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Association Between Maintenance Fluid Tonicity and Hospital-Acquired Hyponatremia

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Abstract

Objective—To evaluate whether the administration of hypotonic fluids, when compared with isotonic fluids, is associated with a greater risk for hyponatremia in hospitalized children.

Study design—Informatics-enabled cohort study of all hospitalizations at Lucile Packard Children's Hospital between April 2009 and March 2011. Extraction and analysis of electronic medical record data identified normonatremic hospitalized children who received either hypotonic or isotonic intravenous maintenance fluids upon admission. The primary exposure was the administration of hypotonic maintenance fluids and the primary outcome was the development of hyponatremia (serum sodium < 135 mEq/L).

Results—1048 normonatremic children received either hypotonic (n=674) or isotonic (n=374) maintenance fluids upon admission. Hyponatremia developed in 260 (38.6%) children receiving hypotonic fluids and 104 (27.8%) of those receiving isotonic fluids (unadjusted OR 1.63; 95th CI 1.24–2.15, p<0.001). After controlling for intergroup differences and potential confounders, patients receiving hypotonic fluids remained more likely to develop hyponatremia (adjusted OR 1.37, 95% CI 1.03–1.84). Multivariable analysis identified additional factors associated with the development of hyponatremia including surgical admission (adjusted OR 1.44, 95% CI 1.09–1.91), cardiac admitting diagnosis (adjusted OR 2.08, 95% CI 1.34–3.20) and hematology/oncology admitting diagnosis (adjusted OR 2.37, 95% CI 1.74–3.25).

Conclusions—Hyponatremia was common regardless of maintenance fluid tonicity, however, the administration of hypotonic maintenance fluids, when compared with isotonic fluids, was associated with a greater risk of developing hospital-acquired hyponatremia. Additional clinical characteristics modified the hyponatremic effect of hypotonic fluid, and it is possible that optimal maintenance fluid therapy now requires a more individualized approach.

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Keywords

Hyponatremia; Maintenance Fluids; Hypotonic; Isotonic

Hyponatremia (serum sodium < 135 mEq/L) is common in hospitalized children, occurring in 19–50% of inpatients.[1–4] Reduced serum sodium levels can lead to encephalopathy, seizures, obtundation, and death.[5, 6] Several factors can contribute to hyponatremia in hospitalized patients including increased water retention related to antidiuretic hormone (ADH) effect, intracranial processes purportedly associated with cerebral salt-wasting, and the administration of excess electrolyte-free water (EFW) through oral or intravenous (IV) hydration. Although ADH plays an important role in osmotic homeostasis, ADH levels can also be elevated in response to non-osmotic stimuli in situations such as hypovolemia, the syndrome of inappropriate ADH secretion (SIADH), and certain disease states (pneumonia, meningitis, pain, and following surgery).[6] Hyponatremia is especially common when excessive EFW is administered in these conditions.

Although pediatricians have traditionally chosen to administer IV maintenance fluids according to the guidelines proposed by Malcolm Holliday and William Segar in 1957, our longstanding adherence to this strategy has recently been questioned. The Holliday-Segar method is based upon repletion of physiologic fluid and electrolyte losses; their calculations determined that hypotonic saline provides the optimal composition for delivery of maintenance fluid and electrolyte requirements in hospitalized children.[7] Citing greater hyponatremic morbidity, as well as an increasing incidence of ADH-associated disease states in hospitalized children, recent literature has promoted an opposition to the use of such hypotonic fluids, which are EFW rich. Even though concerns about the use of hypotonic fluids had been previously raised[5, 8, 9] and the situational use of isotonic fluids discussed[10, 11], it was the 2003 article by Moritz and Ayus which first suggested that practitioners broadly transition to isotonic maintenance fluids.[6] Since then, a number of observational studies and small randomized controlled trials have continued to associate the administration of hypotonic maintenance fluids with the subsequent development of hyponatremia.[12–19]

Although compelling, these studies have been limited by small size, short duration, and examination of only select patient populations. Using an informatics-enabled analysis of electronic medical record (EMR) data, we established a cohort of over 1000 children hospitalized across the entire spectrum of pediatric disease who had normal admission serum sodium values. This, in turn, allowed us to analyze the association between hypotonic maintenance fluids and hyponatremia on a larger and more generalizable scale than ever before.

