

# Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Hyponatremia

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## Knowledge Gaps

Hyponatremia is a common electrolyte disturbance in hospitalized children that is often related to increased action of antidiuretic hormone; practitioners should be familiar with clinical characteristics of children at risk for syndrome of inappropriate secretion of antidiuretic hormone (SIADH), as well as approach to diagnosis. By knowing how to identify children with SIADH or those at risk for developing hyponatremia, modifications can be made in the prescription of intravenous fluid to avoid the development of hyponatremia or to treat hyponatremia.

## Objectives After completing this article, readers should be able to:

1. Review the mechanisms that control water excretion and maintain normal plasma osmolality.
2. Describe the major causes of hyponatremia in children.
3. Apply clinical tests to identify children with hyponatremia to determine the underlying condition.
4. Identify children at risk for syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and modify fluid management to avoid development of hyponatremia.
5. Describe the approach to treatment of hyponatremia and, in particular, hyponatremia secondary to SIADH.

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### ABBREVIATIONS

ADH	antidiuretic hormone
BUN	blood urea nitrogen
CNS	central nervous system
IV	intravenous
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
V2R	vasopressin 2 receptor

The discussion of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) begins with review of the causes of hyponatremia, since SIADH is a major cause of hyponatremia and hyponatremia is usually the abnormal finding that leads to its diagnosis. SIADH is defined as the presence of hypo-osmolality when urine is inappropriately concentrated (osmolality is inappropriately high) and there is no evidence of renal salt wasting or hypovolemia in an individual with normal renal, adrenal, thyroid, cardiac, and liver functions (Table 1). (1) It is reversible with water restriction. In SIADH, antidiuretic hormone (ADH) activity is considered “inappropriate,” since there is no

identifiable osmotic or hemodynamic stimulus for its action. Factors that control plasma osmolality and sodium levels, the major causes of hyponatremia in children and adolescents, how to evaluate the underlying cause of hyponatremia (including SIADH), how to identify children at risk, and how to approach the diagnosis and treatment of SIADH will be reviewed in this article.

## PHYSIOLOGY OF OSMOTIC AND NONOSMOTIC CONTROL OF ADH SECRETION

Arginine vasopressin, also known as *ADH*, is produced by a subset of neurons in the paraventricular and supraoptic nuclei of the hypothalamus, the axons of which extend through the pituitary stalk into the posterior pituitary gland, where ADH is stored in granules. (2)(3) There are osmotic, hemodynamic, and nonhemodynamic or osmotic stimuli for ADH release. (4) The osmotic response for increased ADH secretion occurs with as little as 1% increase in plasma osmolality; the normal threshold is a plasma osmolality of 283 mOsm/kg (283 mmol/kg). Sensory neurons respond to changes in plasma osmolality with inversely proportional changes in cell volume; cells shrink in response to higher osmolality, activating the signaling cascade and resulting in vasopressin release. The thirst response is sensed by neurons in the ventromedial nucleus; thirst is activated at a higher plasma osmolality level than that which triggers ADH release—at 293 mOsm/kg (293 mmol/kg). The hemodynamic stimulation of ADH occurs when baroreceptors located in the carotid sinus, aortic arch, cardiac atria, and pulmonary venous system

respond to decreased effective blood volume or blood pressure. The baroreceptor response is activated after a 5% to 10% decrease in effective blood volume. (2)(3)(5)

The increase in ADH release stimulates water reabsorption through binding to vasopressin 2 receptor (V2R) located on the basolateral (blood) membrane of the collecting duct principal cell; stimulation of V2R induces the movement of aquaporin water channels into the apical membrane. The physiological effect is to allow increased water entry from the lumen of the renal tubule, which results in reduced urine volume and increased urine osmolality. In the absence of ADH, such as when plasma osmolality level decreases below 280 mOsm/kg (280 mmol/kg), urine osmolality may reach less than 100 mOsm/kg (100 mmol/kg), which is the appropriate response to decreased plasma osmolality. However, as plasma osmolality increases to levels above normal, ADH increases free water absorption to lower plasma osmolality, ultimately achieving a urine concentration of approximately 1,200 mOsm/kg (1,200 mmol/kg). There are additional renal effects on sodium and urea transport that will not be discussed further in this review; readers are referred to references 2 and 6 for a detailed discussion. The hemodynamic stimuli for ADH will prevail over osmotic signals to suppress ADH production to restore extracellular volume. In addition, ADH levels may be increased by nonosmotic and nonhemodynamic stimuli, including conditions such as nausea, emesis, hypoxia, stress, pain, anesthesia, and numerous drugs (see Table 2).

