Etiology of postoperative hyponatremia following pediatric intracranial tumor surgery

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OBJECTIVE Cerebral salt wasting (CSW) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) cause postoperative hyponatremia in neurosurgery patients, can be difficult to distinguish clinically, and are associated with increased morbidity. The authors aimed to determine risk factors associated with CSW and SIADH among children undergoing surgery for intracranial tumors.

METHODS This retrospective cohort study included children 0–19 years of age who underwent a first intracranial tumor surgery with postoperative hyponatremia (sodium ≤ 130 mEq/L). CSW was differentiated from SIADH by urine output and fluid balance, exclusive of other causes of hyponatremia. The CSW and SIADH groups were compared with basic bivariate analysis and recursive partitioning.

RESULTS Of 39 hyponatremic patients, 17 (44%) had CSW and 10 (26%) had SIADH. Patients with CSW had significantly greater natriuresis compared with those with SIADH (median urine sodium 211 vs 28 mEq/L, $p = 0.01$). Age ≤ 7 years and female sex were significant risk factors for CSW ($p = 0.03$ and 0.04 , respectively). Both patient groups had hyponatremia onset within the first postoperative week. Children with CSW had trends toward increased sodium variability and symptomatic hyponatremia compared with those with SIADH. Most received treatment, but inappropriate treatment was noted to worsen hyponatremia.

CONCLUSIONS The authors found that CSW was more common following intracranial tumor surgery and was associated with younger age and female sex. Careful assessment of fluid balance and urine output can separate patients with CSW from those who have SIADH, and high urine sodium concentrations (> 100 mEq/L) support a CSW diagnosis. Patients with CSW and SIADH had similar clinical courses, but responded to different interventions, making appropriate diagnosis and treatment imperative to prevent morbidity.

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KEY WORDS cerebral salt wasting; syndrome of inappropriate antidiuretic hormone secretion; hyponatremia; neurosurgery; pediatrics; intracranial neoplasm; oncology

HYONATREMIA occurs in approximately 12% of pediatric patients following intracranial tumor surgery.^{33,34} Hyponatremia from all causes among these children is associated with younger age, hydrocephalus, tumor location, malignant histological findings, and worse neurological outcomes.^{33–35}

Postneurosurgical hyponatremia is frequently attributed to the diagnoses of cerebral salt wasting (CSW) or the syndrome of inappropriate antidiuretic hormone secretion (SIADH), but a clinical distinction between the two disorders can be challenging.^{7,9,11,15,20,25,28,29,31} CSW is

generally regarded as a hypo-osmolar hyponatremic state characterized by primary natriuresis, diuresis, and subsequent volume depletion.^{1,4,7,8,11,15,20,28,29,32} SIADH is generally regarded as a hypo-osmolar hyponatremic state characterized by inappropriate free water retention, subsequent onset of natriuresis, and euvolemia.^{1,4,7,8,15,32} The principal defining feature distinguishing the entities is the patient's volume status, with CSW identified by high urine output and hypovolemia.^{1,5,7–9,15,17,21,25} Other markers of volume status, including heart rate, central venous pressure (CVP), hemoconcentration, red blood cell or plasma volume, and

ABBREVIATIONS CSW = cerebral salt wasting; CVP = central venous pressure; DDAVP = desmopressin; IQR = interquartile range; RR = relative risk; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

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body weight changes, are inconsistently used for definitions, and some markers are infrequently available or of questionable value in clinical practice.^{4,7,10,11,13,15,17,25–27,30–32} Urine sodium concentration is the most common reported laboratory value. Both diagnoses require natriuresis with urine sodium > 20 mEq/L.^{1,12,15,25,31} Some definitions require higher levels (i.e., > 100 mEq/L) for the diagnosis of CSW.^{11,13,27} Appropriate diagnosis is critical given that CSW and SIADH require divergent therapies for correction of hyponatremia, and inappropriate treatment can exacerbate hyponatremia and result in patient harm.^{1,4,7,9,13,31}

Although SIADH and CSW have been reported among a small number of pediatric patients with intracranial tumors,^{7,11–13} studies have not evaluated patient characteristics associated with CSW versus SIADH in children following neurosurgery. In this study, we aimed to determine the proportion of patients with CSW and SIADH following pediatric brain tumor surgery. We used readily available clinical measurements of urine output and fluid balance as markers of volume status, and evaluated risk factors and clinical characteristics associated with CSW and SIADH.