Methods

This is a retrospective, informatics-enabled cohort study; clinical analytics tools allowed extraction of electronic medical record (EMR) data including demographics, comprehensive serum sodium results, IV infusion data (fluid type/composition), medication administration data, admitting diagnosis descriptions, and clinical notes. All data were extracted from the hospital's EMR (PowerChart®, Cerner Corporation, Kansas City, MO, USA) and the Stanford Translational Research Integrated Database Environment (STRIDE);[20] following this, individual EMR data tables were linked and merged in preparation for analysis. This study was approved by the Stanford University Institutional Review Board (IRB#6208, Protocol#20053)

All patients admitted to Lucile Packard Children's Hospital between 4/1/2009 and 3/31/2011 were considered for analysis. Inclusion criteria were admission age < 18 years, normal admission serum sodium (135 – 145 mEq/L), hospitalization > 24 hours, and initiation of IV fluids within 24 hours of admission. For children with multiple hospitalizations, only the first was considered. Patients were included only if ≥ 90% of their total IV fluid intake during the 24 hours after admission was isotonic or hypotonic; patients receiving mixed fluid composition (< 90% isotonic/hypotonic) were excluded. Patients without a serum sodium within 24 hours of admission were excluded because a baseline could not be established. Patients without follow-up sodium values were excluded as the determination of hyponatremia could not be made; because it is standard of care at our institution to monitor chemistries at least every other days in patients receiving IV fluids, this likely eliminated patients receiving fluids for a short duration of time (< 48 hours) who were at low risk for development of hyponatremia. Neonates were excluded because they represent a unique patient population with reduced urinary concentration capacity.

The patient selection and exclusion process is shown in Figure 1. The demographic dataset contained 5498 unique hospitalized patients. This was merged with the serum sodium and IV infusion datasets. After excluding patients > 18 years of age and patients without a normal admission serum sodium, the cohort included 3336 normonatremic children. Further exclusions included 1109 patients without additional sodium tests, 700 patients receiving a mixed IV fluid composition, and 479 neonates. The remaining study cohort consisted of 1048 normonatremic children placed on either hypotonic or isotonic maintenance IV fluids at admission.

Statistical Analyses

Hyponatremia was defined as a serum sodium < 135mEq/L. Sodium values were studied for seven days after the initial 24 hour fluid exposure period. Patients were classified according to their lowest serum sodium value during that period. Hypotonic maintenance IV fluids included: D5W, ¼ Normal Saline (NS), D5-¼NS, ½NS, D5-½NS, and total/peripheral parenteral nutrition (TPN/PPN). No patients received D5W as a maintenance fluid, however, some patients received medications/infusions mixed in D5W which contributed to total free water delivery. Although TPN/PPN and fluids containing 5% dextrose are iso/hyperosmolar, they are effectively hypotonic because the dextrose is rapidly metabolized. The aforementioned solutions containing 20–40mEq/L of KCl were also considered hypotonic. Isotonic maintenance IV fluids included: NS, D5-NS, and Lactated Ringer's solution. Patients were placed into tonicity cohorts based upon the type of IV fluid administered for the initial 24 hours following admission; this allowed us to best capture the empiric maintenance IV fluid decision made upon admission. EMR workflow did not accurately capture the type or volume of oral fluid intake; thus, fluid calculations include only fluids administered intravenously. Admissions were considered surgical if a surgical procedure was performed within +/− 1 day of admit.