Since sodium is the major determinant of plasma osmolality, hyponatremia is usually associated with hypo-osmolality. Solutes confined to the extracellular space, such as sodium and glucose, determine osmolality. The most common laboratory method for measurement of serum sodium level serves to determine the concentration in plasma and then enable calculation of the serum concentration. When there is an increase in the solid-phase components in plasma, such as hyperlipidemia or hyperproteinemia, the serum sodium concentration may be normal, but when measured in total plasma, the level appears low (due to displacement of the aqueous phase). (7) Measurement of plasma osmolality will confirm if hypo-osmolality is truly present. Alternatively, excessive extracellular solutes, such as glucose and mannitol, may increase the plasma osmolality level and cause hyponatremia in the absence of hypo-osmolality. When there is excess solute to which the cell membrane is relatively impermeable, then water moves according to the osmotic gradient from the intracellular space to the extracellular space, resulting in decreased sodium concentration but normal to increased plasma osmolality levels.

**TABLE 1. Definition of Syndrome of Inappropriate Secretion of Antidiuretic Hormone**

Definition of syndrome of inappropriate antidiuretic hormone secretion:
<ul style="list-style-type: none"> <li>• Hypotonicity and hyponatremia (plasma osmolality &lt;280 mOsm/kg, plasma sodium &lt; 135 mEq/L)</li> </ul>
<ul style="list-style-type: none"> <li>• Inappropriately concentrated urine (urine osmolality &gt;100 mOsm/kg)</li> </ul>
<ul style="list-style-type: none"> <li>• High urine sodium concentration (&gt;20 mEq/L, except during sodium restriction)</li> </ul>
<ul style="list-style-type: none"> <li>• Absence of sodium excess (edema) or clinical signs of volume depletion</li> </ul>
<ul style="list-style-type: none"> <li>• Normal renal, cardiac, hepatic, adrenal, and thyroid function</li> </ul>

To convert milliosmoles per kilogram to millimoles per kilogram, multiply by 1. To convert milliequivalents per liter to millimoles per liter, multiply by 1.

TABLE 2. Causes of Syndrome of Inappropriate Secretion of Antidiuretic Hormone in Children

ACUTE CONDITIONS	PULMONARY DISEASE	NEUROLOGICAL DISEASES	MEDICATIONS	MALIGNANT DISEASE	HEREDITARY CAUSES
General anesthesia	Positive pressure ventilation	Meningitis, encephalitis	Carbamazepine	Lymphoma	Gain of function mutation V2R
Stress	Bronchiolitis	Tumors	Vincristine	Ewing sarcoma	
Nausea	Pneumonia	Trauma	Cyclophosphamide	Carcinoma (lung, bladder, etc)	
Pain	Asthma	Hydrocephalus	Tricyclic antidepressants		
Stress	Cystic fibrosis	Brain abscess	Narcotics		
		Rocky mountain spotted fever	NSAIDs		
		Cavernous sinus thrombosis	MDMA (ecstasy)		
		Guillain-Barré syndrome	SSRI		
		Cerebrovascular accident	Desmopressin		
		Subdural hematoma	Ciprofloxacin		
			Amiodarone		

For a complete list, see references 1 and 2.

MDMA=3,4-methylenedioxymethamphetamine, NSAIDs=nonsteroidal anti-inflammatory drugs, SSRI=selective serotonin reuptake inhibitor; V2R=vasopressin 2 receptor.

## DIAGNOSIS OF SIADH AND OTHER HYPONATREMIC DISORDERS

Although the definition of clinically significant hyponatremia has evolved, currently it is defined as the presence of serum sodium level less than 135 mEq/L (135 mmol/L); it is the most common electrolyte disturbance among hospitalized adults, with an estimated incidence of 15% to 30%. Hospital-acquired or iatrogenic hyponatremia has been reported to account for 40% to 75% of all cases of hyponatremia among adults. Certain groups are at increased risk for hyponatremia, including adults with heart failure, adults with cirrhosis, and elderly adults residing in chronic care facilities (related to excess water from tube feedings or flushes and underlying central nervous system [CNS] disease). (8) Hyponatremia can increase the risk for morbidity and mortality among adults; hyponatremia is considered to represent a surrogate marker of overall neurohormonal activation, particularly of the renin-angiotensin system.