Methods

We conducted a single-center retrospective cohort study of children age 0–19 years who were admitted to Primary Children's Hospital between January 2001 and February 2012 following an initial brain tumor surgery. Children were identified from a database previously used to report the incidence of all causes of hyponatremia, timing and severity of hyponatremia, and neurological outcomes following brain tumor surgery.^{2,34,35} Thirty-nine (12%) of the 319 patients in the database developed postoperative hyponatremia,³⁴ defined as a serum sodium level ≤ 130 mEq/L. An additional in-depth review of those 39 electronic and paper medical records was conducted to analyze the etiology of hyponatremia. The University of Utah's institutional review board approved the study, and granted a waiver of need for informed consent.

The etiology was categorized as CSW, SIADH, or other. The potential etiologies of hyponatremia assessed included intravenous fluid type and amount; medications (vasopressin, desmopressin [DDAVP], diuretics, mannitol, chemotherapy, antiepileptics); dilutional hyponatremia (fluid overload state, heart failure, liver failure, renal failure, anasarca); hyperosmolar hyponatremia (hyperglycemia); hypovolemic hyponatremia from vomiting or diarrhea; adrenal insufficiency; hypothyroidism; CSW; and SIADH. Prereview definitions for CSW and SIADH were consistent with previous reports in which available clinical data were used to assess volume status.^{4,7,11,13,25,27,32} CSW was defined by evidence of hypovolemia (urine output ≥ 3 ml/kg/hr and fluid balance ≤ 100 ml). SIADH was defined by evidence of euvolemia (urine output ≤ 2 ml/kg/hr and fluid balance ≥ 200 ml). The etiology was classified as "other" if patients did not meet criteria for SIADH or CSW, or if another etiology was identified on review. Patients in the "other" classification were not included in the between-group analyses. Data for urine output (in ml/kg/hr) and fluid balance (total intake minus total output in

ml) were calculated for up to a 12-hour period preceding the onset of hyponatremia for analysis. Most patients had hourly recordings for input and output, and all patients had recordings at least every 4 hours.

Other potential markers of volume status, including CVP and heart rate standardized to age,¹⁸ were assessed when available. Urine sodium concentrations were collected when available. Urine sodium measurements > 20 – 100 mEq/L were considered consistent with SIADH and measurements > 100 mEq/L were considered consistent with CSW.^{11,13,27} No patient had measured values inconsistent with the initial assigned diagnosis.

Tumor locations, metastases, histological findings, hydrocephalus, and stroke were collected from radiological, surgical, and pathology reports.³⁴ Infection included pneumonia, bacteremia, meningitis, and urinary tract infections. Sodium variability and severity of hyponatremia were obtained from laboratory data consistent with our previous report.² One patient with SIADH had pre- and postoperative hyponatremia, and only the postoperative course was analyzed in that individual.

Times of low sodium values were used to review for the presence of hyponatremia symptoms, including altered mental status and seizures.³⁴ The sodium level at the time of the symptom and any treatments received were also recorded. Treatment of hyponatremia included normal saline fluid bolus, hypertonic saline infusion, enteral sodium chloride supplementation, a change to the maintenance intravenous fluid rate or type of fluid, and fluid intake restriction. The response to treatment, evaluated by changes in serum sodium, was noted.

Data were analyzed with the R statistical analysis program (version 2.15.2, www.R-project.com). Univariate results were expressed as counts with percentages for categorical variables, and as medians with the interquartile range (IQR) for continuous variables. Bivariate analyses for differences between the CSW and SIADH groups were conducted using Fisher exact (categorical variables) and Kruskal-Wallis (continuous variables) methods. Relative risk (RR) with a 95% CI was calculated when applicable. All tests were 2-tailed. Significance was defined as $p < 0.05$. Recursive partitioning was used to create a risk-stratified flow diagram for risk of CSW between the 2 study groups by using significant variables from the bivariate analyses.