In an attempt to control for different disease states in patients, we categorized the admitting diagnosis for each patient into one of eight system/disease groups: cardiology, gastroenterology, hematology/oncology, infectious disease, nephrology, neurology/neurosurgery, pulmonology, and other. Infectious admissions were grouped in a single category regardless of the location of the infection.

The primary endpoint was development of hyponatremia within 7 days of initiation of IV maintenance fluid therapy. To identify potential confounders, in addition to maintenance fluid composition, we evaluated clinically relevant variables including age at admission, sex, race-ethnicity, whether the admission was surgical or medical, admitting diagnosis disease category, and diuretic administration. All variables which were associated with

administration of hypotonic fluids or with the development of hyponatremia in the univariate analysis were eligible for the multivariable analyses. Using step-wise logistic regression modeling, we built a final multivariable model estimating the effect of hypotonic fluids on the development of hyponatremia. Variables remaining in the model were either significant ($p<0.1$) and/or confounders (modification of outcome by ≥ 20%). Additionally, a log-rank statistic time-toevent analysis was performed to estimate the effect of fluid tonicity on time to development of hyponatremia; the associated Kaplan-Meier plot is shown in Figure 2. All analyses were performed in R (R Development Core Team (2011). Vienna, Austria. http://www.R-project.org/). Results are presented as mean ± standard deviation or median (interquartile range) based upon data distribution. Odds ratios are presented as OR (95^{th} confidence interval, p-value).

Results

Of the 1048 hospitalized children included, 674 (64.3%) received hypotonic maintenance IV fluids and 374 (35.5%) received isotonic maintenance IV fluids upon admission. Demographic data are shown in Table I. Patients who received hypotonic fluids were younger than those who received isotonic fluids (mean ± SD, 7.0 ± 5.8 years vs. 8.6 ± 5.2 years, $p<0.001$). Of the patients receiving isotonic fluids, 47.9% were female compared with 47.3% of the patients receiving hypotonic fluids ($p=0.87$). There were slight racial differences between the two cohorts of patients ($p=0.03$). 23.3% of the patients receiving isotonic fluids and 16.9% of the patients receiving hypotonic fluids were Asian; 70.9% and 76.4% of those in the isotonic and hypotonic cohorts were Caucasian, respectively. When the admitting diagnosis category was examined, significant differences between the two cohorts were noted. There were more children with cardiac (14.1% vs. 3.5%), gastrointestinal (24.3% vs. 11.8%), hematologic/oncologic (26.9% vs. 15.0%), and nephrologic (7.4% vs. 4.0%) diagnoses in the hypotonic fluid cohort ($p<0.01$); there were more children with neurologic (35.0% vs. 2.5%) and “other” (12.0% vs. 7.3%) diseases in the isotonic fluid cohort ($p<0.01$). Patients with infectious disease and pulmonary diagnoses were equally represented between the two cohorts. Patients who received hypotonic maintenance fluids were less likely to have been admitted for a surgical procedure than patients who received isotonic fluids (30.3% vs. 39.3%; $p=0.003$). Diuretic use was similar between the two groups (7.8% of those receiving isotonic fluids and 7.4% of those receiving hypotonic fluids, $p=0.84$).

Risk of Developing Hyponatremia

Out of the 1048 hospitalized children with normal baseline sodium values, 364 (34.7%) developed hyponatremia. Hyponatremia was seen in 38.6% of the children who were placed on hypotonic maintenance fluids and 27.8% of children who were placed on isotonic maintenance fluids (unadjusted OR 1.63; 95th CI 1.24 – 2.15, $p<0.001$). Administration of hypotonic maintenance fluids remained independently associated with the development of hyponatremia in the multivariable analysis (adjusted OR 1.37, 95% CI 1.03 – 1.84), after adjusting for admitting diagnoses, admission age, surgical admission, and administration of diuretics (Table II). Time-to-event (development of hyponatremia) analysis for the two cohorts is shown in Figure 2; hyponatremia developed significantly earlier in patients receiving hypotonic fluids when compared with those receiving isotonic fluids. The multivariable analysis highlighted several other clinical factors associated with the development of hyponatremia. Surgical admissions were more likely to develop hyponatremia than medical admissions (adjusted OR 1.44, 95% CI 1.09 – 1.91). Additionally, both cardiac (adjusted OR 2.08, 95% CI 1.34 – 3.20, $p=0.001$) and hematology/oncology (adjusted OR 2.37, 95% CI 1.74 – 3.25, $p<0.001$) admitting diagnoses were associated with over two-fold greater hyponatremic risk. Although there was a trend