The incidence of hyponatremia among hospitalized children has been reported to be 1.4% to 45%, depending on the definition (<130 mmol/L or <135 mmol/L) and whether hyponatremia was present at initial evaluation or developed after administration of intravenous (IV) fluids. (4) Incidence of patients with sodium level less than 135 mEq/L (135 mmol/L) at admission ranged from 17% to 45% (9)(10)(11), while patients with more severe hyponatremia (<130 mEq/L [<130 mmol/L]) comprised 3.7% of admissions (11); hospital-acquired hyponatremia (<135 mEq/L

[<135 mmol/L]) occurred in 20% to 35% of patients, (10) (12)(13) while 1.4% to 5% of patients had sodium levels less than 130 mEq/L (130 mmol/L). (12)(14) Hyponatremia can be classified as that related to the acute illness (present at initial evaluation) or hospital acquired (or iatrogenic). Among children hospitalized at Texas Children's Hospital over 12 months, at admission, 161 of 11,702 patients (1.4%) had a serum sodium level less than 130 mEq/L (130 mmol/L). (14) Of these, 43% had hyponatremia at admission, and 57% developed hospital-acquired hyponatremia. This level of hyponatremia would be defined as moderate to severe by current standards. Most children (77%) with hyponatremia had some form of chronic medical condition. The most common etiologic origins identified were gastroenteritis, which was the most common cause at admission, and diuretics, which were the most common cause of hospital-acquired hyponatremia. Other common causes were SIADH, nasogastric or chest tube fluid loss, and hyperglycemia. (14) The incidence of hyponatremia (sodium level <135 mmol/L) in children with community-acquired pneumonia was 45%; moderate (sodium level < 130 mmol/L) to severe (sodium level <125 mmol/L) hyponatremia was present in 3.7%. (11) The prevalence of hyponatremia at admission to the pediatric intensive care unit was 33% in a prospective, randomized, single-center cohort study also designed to evaluate the effect of hypotonic versus isotonic fluids on serial serum sodium levels. (15) In another study designed to analyze risk factors for development of hyponatremia after administration of IV fluid, 22% of children in whom at least

2 sodium levels were measured had hyponatremia (sodium level < 130 mmol/L). Of those with hyponatremia, 64% had hyponatremia at baseline assessment. Some patients who initially presented with hyponatremia had hyponatremia reoccur: A total of 9% (40 of 432) developed hyponatremia during hospitalization, with decrease in mean serum sodium level  $\pm$  SD from  $139 \pm 3$  mEq/L ( $139 \pm 3$  mmol/L) to  $133 \pm 3$  mEq/L ( $133 \pm 3$  mmol/L). (10) Children with iatrogenic hyponatremia were more likely to exhibit nausea and vomiting, to have postoperative status, and to have received a greater volume of electrolyte-free water (further discussion to follow). Morbidity and mortality related to hyponatremia have been reported in children, particularly those who receive anesthesia or are in the postoperative state. Since many children undergoing surgical procedures do not have serum electrolyte levels measured prior to surgery, the incidence of hyponatremia, particularly baseline hyponatremia, may be underestimated; only 6% of patients enrolled in a prospective, randomized study of a pediatric surgical cohort had baseline serum sodium levels measured. (16)

