonstrated that isotonic solutions significantly reduce the risk of HAH without increasing hypernatremia, metabolic acidosis, or fluid overload[19,22-24]. Consequently, major guidelines—including those from the AAP, the NICE, and the ESPNIC—now recommend isotonic maintenance fluids for most hospitalized children[8,10,11]. Despite this paradigm shift, HAH has not been fully eliminated, underscoring that its pathogenesis is multifactorial and extends beyond fluid tonicity.

Although our study was conducted before widespread adoption of isotonic maintenance therapy, it offers valuable real-world insight into the clinical factors contributing to HAH. At that time, isotonic fluids were not routinely used; nevertheless, hyponatremia developed predominantly in patients with underlying comorbidities, prolonged hospital stays, and a positive fluid balance. These findings highlight the continued relevance of non-fluid-related contributors to hyponatremia, including the syndrome of inappropriate antidiuretic hormone secretion (SIADH), stress-induced ADH release, and low dietary sodium intake. SIADH remains the leading cause of euvolemic hyponatremia in hospitalized patients and results from persistent ADH secretion independent of serum osmolality or intravascular volume, leading to hypotonic water retention and dilutional hyponatremia[25,26]. SIADH may be triggered by medications, pulmonary disease, malignancies, central nervous system pathology, or the physiological stress of illness, pain, and surgery[26].

Beyond fluid type and volume, our biochemical findings provide additional mechanistic insights. Serum sodium showed an inverse correlation with BUN and proBNP, a positive correlation with total sodium intake (IV and oral), and no correlation with total IVF volume. Despite the lack of an association between serum sodium concentration and total IVF volume, urinary sodium excretion was markedly elevated in older children, with 87.8% of patients older than 100 days exhibiting elevated urinary sodium, supporting the concept that HAH reflects impaired free water excretion and dysregulated neurohormonal responses rather than fluid overload alone. Although ProBNP levels were elevated among hyponatremic patients, clinical signs of hypervolemia—such as hypertension, edema, or hepatomegaly—were generally absent. Elevated proBNP may, therefore, represent an early biochemical indicator of subtle volume shifts or myocardial wall stress, rather than frank hypervolemia. However, because an objective assessment of volume status using inferior vena cava (IVC) diameter or bioimpedance analysis could not be performed, we cannot entirely exclude early or subclinical volume expansion. BNP and proBNP—released in response to myocardial stretch—oppose Renin-angiotensin-aldosterone System and ADH activity by promoting natriuresis and vasodilation[27], and the elevation observed in our cohort may reflect compensatory neurohormonal activation rather than overt circulatory overload.

Consistent with prior studies, HAH was significantly more common among neonates, oncology patients, and those admitted to the pediatric intensive care unit, with rates of 38.9%, 24.9%, and 13.7%, respectively. Critically ill children are known to have an increased risk of hyponatremia owing to non-osmotic ADH release triggered by pain, stress, inflammation, mechanical ventilation, and postoperative states[28-30]. Likewise, pediatric oncology patients are particularly vulnerable due to chemotherapy-induced nausea, gastrointestinal sodium losses, adrenal suppression, and medication-associated SIADH, notably from agents such as vincristine, cyclophosphamide, and carboplatin. Hyponatremia rates of 15-40% have been reported in oncology cohorts, consistent with our findings[31-33]. During the study period, the routine use of hypotonic fluids likely increased susceptibility in these high-risk groups. These results collectively reinforce the importance of individualized fluid prescriptions and proactive electrolyte monitoring, even in the current era of isotonic maintenance therapy.

Recent uncertainty regarding the optimal tonicity of maintenance fluids in neonates has been clarified, at least in part, by the large multicenter prospective NEOFLUID study-the strongest available evidence in this population. In 420 term newborns, hypotonic fluids resulted in a significantly greater decline in serum sodium levels and a markedly higher incidence of hyponatremia, whereas isotonic fluids maintained stable sodium levels without increasing hypernatremia. This challenges the long-standing assumption that hypotonic solutions are physiologic for neonates and suggests that isotonic fluids may be the safer optiononce postnatal renal adaptation is complete[34]. Importantly, our findings paralel this interpretation: while fluid tonicity contributes to risk, HAH in our cohort was best explained by the interaction of fluid choice with patient-specific clinical factors. Taken together with the NEOFLUID data, our results support a morenuanced understanding of HAH-one in which hypotonic fluids may heighten vulnerability, but the ultimate development of hyponatremia is determined by a broader constellation of neurohormonal, clinical, and iatrogenic influences.

In line with current international guidelines (AAP, NICE, ESPNIC)[8,10,11], our findings support the use of isotonic maintenance fluids and close monitoring of serum sodium, particularly in neonates and other high-risk pediatric populations. Given the high incidence of HAH in infants and critically ill children, fluid therapy should be individualized, with regular reassessment of sodium intake, urine sodium losses, and volume status , rather than relying on fluid volume alone. In neonates and patients with prolonged hospitalization, careful attention to cumulative sodium balance and early recognition of inappropriate ADH activity may help prevent hyponatremia.

Study Limitations

This study has several notable strengths. Unlike many previous reports, we evaluated all administered

fluids—including maintenance solutions, boluses, and TPN—allowing for a comprehensive assessment of total sodium and water exposure. The inclusion of enteral sodium intake (oral and dietary sources) further strengthened our analysis by providing a more accurate estimation of overall sodium balance. Additionally, the inclusion of patients with prolonged hospitalizations, who are often underrepresented in prior studies, offered valuable insights into late-onset and cumulative-risk forms of hyponatremia.

However, certain limitations should be acknowledged. Due to technical constraints, we were unable to assess intravascular volume status using IVC diameter or bioimpedance analysis. The absence of these objective measurements limits our ability to fully exclude subtle or early hypervolemia in some patients. Furthermore, because the study was conducted at a single center during a period when isotonic fluids were not yet widely implemented, the findings may not fully reflect current practice patterns. Nonetheless, the detailed fluid accounting and inclusion of diverse patient populations enhance the clinical relevance and generalizability of our results.

CONCLUSION

In conclusion, HAH remains an important and preventable complication in pediatric practice, occurring not only early in hospitalization but also during prolonged stays and in high-risk groups such as neonates, critically ill children, and oncology patients. While fluid tonicity contributes to susceptibility, our findings underscore that HAH develop sthrough a complex interaction of clinical, neurohormonal, and iatrogenic factors, emphasizing the importance of individualized fluid management and vigilant electrolyte monitoring. By accounting for all administered fluids—including TPN—and enteral sodium intake, our study provides a comprehensive assessment of sodium balance and highlights that IVF therapy can itself be a potent medical treatment with potential adverse effects. As clinicians, we must remain mindful of the principle primum non-nocere—first, do not harm— ensuring that fluid therapy is applied thoughtfully, safely, and with careful attention to each patient's dynamic physiologic needs.

Ethics

Ethical Approval: Ethics committee approval of the study was obtained from the Erciyes University Non-Interventional Clinical Research Ethics Committee (decision no: 2013/514, date: 30.07.2013). The study was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Consent was obtained from the parents of the patients included in the study.

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Footnotes

Author Contributions: Pınarbaşı AS: Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Yel S: Data Collection or Processing, Analysis or Interpretation.; Oğuzhan Gülmez M: Data Collection or Processing, Analysis or Interpretation.; Poyrazoğlu MH: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation.

Conflict of Interest: The authors have no conflicts of interest to declare.

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