towards greater risk of developing hyponatremia in younger patients and those receiving diuretics, these two findings did not reach statistical significance.

Discussion

The use of hypotonic intravenous maintenance fluids in hospitalized children has been considered the standard of care since 1957, when Holliday and Segar published their landmark paper.[7] Although this approach was essentially unquestioned for over four decades, case reports of profound hyponatremia in children receiving hypotonic fluids began to arise.[5, 10, 21–23] Subsequently, two reports, one co-authored by Halberthal, Halperin, and Bohn[10] and the second co-authored by Moritz and Ayus,[6] underscored this potential association. Moritz and Ayus, in particular, argued that isotonic fluids should become the standard for all hospitalized children.[6] Since then, this subject has been highly contested, with strong proponents on each side of the hypotonic/isotonic debate.[24–29]

This study examines the association between the type of maintenance fluid administration and the subsequent development of hyponatremia in hospitalized children. We found that across a broad pediatric inpatient population, children who received hypotonic IV fluids were significantly more likely to develop hyponatremia than those who received isotonic IV fluids. This finding remained significant even after adjusting for intergroup differences and potential confounders. Even though the association between hypotonic fluid administration and increased rates of hyponatremia has been previously described, existing studies have primarily focused upon patient populations at higher hyponatremic risk such as those who are either critically ill[17, 19] or have undergone surgical procedures.[1, 12, 13, 18] Our study, on a larger scale than ever before, extends this association across the entire spectrum of pediatric inpatient disease.

Our findings are in line with several studies that have demonstrated that hyponatremia is common among hospitalized children; our incidence of 34.7% is similar to the rates of hyponatremia in earlier studies which ranged from 18.5% to 50%.[2, 3] Additionally, our results are consistent with several studies which found that hyponatremia was more common in patients receiving hypotonic fluids than those receiving isotonic fluids.[13, 16–19, 30, 31] However, one of the most striking findings in our study is the relatively high rate of hyponatremia even in those receiving isotonic fluids (27.8%). Although hypotonic fluids were associated with greater hyponatremic risk, the effect was mitigated to a certain degree in the multivariable analysis. In fact, in our analysis, surgical admissions and certain admitting diagnoses seemed to have a stronger impact on the development of hyponatremia than the tonicity of maintenance fluids administered. Although this study was not designed to do so, it certainly suggests that factors other than just fluid tonicity contribute substantially to hyponatremic risk in hospitalized children. This is consistent with select studies which suggest that additional factors, such as administration of greater fluid volumes and the presence of uncorrected volume deficits, contribute to the development of hyponatremia.[15, 24, 32]

It is important to interpret our results in the context of the study's limitations. First, intergroup differences exist between the patients who received hypotonic and isotonic fluids; it is possible that despite controlling for covariates, these disparities contributed to the differential rates of hyponatremia between the two groups. Although we attempted to control for different disease processes through the use of the admitting diagnosis variable, it is possible that our multivariable analysis did not adequately control for severity or type of illness. Second, although this study suggests that hypotonic maintenance fluid administration is more likely to cause hyponatremia than isotonic fluid administration, it was not designed to assess the relative benefit of isotonic fluids. Use of isotonic, instead of

hypotonic, maintenance fluids may be associated with different morbidities such as hypertension, edema, hypernatremia, and volume overload. Third, we were not able to assess patient volume status at admission and cannot comment on the adequacy of the initial volume resuscitation; intravascular volume depletion and inadequate resuscitation could contribute to persistent ADH release and subsequent hyponatremia. This inability also made it challenging to determine the appropriateness of the fluid volume administered; patients who received fluids in excess of their calculated maintenance may have merely received adequate resuscitation. This, unfortunately, made it impossible to assess the impact of fluid volume on development of hyponatremia.