#### CLINICAL SIGNS AND SYMPTOMS OF HYPONATREMIA

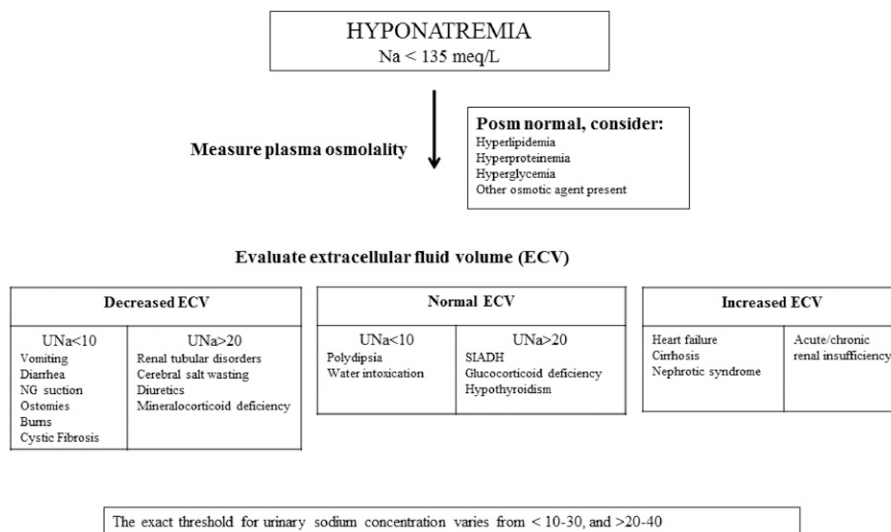
Symptoms of hyponatremia are nonspecific and include headache, nausea, vomiting, muscle cramps, lethargy, restlessness, confusion, and seizures. Rapid change in serum sodium concentration is associated with acute neurological compromise. The major physiological effect of hyponatremia is neurological dysfunction related to cerebral edema, a condition known as *hyponatremic encephalopathy*. Because of the inability of sodium to cross the blood-brain barrier, hyponatremic encephalopathy is the result of cerebral cell swelling caused by water movement into the cell to establish equal osmolality between the extracellular and intracellular spaces. Regulatory mechanisms to restore cell volume toward baseline include efflux of electrolytes and reduction of cell volume. Slower adaptation occurs with generation of organic osmolytes that can be released to maintain cell volume toward normal. If plasma tonicity rapidly increases, brain cells, which contain a lower-than-normal quantity of osmolytes, will respond by decreasing cell volume as water moves from the intracellular to the extracellular space. Thus, rapid correction of hyponatremia may potentially lead to additional neurological sequelae, known as *pontine myelinolysis*, which is characterized by demyelination of pontine and extrapontine neurons (osmotic demyelination); clinically, this may manifest as seizures, coma, paralysis, and death. (7) Osmotic demyelination is extremely rare in children. The reader is referred to reference 4 for an excellent review of hyponatremic encephalopathy in children.

Most reviews on the subject of hyponatremia focus on adults and provide exhaustive lists of potential causes, while there is a paucity of information on the epidemiology of hyponatremia in children. Much of the current literature addresses how best to approach the prescription of IV fluid therapy in hospitalized children at risk for SIADH in an effort to avoid the development of hyponatremia (to be covered in the following sections). In general, hyponatremia is caused by solute loss (sodium deficiency) or water excess (water retention in excess of sodium retention). (1)(2)(17)

The classic diagnostic approach to determine whether hypo-osmolality or true hyponatremia is present is via measurement of the plasma osmolality. If hypo-osmolality is confirmed, the etiologic origin of hyponatremia can be classified into 3 major categories on the basis of the extracellular fluid volume: decreased, normal, or increased (Fig). Further classification depends on the urinary sodium excretion.

Causes of hypovolemic hyponatremia can be classified into renal and extrarenal sodium loss. Among children, the most common causes include (a) gastrointestinal losses of fluid and electrolytes from gastroenteritis and acute intra-abdominal processes, such as nasogastric suction, ostomies, and fistulas; (b) renal losses from salt-wasting nephropathies, osmotic diuresis, diuretic medications, or adrenal insufficiency; (c) skin loss from burns and, rarely, cystic fibrosis; and (d) conditions associated with third-space sequestration, such as sepsis and anaphylaxis. Urinary sodium concentration and excretion can be used to differentiate between primary salt-wasting disorders and conditions with nonrenal loss. When hypo-osmolality occurs in the setting of hypovolemia or reduced effective plasma volume (third-spacing), the nonosmotic stimulus for ADH secretion will override the osmotic signals and result in higher-than-appropriate urine osmolality. Repletion of the vascular volume with isotonic fluid would be expected to reverse the process and result in an ability to excrete a dilute urine and normalization of serum sodium concentration. Factors that help to differentiate hypovolemic hyponatremia from hyponatremia with normal or increased extracellular fluid volume include a history of fluid loss and/or decreased oral intake, increase in heart rate or decrease in blood pressure, orthostatic change in blood pressure or heart rate, increased blood urea nitrogen (BUN) or BUN/creatinine level, and increased serum uric acid level. Provision of isotonic fluid will correct hyponatremia in this setting.