Results

Thirty-nine patients had postneurosurgical hyponatremia—17 (44%) had CSW, 10 (26%) had SIADH, and 12 (31%) had other etiologies identified (Table 1). All patients received postoperative dexamethasone, and they received intravenous fluid at maintenance rates until they tolerated enteral diets. The intravenous fluid type varied during the study period ($p = 0.009$). The rate of hyponatremia did not vary with study year or intravenous fluid type.³⁴ The etiology of hyponatremia did not vary by year ($p = 0.9$). Sodium content and rate of fluid varied at the onset of hyponatremia but were similar between groups; more than half of patients ($n = 9$ with CSW, $n = 6$ with SIADH) were receiving maintenance intravenous 0.9% saline, and the

TABLE 1. Etiologies other than CSW or SIADH for postoperative hyponatremia in 12 patients

Other Etiology	No. of Patients
Vasopressin or DDAVP administration	5
Chemotherapy & concurrent hyponatremic fluid administration	3
Severe vomiting & dehydration	1
Fluid overload following aspiration-induced ARDS	1
Indeterminate/multiple possible etiologies	2

ARDS = acute respiratory distress syndrome.

rest (n = 8 with CSW, n = 4 with SIADH) were receiving intravenous 0.45% saline, enteral feeding only, or a combination of intravenous fluids and feeding methods. Fewer patients were receiving 0.9% saline at the onset of hyponatremia as time from the surgical procedure increased (p = 0.007). No patients with CSW or SIADH were receiving diuretics prior to hyponatremia onset.

Demographic and clinical characteristics for the patients with CSW and SIADH are presented in Table 2. Patients with CSW were significantly younger (p = 0.02),

and a higher proportion was female (RR 1.9, 95% CI 1.1–3.3). The median age was 1.6 years for patients with CSW and 8.1 years for those with SIADH, with age < 4.3 years in 75% of patients with CSW. Recursive partitioning revealed age ≤ 7 years as the most significant risk factor for CSW, and female sex portended an even greater risk among young patients (Fig. 1).

Urine sodium measurements were obtained in approximately half of patients at the onset of hyponatremia. When measured, all patients classified as CSW (n = 11) had urine sodium measurements > 140 mEq/L and all patients classified as SIADH (n = 3) had urine sodium measurements > 25 and < 70 mEq/L. Most patients underwent resection for their intracranial tumor, but 1 patient with CSW underwent biopsy only prior to hyponatremia. Tumor characteristics did not vary by group. Obstructive hydrocephalus and related ventriculostomy or shunt placement were common and similar between groups. No patients had an infection diagnosed prior to hyponatremia onset.

Markers of hyponatremia severity and sodium variability for patients with CSW and SIADH are presented in Table 3. Rapid serum sodium drops of > 10 mEq/L within any 24-hour period occurred in a higher but nonsignificant proportion (41% vs 10%) of patients with CSW (RR

TABLE 2. Demographic and clinical characteristics by etiology of hyponatremia

Characteristic	CSW	SIADH	p Value
No. of patients	17	10	
Median age in yrs (IQR)	1.6 (1.4–4.3)	8.1 (2.8–11)	0.02
Female sex	9 (53%)	1 (10%)	0.04
Race/ethnicity			0.33
Caucasian	15 (88%)	7 (70%)	
Other	2 (12%)	3 (30%)	
Median fluid balance in ml (IQR)	–156 (–326 to 3)	348 (298–444)	*
Median urine output in ml/kg/hr (IQR)	3.9 (3.5–5.1)	1.4 (1.1–1.6)	*
Median CVP in mm Hg (IQR)†	2 (1–3)	6 (3–9)	0.06
Heart rate for age‡			>0.99
Tachycardia	3 (18%)	1 (10%)	
Bradycardia	1 (6%)	0	
Normal	13 (76%)	9 (90%)	
Median urine sodium in mEq/L (IQR)§	211 (186–254)	28 (27–45)	0.01
Tumor location			0.80
Cortex	1 (6%)	2 (20%)	
Cerebellum or brainstem	5 (29%)	2 (20%)	
Deep brain or ventricles	6 (35%)	3 (30%)	
Overlapping	5 (29%)	3 (30%)	
Malignant histological findings	11 (65%)	8 (80%)	0.67
Metastases	4 (24%)	2 (20%)	>0.99
Obstructive hydrocephalus	14 (82%)	7 (70%)	0.64
Ventriculostomy	13 (76%)	7 (70%)	>0.99
Ventriculoperitoneal shunt	4 (24%)	3 (30%)	>0.99
Postop stroke	2 (12%)	0	0.52

* These characteristics were used to define groups of patients with CSW or SIADH; a statistical test was not used to compare the groups.