Despite these limitations, our data augment the existing literature and indicate that the administration of hypotonic fluids is associated with the development of hyponatremia in hospitalized children. However, it is not possible to state that a transition to isotonic maintenance fluids would fully address the problem of iatrogenic hyponatremia. This is underscored by our finding that over 25% of the children who received isotonic fluids still developed hyponatremia. Although isotonic fluids contain less electrolyte free water than hypotonic fluids, preferential retention of water can still occur in the setting of elevated ADH levels. Hospitalized patients today are complex and often have multisystem disease; many have non-osmotic stimuli for ADH release and might benefit from administration of lower volumes. Although this study was not designed to investigate fluid volume, it is possible that administration of “maintenance fluids” at a reduced or “restricted” rate, which provides both less electrolyte-free water and a smaller total volume of fluid, would similarly, or more effectively, reduce iatrogenic hyponatremia. This approach, which will be the subject of future investigations, is especially important to consider as evidence mounts regarding the morbidity and mortality associated with fluid overload itself. [33, 34] Additionally, in our study, factors other than fluid tonicity contributed to increased risk for iatrogenic hyponatremia. These factors, which included surgical intervention and certain admitting diagnosis categories, are available for consideration upon admission; they could, in theory, be used to optimize fluid management strategies. It is quite possible that a one-size-fits-all approach to intravenous maintenance fluid management is no longer tenable. Future investigations will work to identify factors that can be used to guide fluid management in hospitalized children.

In summary, our findings demonstrate that administration of hypotonic maintenance fluid, when compared with isotonic fluid, is associated with a greater risk for hospital acquired hyponatremia. Although it is possible that a transition to isotonic maintenance fluids in hospitalized children would reduce the rate of iatrogenic hyponatremia, our study suggests that such a change would not eliminate the problem completely as iatrogenic hyponatremia was still common in children receiving isotonic fluids. Rather than focusing solely on fluid composition, future studies designed to determine optimal fluid strategies in hospitalized children should aim to identify additional clinical hyponatremic risk factors, examine alternative approaches to deliver less electrolyte free water such as reduced maintenance fluid volumes in the setting of non-osmotic stimuli for ADH production, and assess the ramifications of greater use of isotonic fluids.

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Abbreviations

ADH antidiuretic hormone

EFW	electrolyte free water
IV	intravenous
SIADH	syndrome of inappropriate antidiuretic hormone secretion
EMR	electronic medical record
NS	normal saline
LOS	length of stay
OR	odds ratio