Causes of hyponatremia with normal extracellular fluid volume include SIADH as the major cause, with glucocorticoid and hypothyroidism as minor causes. In most cases of SIADH, urinary sodium level is high, greater than 20 mEq/L (20 mmol/L); however, in cases of poor oral intake



**Figure.** Proposed approach to the diagnostic evaluation of hyponatremia. Initially confirm that the patient has hypo-osmotic hyponatremia by measuring the plasma osmolality. If the patient has hypo-osmotic hyponatremia, then evaluate volume status and urinary sodium excretion. ECV=extracellular fluid volume, NG=nasogastric, Posm=plasma osmolality, SIADH=syndrome of inappropriate secretion of antidiuretic hormone, UNa=urine sodium.

or low sodium intake, the urinary sodium levels in individuals with SIADH may be low. Low BUN and uric levels support SIADH as the underlying diagnosis. Approach to the treatment of SIADH will be discussed in the section below. Hyponatremia secondary to polydipsia is rare in children; however, urine osmolality level less than 100 mmol/kg should raise concern about the possibility of water intoxication (such as improper feeding of an infant or near-drowning).

In conditions in which the effective plasma volume is low, the nonosmotic stimulus for ADH secretion will override the osmotic stimulus, leading to total-body sodium overload with excess of water. Major causes of hyponatremia with extracellular fluid volume excess include nephrotic syndrome, congestive heart failure, kidney failure, and cirrhosis. Approach to correction of these disorders often includes fluid restriction and diuretics.

When serum sodium level is found to be lower than normal (<135 mEq/L [ $<135$  mmol/L]), repeating measurement of serum electrolyte levels, BUN levels, glucose levels, and plasma osmolality levels is advised to rule out sampling or measurement error and to assess the patient for pseudohyponatremia and hyperglycemia. Urine osmolality, potassium, and sodium levels should also be obtained to assist with the diagnostic evaluation of the underlying cause and to assist with planned correction. Other helpful tests include serum uric acid level, which is high in hypovolemia and normal to low in SIADH.

For symptomatic patients with hyponatremia, a modest increase in the serum sodium level is recommended via administration of 3% saline, 2 mL/kg delivered as a bolus with maximum volume of 100 mL. (4) This can be repeated

if neurological symptoms persist. Overall correction of hyponatremia should occur slowly to prevent osmotic demyelination—no faster than 8 to 10 mEq/L (8–10 mmol/L) over the first 24 hours and no more than 18 to 25 mEq/L (18–25 mmol/L) over the first 48 hours. Tolerance to correction will depend on the duration of hyponatremia, since the compensatory mechanisms of the central nervous system will be more established with chronic hyponatremia. Chronic hyponatremia requires more gradual correction than acute hyponatremia to avoid CNS complications, so the current guidelines recommend the goal of 10 mEq/L (10 mmol/L) per 24 hours for acute hyponatremia and 6 to 8 mEq/L (6–8 mmol/L) per 24 hours for chronic hyponatremia. (18)

Formulas used to estimate the effect of the sodium concentration of IV fluids used for correction of hyponatremia on the serum sodium level are available; (1) however, they may actually lead to underestimation of the rate of increase in serum sodium level in some patients. One reason for the inaccuracy of these formulas is that there may be escape from the ADH effect once hypovolemia has been corrected. (2) This escape from ADH effect would be accompanied by greater ability to dilute the urine due to increased free water excretion, resulting in a more rapid increase in the serum sodium level. The formula proposed by Adrogué and Madias (7) was formally tested in adults with hyponatremia. (19) The predicted sodium concentration tended to be slightly lower than the actual sodium concentration at 12, 24, and 36 hours; however, in individuals with hypovolemia due to extracellular volume depletion, the predicted sodium concentration at 24 hours was 5 to 6 mEq/L (5–6 mmol/L) lower than the actual

sodium concentration. Therefore, no formula is consistently accurate in predicting the rate of increase of the serum sodium level. Careful monitoring of electrolyte levels and fluid balance is required to avoid overly rapid correction.

### TRUE SIADH AND HYPONATREMIA SECONDARY TO APPROPRIATE BUT NONOSMOTIC CONTROL OF ADH SECRETION

When the plasma osmolality is less than 275 mOsm/kg (275 mmol/kg), the normal renal response is to excrete a dilute urine so that urine osmolality should be approximately 100 mOsm/kg (100 mmol/kg). Therefore, if the urine is more concentrated than 100 mOsm/kg (100 mmol/kg) when the plasma osmolality is less than 275 mOsm/kg (275 mmol/kg), a nonosmotic stimulus for ADH or inappropriate secretion of ADH must be present. Such nonosmotic stimuli include low effective plasma volume or nonhemodynamic or nonosmotic stimuli, such as pain, nausea, stress, and numerous pharmacological agents and disease states (see the following discussion).