† The CVP measurements were available for 7 (41%) of the patients with CSW and 4 (40%) of the patients with SIADH.

‡ All patients had measurements. One patient with bradycardia and CSW was receiving continuous sedative infusion.

§ Urine sodium measurements were available in 11 (65%) of the patients with CSW and 3 (30%) of the patients with SIADH.

FIG. 1. Multivariable modeling with recursive partitioning revealed that patient age ≤ 7 years was the most important risk factor for CSW. Following age, female sex portended greater risk of CSW versus SIADH.

1.7, 95% CI 1.0–2.7). There was a nonsignificant trend toward lower sodium nadir and higher maximum sodium among patients with CSW compared with SIADH. Serum sodium values ≤ 135 mEq/L manifested in all patients within 6 postoperative days, and onset was within 2 postoperative days for 75% of patients in both groups. Time to first serum sodium value ≤ 130 mEq/L was more variable, occurring within 5 postoperative days for 75% of patients, but up to 13 days for the CSW group and up to 21 days for the SIADH group.

Symptomatic hyponatremia with altered mental status or hyponatremic seizures occurred in a nonsignificant but higher proportion of patients with CSW versus SIADH (47% vs 20%; RR 1.5, 95% CI 0.9–2.6). Hyponatremic seizures occurred in 5 (29%) patients with CSW and no patients with SIADH (RR 1.8, 95% CI 1.3–2.7). The median serum sodium level for all patients with altered mental status was 126 mEq/L (IQR 123, 129; Range 120–130) and with hyponatremic seizures it was 123 mEq/L (IQR 120, 127; Range 110–130), and this did not vary by group

($p = 0.89$). All patients with hyponatremic seizures were treated with hypertonic saline infusion. Seventy-five percent of patients with altered mental status were treated with hypertonic saline, whereas others received normal saline boluses or enteral salt supplementation at the time of the symptom.

Nine (90%) patients in the SIADH group were treated with fluid restriction, enteral sodium supplementation, and/or hypertonic saline. One (10%) patient with SIADH did not receive treatment, had a sodium nadir of 130 mEq/L, and was asymptomatic. All patients with CSW were eventually treated with increased fluid and sodium supplementation; however, 4 (24%) patients with CSW were treated with fluid restriction prior to receiving appropriate therapy. Three of these 4 patients had no symptoms or significant worsening of hyponatremia prior to recognition and a change to appropriate management. One of these 4 patients with CSW had a sodium decrease from 131 to 124 mEq/L after institution of fluid restriction, and experienced altered mental status prior to being treated

TABLE 3. Sodium measurements by etiology of hyponatremia

Sodium Measurement	CSW	SIADH	p Value
No. of patients	17	10	
Decrease >10 mEq/L in 24 hrs	7 (41%)	1 (10%)	0.19
Median value (IQR)			
Average sodium, in mEq/L	135.9 (134.3–136.8)	134.7 (133–136.6)	0.25
Nadir sodium, in mEq/L	127 (124–130)	130 (127.5–130)	0.24
Maximum sodium, in mEq/L	144 (141–148)	141.5 (139.3–143.8)	0.14
Onset of sodium ≤ 130 mEq/L, in days	1.7 (0.99–2.65)	1.26 (0.28–4.28)	0.62
Onset of sodium ≤ 135 mEq/L, in days	0.83 (0.38–1.43)	0.17 (0.06–0.65)	0.05
Duration of sodium ≤ 130 mEq/L, in days	0.65 (0.32–1.26)	0.49 (0.19–1.14)	0.48
Duration of sodium ≤ 135 mEq/L, in days	7.56 (4.45–19.97)	9.08 (5.5–18.9)	0.80
Episodes of sodium ≤ 130 mEq/L	2 (1–5)	1.5 (1–4.25)	0.62
Episodes of sodium ≤ 135 mEq/L	6 (2–11)	2 (2–8)	0.27

with hypertonic saline and increased maintenance fluids, which corrected the hyponatremia.