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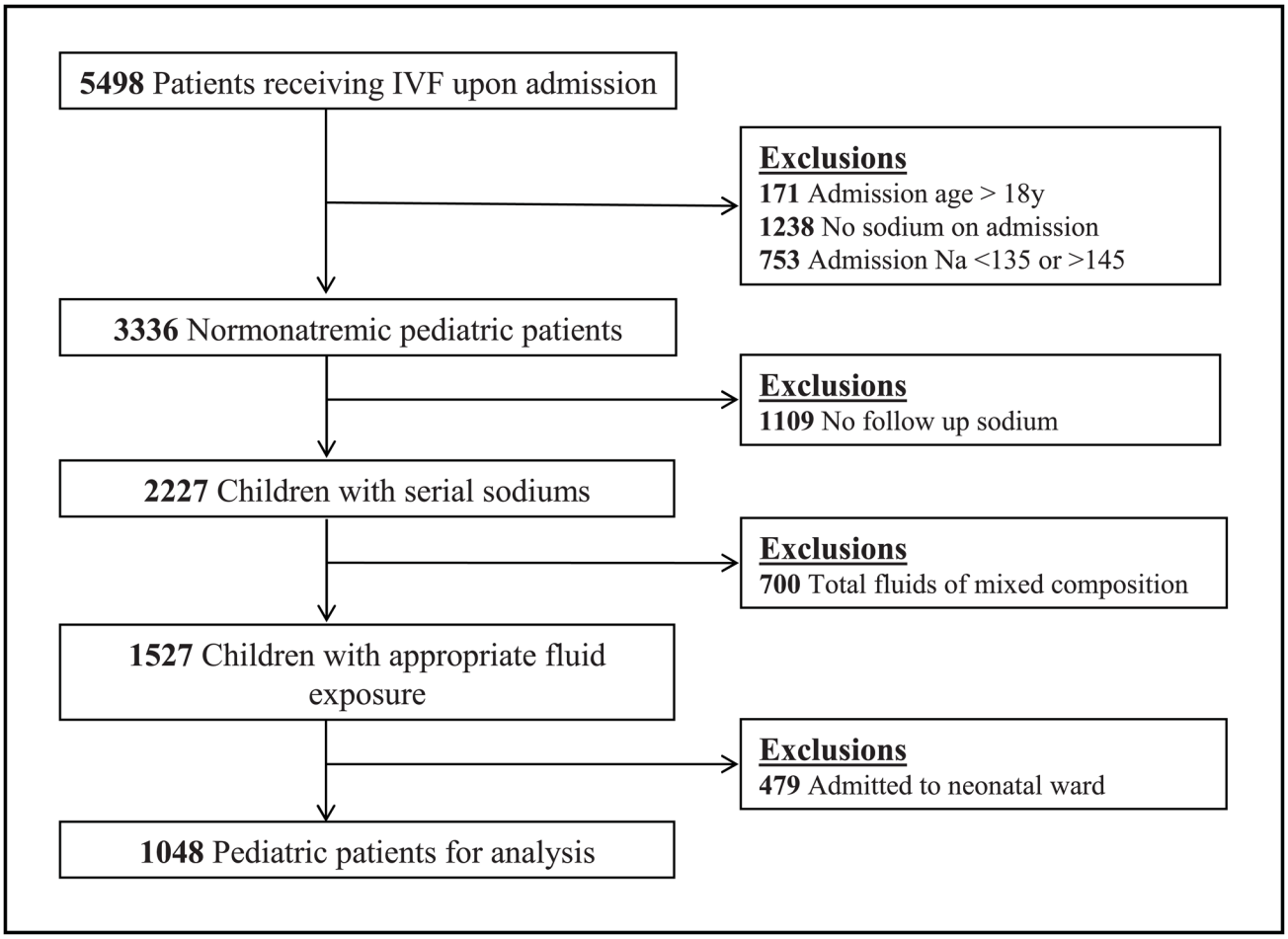

Figure 1. Cohort Creation and Patient Exclusion Criteria

Potential patient numbers and excluded patients. Reasons for exclusion are listed for all patients not ultimately included in the analysis.