Four mechanisms have been described for the actions of vasopressin during hypo-osmolality: nonosmotic release induced by stimuli from the paraventricular or supraoptic nuclei, ectopic production, factors that enhance the renal effects of vasopressin, and an activating mutation of the vasopressin receptor. (2) The presence of inappropriately concentrated urine ( $>100$  mOsm/kg [ $>100$  mmol/kg]) in a child with true hyponatremia indicates that a nonosmotic stimulus for ADH is present, such as a hemodynamic stimulus or a nonosmotic or hemodynamic stimulus. One should suspect that SIADH is present in acute care settings known to increase the risk for nonosmotic release or actions of ADH, such as children with pain, nausea or vomiting, postanesthetic status, or pulmonary or CNS disease (see Table 2). In these children, SIADH is an acute condition that is suspected to resolve. Chronic hyponatremia due to SIADH is not common in children but may occur in children with chronic CNS or pulmonary conditions. The nephrogenic syndrome of inappropriate antidiuresis is a rare disorder described in children who have the clinical picture of SIADH but have no detectable circulating ADH. The reported cases of this syndrome are the result of a gain of function mutation in V2R. This mutation results in sustained generation of cyclic adenosine monophosphate, which leads to insertion of more water channels on the apical surface of the collecting duct, resulting in increased water reabsorption and hyponatremia. (20)(21)

Treatment of SIADH should start with prevention. Recognition of children at risk can allow tailored IV or fluid therapy and more careful monitoring. Once SIADH is

present, therapy includes (a) identification and treatment of the underlying cause and (b) measures to gradually correct the serum sodium level toward normal values at a safe rate. The major causes of SIADH (modified to those more likely to occur in children) are listed in Table 2.

The first-line treatment of SIADH is fluid restriction, although there are no clear guidelines regarding the exact amount of fluid restriction required. Alternative therapies include (a) furosemide and sodium supplementation, (b) urea administration, and (c) vasopressin receptor antagonist administration. Demeclocycline and lithium, agents for which the side effects include nephrogenic diabetes insipidus, have been used to treat chronic SIADH in the past but are no longer drugs of choice. The use of furosemide to treat hyponatremia related to SIADH seems counterintuitive; however, loop diuretics inhibit free water absorption, which overrides their effect of increasing sodium and potassium excretion; however, supplemental sodium chloride and/or potassium chloride may be required to avoid negative sodium or potassium balance. (22) Urea supplementation is also used to treat chronic SIADH by increasing the excretion of electrolyte-free water. As an osmotic agent, urea increases water excretion by inducing an osmotic diuresis and is also associated with a decrease in urinary sodium excretion in patients with SIADH. (23) The recommended starting dose is 0.1 g/kg per day, divided into 4 doses, with a maximum dose of 2 g/kg per day. (24) Urea had equivalent effectiveness and tolerance in adults with SIADH, as compared to vaptans (see the following discussion). (23)

A class of drugs known as *vaptans* shows promise for treatment of chronic hyponatremia, including SIADH. Vaptans inhibit the vasopressin receptor, resulting in increased free water excretion, or aquaresis. Conivaptan inhibits both V1a and V2 receptors and is available only in IV form, whereas tolvaptan is a specific antagonist of V2R and is available in oral form. Vaptans have been successfully used to treat hyponatremia in adults with SIADH and hyponatremia from other etiologic origins, such as congestive heart failure, and was approved by the Food and Drug Administration in 2009 for treatment of euvolemic and hypervolemic hyponatremia. Studies in adults with hyponatremia (including SIADH) indicate that both conivaptan and tolvaptan are effective in the correction of hyponatremia and are well tolerated. Common effects associated with vaptans include increased thirst and dry mouth due to increased urine volume. (25)(26) Reports of the use of vaptans in children are limited. Continuous conivaptan infusion (20–30 mg per 24 hours) was used to treat refractory hyponatremia secondary to SIADH in a 13-year-old with large cell lymphoma to allow aggressive hydration for induction chemotherapy. (27) Intermittent bolus IV conivaptan (0.15 mg/kg) was used to treat SIADH in a

19-month-old with traumatic brain injury. (28) Tolvaptan was used to treat hyponatremia in 2 infants with SIADH by using doses of 0.1 to 0.6 mg/kg per day by crushing the tablets and mixing them with water. (29) Two additional case reports indicate successful treatment of fluid overload secondary to congestive heart failure with tolvaptan (0.1 mg/kg per day). (30)(31)

For symptomatic hyponatremia in children, Moritz and Ayus recommend the administration of 3% NaCl in children with a suspected hyponatremic encephalopathy: 2 mL/kg with a maximum of 100 mL, which can be repeated as needed until CNS symptoms improve. (4)