Discussion

We classified hyponatremia etiology by excluding other known causes and using the commonly available measures of urine output and fluid balance as surrogates for the patient's volume status, consistent with previous reports.^{4,7,11,13,25,27,32} No universal diagnostic criteria exist to distinguish SIADH and CSW despite a recent systematic review²⁰ and published European guidelines on hyponatremia,²⁸ although differences in volume status are reinforced. Invasive measures of volume status are often not available and are impractical when managing hyponatremia in the acute setting. Given these limitations, clinicians are faced with determining volume status by clinical judgment and available surrogates, like urine volume and fluid balance, which are the variables we chose to define groups. Urine volume and fluid balance often vary in the postoperative period, so we chose to calculate totals for the 12 hours preceding hyponatremia documentation in hopes of capturing only the most recent patient trends. Our classifications were supported by urine sodium measurements when available, because patients with CSW had significantly greater natriuresis (urine sodium > 100 mEq/L), consistent with previous reports.^{11,13,27,32} Additionally, our proportion of patients with CSW is consistent with a smaller postoperative study of pediatric patients treated for brain tumor, which reported that 50% of hyponatremic patients had CSW.¹¹ Our patients also showed improvement with appropriate therapy.

Other clinical markers of volume status (heart rate and CVP) did not differ between groups and were not useful to estimate volume status, similar to findings in other reports.^{7,13,32} Heart rate is a nonspecific marker of volume status in neurosurgical patients, given the commonly encountered confounders of pain, sedative medications, anemia, and so on in the postoperative period. The CVP has been used as the sole determinant of volume status and hyponatremia etiology;^{10,17} however, this marker has been questioned as a surrogate for volume status^{4,15,16} and is infrequently available postoperatively among pediatric patients who have been treated for brain tumors.¹¹ Among our patients, trends toward lower CVP with CSW compared with SIADH were seen, but few had measurements available. Historically, central venous catheters were placed for intraoperative monitoring and vascular access, but are now infrequent, and when placed are often removed in the immediate postoperative period.

Age ≤ 7 years and female sex were important risk factors for CSW compared with SIADH. We previously reported a significant association between all causes of hyponatremia and young age.^{2,34} Hardesty et al. also noted an association between young age and CSW in hyponatremic patients compared with eunatremic patients.¹¹ The association between age and CSW may reflect the relative immaturity of renal and brain tissues in young patients. One hypothesis for the cause of CSW is disruption of sympathetic signaling to the kidney,^{5,8,9,21,31} so young patients with immature sympathetic nervous systems may be at in-

creased risk of the disorder. A study of adult neurosurgical patients, including a proportion with tumors, found that SIADH was more common compared with CSW (62% vs 5%).²⁵ Sex hormones have been associated with antidiuretic hormone release,²¹ which may account for some increased risk of SIADH in older pubertal children and adults. Overall hyponatremia risk does not vary by sex in adults, but premenopausal females have been reported to be more likely to suffer morbidity from hyponatremic encephalopathy thought to be a result of hormonal differences.^{19,21} Additionally, the vasopressin receptor V2 is encoded on the X chromosome and transcription may occur in higher levels in females,¹⁴ which may predispose to sex differences.

We did not find differences in tumor locations between CSW and SIADH groups, although numbers of tumors in each region were low. Prior studies reported an association between CSW and chiasmatic/hypothalamic tumors when patients with CSW were compared to eunatremic patients¹¹ and an association between SIADH and cortical tumors when patients with SIADH were compared to patients with diabetes insipidus.¹² No prior studies have compared tumor locations between patients with SIADH and CSW. The pathogenesis of SIADH relates to loss of normal feedback mechanisms and release of antidiuretic hormone from the supraoptic and paraventricular nuclei of the hypothalamus,^{9,21,31} so tumors or surgeries in this area may contribute to the development of this syndrome.^{31,33} However, SIADH can result from location-independent variables, including stress, pain, and nausea,^{9,19} and elevated levels of ADH are found in patients with CSW due to hypovolemia.^{6,21,30,31} Additionally, natriuretic peptides released by the hypothalamus may contribute to the development of CSW.⁷⁻⁹ However, the distribution of natriuretic peptides is not uniform in the brain,³ their elevation in CSW is not consistent,^{8,9,26} and they can be elevated in patients with SIADH.^{24,30} Until we understand the exact pathogenesis of CSW and SIADH, an association with tumor or surgical location may not be found.