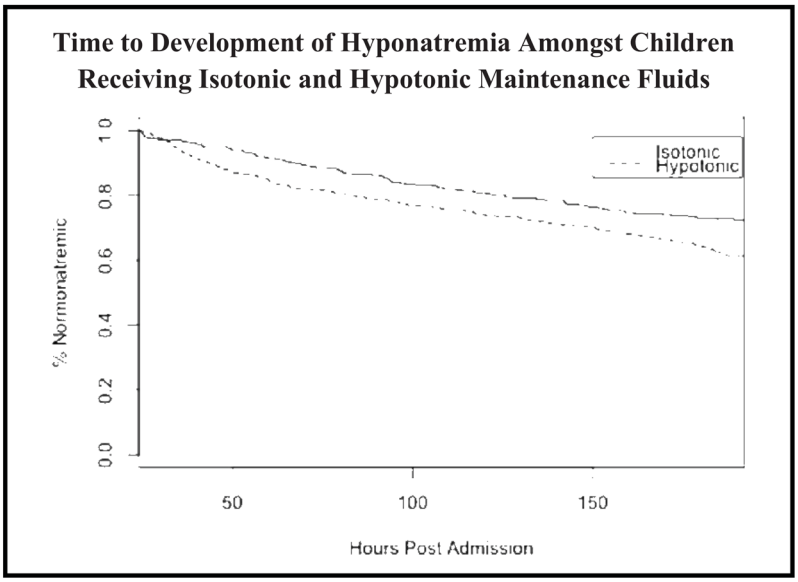

Figure 2. Hyponatremic time-to-event analysis for patients receiving isotonic and hypotonic fluids

Over time patients develop hyponatremia, leading to a decline in the percent of patients remaining normonatremic. Patients receiving hypotonic fluids develop hyponatremia more quickly than patients receiving isotonic fluids. Initial serum sodium values in the two cohorts were equivalent, 138.5 ± 2.6 mEq/L in the isotonic cohort and 138.0 ± 2.5 mEq/L in the hypotonic cohort..

Table 1

Demographics for children receiving isotonic and hypotonic fluids

	Isotonic Maintenance Fluids N=374	Hypotonic Maintenance Fluids N=674	p-value
Age in years, mean ± SD	**8.6 ± 5.2**	**7.0 ± 5.8**	
Less than 1 year (n=149), No. (%)	*31 (8.3)*	*118 (17.5)*	
1 – 6 years (n=399)	*126 (33.6)*	*273 (40.5)*	< 0.001
7 – 12 years (n=253)	*127 (34.0)*	*126 (18.7)*	
13 – 17 years (n=247)	*90 (24.1)*	*157 (23.3)*	
Sex, No. (%)			
Female (n=498)	179 (47.9)	319 (47.3)	0.87
Male (n=550)	195 (52.1)	355 (52.7)	
Race, No. (%)			
African American (n=46)	17 (4.5)	29 (4.3)	
Asian (n=201)	87 (23.3)	114 (16.9)	0.03
Caucasian (n=780)	265 (70.9)	515 (76.4)	
Other (n=21)	5 (1.3)	16 (2.4)	
Admitting Diagnosis, No. (%)			
Cardiology (n=108)	13 (3.5)	95 (14.1)	
Gastroenterology (n=208)	44 (11.8)	164 (24.3)	
Hematology/Oncology (n=237)	56 (15.0)	181 (26.9)	
Infectious Disease (n=95)	31 (8.3)	64 (9.5)	< 0.001
Nephrology (n=65)	15 (4.0)	50 (7.4)	
Neurology/Neurosurgery (n=148)	131 (35.0)	17 (2.5)	
Pulmonology (n=93)	39 (10.4)	54 (8.0)	
Other (n=94)	45 (12)	49 (7.3)	
Surgical Admission, No. (%)			
Yes (n=351)	147 (39.3)	204 (30.3)	0.003
No (n=697)	227 (60.7)	470 (69.7)	
Received Diuretics, No. (%)			
Yes (n=79)	29 (7.8)	50 (7.4)	0.84
No (n=969)	345 (92.2)	624 (92.6)	

Table 2

Multivariable Model Results for Development of Hyponatremia

	Odds Ratio*	95% CI	p-value
Hypotonic Fluids	1.37	1.03 – 1.84	0.03
Hematology/Oncology Diagnosis	2.37	1.74 – 3.25	<0.001
Cardiology Diagnosis	2.08	1.34 – 3.20	0.001
Diuretic Administration	1.52	0.93 – 2.45	0.09
Surgical Admission	1.44	1.09 – 1.91	0.01
Age	0.98	0.95 – 1.00	0.06

* Odds ratios adjusted for all other variables in table