#### IV FLUID THERAPY IN HOSPITALIZED PEDIATRIC PATIENTS

Hospitalized children are at increased risk for hyponatremia secondary to SIADH because of the presence of conditions that stimulate ADH release by nonosmotic and nonhemodynamic stimuli. (32) Conditions associated with increased ADH release include nausea, stress, pain, surgery, and certain medications, as well as pulmonary and CNS diseases commonly seen among hospitalized children, such as pneumonia, bronchiolitis, asthma, positive pressure ventilation, CNS infection, and head trauma (see Table 2). (33) Among children hospitalized with gastroenteritis or febrile illness, plasma ADH levels were found to be inappropriately increased in children with hyponatremia at admission. (9)(34) Furthermore, administration of hypotonic IV fluids has been shown to increase risk for the development of hyponatremia after hospital admission. (10) A recent meta-analysis of available randomized clinical trials in children demonstrated that the relative risk for hyponatremia among children receiving hypotonic IV fluids was 2.37 (range, 1.72–3.26), with relative risk for moderate hyponatremia (<130 mEq/L [ $<130$  mmol/L]) of 6.1 (range, 2.2–17.3). (35) These findings were similar to those previously reported in a meta-analysis, which included cohort studies and available randomized trials of hypotonic versus isotonic fluid. (36) Over the past 2 decades, experts have urged clinicians to change from the classic approach to fluid and electrolyte management, as outlined by Holliday et al, to a preference of isotonic fluids for maintenance therapy. (32)(33)(37) Exceptions to this include children with increased ongoing water loss, such as renal concentrating defects and extrarenal losses of fluid.

When Moritz and Ayus published their argument that using isotonic IV fluids, such as normal saline or lactated

Ringer solution, would prevent hospital-acquired hyponatremia, (33) a debate was initiated between their proposal and the standard parenteral fluid therapy originally outlined by Holliday et al, adopted universally by practicing pediatricians and taught to pediatric house staff for decades. (38) (39) While acknowledging that many hospitalized children are at risk for alternations in renal water excretion due to nonosmotic stimuli for ADH secretion, those in favor of the method of Holliday et al postulated that the use of isotonic fluid would result in hypernatremia and/or fluid overload. (40) Most importantly, IV fluid should be prescribed with the same care as other medical treatments and medications, and the patient must be carefully monitored.

In summary, hyponatremia is relatively common, particularly in hospitalized children who are at risk for SIADH.

#### SUMMARY

1. On the basis of strong research evidence (level A), administration of isotonic fluid is recommended as the first choice for intravenous (IV) fluid in hospitalized children. (10)(15)(16)(35)(36)(37)
2. On the basis of primarily consensus, due to lack of relevant clinical studies (level D), careful monitoring of serum electrolyte levels is required after initiation of IV fluids to avoid hyponatremia. (4)(41) Evaluation of children with hyponatremia is aimed at determining the underlying cause so that treatment can be appropriately outlined.
3. On the basis of strong research evidence (level B), symptomatic hyponatremia deserves immediate treatment with hypertonic saline, but thereafter, hyponatremia should be corrected slowly to avoid further central nervous system sequelae. (2)(4)(7)(8)(42)
4. On the basis of some research evidence, as well as consensus (level C), syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a common underlying cause of hyponatremia in children, and most cases are acute and transient conditions. (9)(11)(14)(33)(34)
5. In cases of chronic hyponatremia due to SIADH, treatment options, in addition to fluid restriction, include furosemide, urea, and tolvaptan; treatment recommendations are largely based on some research evidence, as well as consensus (level C). (8)(17)(22)(23)(24)(25)(26)(27)(28)
6. More information will be needed to guide specific recommendations regarding the ideal choice of therapy for children with chronic hyponatremia.