Both groups had sodium levels ≤ 135 mEq/L, and most had sodium levels ≤ 130 mEq/L within the first postoperative week. Our data are consistent with studies showing a similar onset within the first week after any neurological insult for patients with CSW or SIADH.^{4,7,11-13,17,23,25,27,32} Most patients had a limited duration of hyponatremia, which is consistent with previous reports that SIADH and CSW are usually self-limited;^{7,11-13,17,25,32} however, some patients with CSW and SIADH had prolonged courses lasting for weeks.^{7,11,13,22,32} Larger studies could assess patient or disease characteristics that could account for later onset and prolonged disease.

We noted a trend toward increased sodium variability in patients with CSW compared to those with SIADH, and we are unaware of other studies assessing sodium variability between these diagnoses. It is unclear if sodium variability reflects pathophysiological mechanisms or response to treatment. We also noted a trend toward increased symptomatic hyponatremia among patients with CSW. Hardesty et al. noted a high incidence of seizures among pediatric patients with brain tumors who had CSW.¹¹ The concern with hyponatremia is the develop-

ment of neurological complications from cerebral edema,^{5,19,21} which is more likely to occur with acute decreases in serum sodium,^{9,21} and is less well tolerated among pediatric patients and those with neurological disease.^{19,21,24,31}

The need for proper identification and treatment of SIADH and CSW to prevent patient harm is well documented.^{1,4,7,9,13,31} Most of our patients received appropriate therapies; however, 1 patient had worsening hyponatremia and encephalopathy after apparently improper management. This patient had urine output > 3 ml/kg/hr, negative fluid balance, and urine sodium > 200 mEq/L. Careful review of these available data may have been able to prevent the subsequent worsening of hyponatremia after fluid restriction if the diagnosis of CSW had been made initially. This case and others⁷ reported as receiving improper treatment highlight the difficulty sometimes present in distinguishing these conditions. Despite the variability that exists in defining the diagnosis of CSW, there appear to be readily available clinical tools (urine output and fluid balance) to help steer clinicians toward proper diagnosis and to prompt further investigation, such as urine sodium, when the diagnosis is unclear.

Our study has several limitations to consider. The retrospective nature of data collection cannot ensure the accuracy of all collected variables. Even though this is the largest cohort of hyponatremic pediatric patients with brain tumors in which etiology was evaluated, our sample was inadequately powered to detect differences in some clinical characteristics, so caution is needed when interpreting data trends. Care practices at our institution have evolved over the study period, particularly with regard to sodium content of intravenous fluids, and the effect of changing practices could not be assessed with the small sample size. Additionally, because a universally accepted definition for the diagnosis of CSW does not exist, the accuracy of our classifications cannot be ensured, although they were supported by review of urine sodium measurements and response to treatments, consistent with previously reported definitions, and our results were similar to those reported in the literature for other neurosurgical patients. Future research assessing differences between the characteristics of patients with CSW and those with SIADH should include a larger cohort of patients, consideration of prospective data collection with inclusion of additional markers of volume status, and standardized diagnostic and treatment protocols to limit confounding variables.

Conclusions

Our previous works have shown that hyponatremia after pediatric brain tumor surgery is common, particularly among young children with hydrocephalus, and is associated with worsened cognitive outcome.^{2,33–35} CSW was the most common cause of hyponatremia among our cohort and, compared with SIADH, was significantly associated with young age and female sex. Both conditions manifest within the first postoperative week. The commonly available clinical measurements of fluid balance and urine volume can establish a diagnosis of CSW or SIADH in most cases. Urine sodium measurements may provide an additional distinction, because patients with CSW exhibited

a significantly greater natriuresis at the onset of hyponatremia (CSW > 140 mEq/L vs SIADH > 25–70 mEq/L). Given this information, we recommend the routine use of 0.9% saline when intravenous fluid supplementation is required and that serum sodium be closely monitored for at least several days after surgery, especially in young children with hydrocephalus. When hyponatremia occurs, we recommend evaluation of the patient's volume status, with fluid balance and urine volume, and urine sodium measurements to distinguish CSW from SIADH and to help guide therapy.

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Disclosures

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Author Contributions

Conception and design: Williams. Acquisition of data: Williams. Analysis and interpretation of data: all authors. Drafting the article: Williams. Critically revising the article: Riva-Cambrin, Bratton. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Williams. Statistical analysis: Williams, Bratton. Administrative/technical/material support: Riva-Cambrin. Study supervision: Bratton.

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