*References for this article are at <http://pedsinreview.aappublications.org/content/39/1/27>.*

## PIR Quiz

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1. A 5-year-old boy is brought to the emergency department with a 5-day history of vomiting and diarrhea. His parents report a 1.6-kg weight loss. He has been drinking only water. His physical examination findings show signs of moderate volume depletion, with a heart rate of 110 beats/minute. He has not produced any urine for at least a few hours. His laboratory values are sodium level of 130 mEq/L (130 mmol/L), potassium level of 5 mEq/L (5 mmol/L), bicarbonate level of 15 mmol/L, chloride level of 110 mEq/L (110 mmol/L), creatinine level of 1.0 mg/dL (88.4  $\mu$ mol/L), blood urea nitrogen (BUN) level of 20 mg/dL (7.14 mmol/L), blood glucose level of 100 mg/dL (5.55 mmol/L), serum osmolality of 271 mmol/kg, and urine sodium level of <5 mmol/L. Which of the following mechanisms is likely to be occurring in this child?
  - A. Decreased baroreceptor response to volume depletion.
  - B. Decreased thirst due to hypo-osmolality.
  - C. Increased antidiuretic hormone (ADH) secretion response to hypovolemia.
  - D. Increased cell volume due to water retention.
  - E. Increased sodium excretion due to hypovolemia.
2. A 4-year-old girl is brought to the emergency department with cough and fever measured at home at 104°F (40°C). At physical examination, she has rales in the right lower lung field, and a chest radiograph shows a right lower lobe infiltrate. Her parents refuse blood tests and intravenous (IV) line placement and request only oral treatment. What is the likelihood that this child has a serum sodium level less than 135 mEq/L (135 mmol/L) at this time?
  - A. 1% to 5%.
  - B. 5% to 10%.
  - C. 10% to 15%.
  - D. 20% to 45%.
  - E. 60% to 75%.
3. The patient described in question 2 progresses to worsening tachypnea and hypoxia. Her oxygen saturation level is 90%, with 2 L delivered via nasal cannula. Her parents agree to allow IV placement and inpatient admission. Her serum electrolyte levels are sodium level of 134 mEq/L (134 mmol/L), potassium level of 3.5 mEq/L (3.5 mmol/L), bicarbonate level of 28 mEq/L (28 mmol/L), and chloride level of 110 mmol/L. What is the best IV fluid choice for maintenance fluid delivery for this patient?
  - A. 5% dextrose with 0.35 normal saline.
  - B. 0.22 ("quarter-normal") saline with 20 mEq/L KCl.
  - C. 5% dextrose with 0.22 ("quarter-normal") saline and 5 mEq/L KCl.
  - D. 5% dextrose with 0.45 ("half-normal") saline and 10 mEq/L KCl.
  - E. 5% dextrose with 0.9 ("normal") saline and 10 mEq/L KCl.
4. An 8-year-old boy is referred to the emergency department with a history of headache for the past 24 hours and nausea and vomiting for the past 7 days. Serum sodium level measured at an urgent care center was 120 mEq/L (120 mmol/L). His past medical history is unremarkable. Physical examination shows heart rate of 100 beats/minute, blood pressure of 80/35 mm Hg, and dry mucous membranes. His laboratory values are sodium level of 120 mEq/L (120 mmol/L), potassium level of 3.2 mEq/L (3.2 mmol/L), bicarbonate level of 25 mEq/L (25 mmol/L), chloride level of 89 mEq/L (89 mmol/L), and osmolality level of 275 mmol/L. Urine sodium level is <10 mmol/L, and specific gravity is higher than 1.030. Which of the following diagnoses is most likely to explain his electrolyte abnormalities?

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- A. Cerebral salt wasting.
  - B. Congestive heart failure.
  - C. Gastroenteritis.
  - D. Renal failure.
  - E. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
5. A previously healthy 9-year-old girl is seen for evaluation of headache and mild nausea that has developed gradually over the past 2 or 3 weeks. She has not had any vomiting or diarrhea, although her appetite seems to have decreased. She is not taking any medications. Her heart rate is 75 beats per minute, and her blood pressure is 90/50 mm Hg. Her physical examination findings show no abnormalities, except for tenderness over her right pelvic brim. She has no edema. Her laboratory values include sodium level of 118 mEq/L (118 mmol/L), potassium level of 3.8 mEq/L (3.8 mmol/L), bicarbonate level of 22 mEq/L (22 mmol/L), chloride level of 90 mEq/L (90 mmol/L), BUN level of 4 mg/dL (1.43 mmol/L), creatinine level of 0.5 mg/dL (44.20  $\mu$ mol/L), and serum osmolality of 250 mmol/kg. Urine sodium level is 45 mEq/L (45 mmol/L), and urine osmolality is 400 mOsm/kg (400 mmol/kg). Which of the following diagnoses is most likely to explain her hypo-osmolar state?
- A. Congestive heart failure.
  - B. Gastroenteritis.
  - C. Hepatic failure.
  - D. Psychogenic polydipsia.
  - E. SIADH.

# Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Hyponatremia

Deborah P. Jones

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